Sociedad Mexicana
de Bioquímica
Neurobiología

SMB

PROGRAM

3rd Neurobiology Meeting of the Mexican Society for Biochemistry

Pre-Meeting Workshop on Computational Neuroscience

September 22-26th, 2019

Sociedad Mexicana
de Bioquímica
Neurobiología

SMB

PROGRAM

III Neurobiology Meeting of the Mexican Society for Biochemistry

Pre-Meeting Workshop on Computational Neuroscience

Open House for the public / Día de Puertas Abiertas

Gran Plaza Hotel & Convention Center, Guanajuato, México
September 22-26, 2019

Organizing Committee:
Ignacio Camacho Arroyo, INPer-Facultad de Química, UNAM
Susana Castro Obregón, Instituto de Fisiología Celular, UNAM
Octavio García, Facultad de Psicología, UNAM
Aliesha González Arenas, Instituto de Investigaciones Biomédicas, UNAM
Hugo Merchant, Instituto de Neurobiología, UNAM
Silvia Solís Ortiz, Departamento de Ciencias Médicas, Universidad de Guanajuato

SUNDAY, SEPTEMBER 22

Pre-Meeting Workshop on Computational Neuroscience




Organizer: Dr. Victor de Lafuente
Instituto de Neurobiología, UNAM campus Juriquilla

9:00-11: 00 *Introduction to Computational Neuroscience: Matlab tools to study neurophysiological signals*
Dr. Victor de Lafuente
Instituto de Neurobiología, UNAM campus Juriquilla, México

11:00-11:30 Coffee Break

11:30-13:30 *Neural encoding and decoding for neuroprosthetics*
Dr. Mark Churchland
Columbia University Medical Center, USA

13:30-14:30 **Lunch**

14:30–15:30 *Machine Learning: theoretical and practical aspects*
Dr. Mario Treviño
Instituto de Neurociencias, Universidad de Guadalajara, Jalisco, México

15:30- 16:30 *Analytical tools for Magnetic Resonance Imaging*
Dr. Alonso Ramirez
Centro de Ivestigación en Matemáticas, CONACYT, Guanajuato, México

SUNDAY, SEPTEMBER 22

Open House for the public / Día de Puertas Abiertas



10:00-14:00 *Neuronas en acción.*
Actividades y demostraciones dirigidas a público menor de 12 años.
Dra. Luz Lazos
Coordinadora de Divulgación y Promoción Científica del Instituto de Fisiología Celular, UNAM.

11:00-12:00 *¿Qué hacen las hormonas sexuales en nuestro cerebro?*
Dr. Ignacio Camacho Arroyo
INPer-Facultad de Química, U.N.A.M.

12:00-13:00 *Te enamoras con el cerebro y no con el corazón*
Dra. Martha Silvia Solís Ortiz
Departamento de Ciencias Médicas, Universidad de Guanajuato

13:00-14:00 *Demostraciones de la música en el cerebro*
Dra. Martha Silvia Solís Ortiz
Departamento de Ciencias Médicas, Universidad de Guanajuato

General Interest

16:40 – 17:00 *Research oportunities in Germany*
Dra. Susana Castro Obregón
Ambassador Scientist, Alexander von Humboldt-Stiftung/Foundation
Instituto de Fisiología Celular, UNAM

17:00 – 17:20 *Mexican Sincrotrón in Hidalgo. Research opportunities for research on neurobiology.*
Dra. Brenda Valderrama
Coordinator, National Scientific Committee for the Mexican Sincrotrón
Instituto de Biotecnología, UNAM

SUNDAY, SEPTEMBER 22

III Neurobiology Meeting

17:45-18:00 **Welcome ceremony**

18:00–19:00 **Opening Talk**

Movement dynamics in the motor cortex
Dr. Mark Churchland
Columbia University Medical Center, USA

Chair: Dr. Hugo Merchant
Instituto de Neurobiología, UNAM

19:00 **Social hour with lite bites**

9:00–11:00 **Symposium I**

MONDAY, SEPTEMBER 23

NEURODEVELOPMENT




Coordinator and chair: Dr. Luis Covarrubias
Instituto de Biotecnologia, UNAM

I.1 Epigenetic instructions for building the cerebral cortex
Dr. Manuel Baizabal
Department of Neurobiology, Harvard Medical School, USA
I.2 Phospholipid phosphatase-3, a novel marker of neural stem cells, participates in the ventricular system remodeling and adult neurogenesis in mice
Dr. Diana Escalante
Instituto de Fisiología Celular, UNAM, México
I.3 Development of large-scale brain networks from infancy to adulthood
Dr. Sarael Alcauter
Instituto de Neurobiología, UNAM, campus Juriquilla, México
I.4 Engineering neurogenesis for the postnatal brain
Dr. Benedikt Berninger
Center for Developmental Neurobiology, King´s College, UK

11:00–11:30 **Coffee Break**

11:30 – 12:30 **Plenary Lecture I**

From hidden to overt: uncovering the roles of glia in hearing and hearing loss
Prof. Dr. Gabriel Corfas
Director Kresge Hearing Research Institute, University of Michigan, USA

Chair: Dr. Octavio García González
Facultad de Psicología, UNAM

12:30–13:30 **Oral Presentations I**

Chair: Dr. Lourdes Massieu Trigo
Instituto de Fisiología Celular, UNAM. Ciudad Universitaria. México

12:30 – 12:45 *Social behavior in ants relies on a specialized olfactory system.*
Leonora Olivos Cisneros
The Rockefeller University, USA
12:45 – 13:00 *Effects of maternal conditions on sexual preference of the male progeny.*
Alejandra Hernández González
CINVESTAV Sur, México
13:00 – 13:15 *Dual NMDAR signaling in cultured astrocytes: flux-independent pH sensor and flux-dependent regulator of mitochondrial membrane potential (m$\Delta\psi$) through cell membrane-mitochondria communication*.
Pavel Montes Oca Balderas
Instituto Nacional de Neurología y Neurocirugía / Instituto de Fisiología Celular, UNAM
13:15 – 13:30 *Th1/Th17 and Th2 Cytokines in Women with Severe Anxiety and Depression during late pregnancy.*
Philippe Leff-Gelman
Instituto Nacional de Perinatología “Isidro Espinosa de los Reyes”, México

13:30 -15:00 **Lunch**

15:00–17:00 **Symposium II**

NEUROBIOLOGY OF FEEDING IN HEALTH AND DISEASE




Chair: Dr. Yazmin Macotela
Instituto de Neurobiología, UNAM, campus Juriquilla, México
Coordinator: Dr. Ranier Gutiérrez
Laboratorio de Neurobiología del Apetito, Departamento de Farmacología, CINVESTAV, México

II.1 Striatal integration of food reward and satiety
Dr. Luis Tellez
Instituto de Neurobiología, UNAM campus Juriquilla, México
II.2 Visceral control of Brain reward systems
Dr. Ivan de Araujo
Icahn School of Medicine at Mount Sinai, New York City, USA
II.3 A hypothalamic-BNST circuit regulates delay discounting in decision making
Dr. Henry H. Yin
Duke University, USA
II.4 Lateral hypothalamus GABAergic neurons encode sucrose's palatability
Dr. Ranier Gutiérrez
Laboratorio de Neurobiología del Apetito, Departmento de Farmacología, CINVESTAV, México

17:00 – 17:05 **1 min talks for poster advertisings**

Chair: Dr. Gustavo Pedraza
Instituto de Biotecnología, UNAM, México

Demyelination associated to chronic arsenic exposure in Wistar rats.
Sandra A. Niño
Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí
Social Interaction: Adjustment to interdependent contingencies in a competition task with Long Evans rats
Diana Laura Jacobo Godínez
Facultad de Psicología. UNAM
Combined early life stress and neonatal lipopolysaccharide affect hippocampal glial cells and induce long term behavioral alterations.
Luis Miguel Saavedra Pimentel
Universidad Michoacana de San Nicolás de Hidalgo
The fascinating effects of music on the brain.
Miguel Ángel Mayoral-Chávez
Facultad de Medicina UNAM-Universidad Autónoma Benito Juárez de Oaxaca

Plasmid Transfection in mouse brain using cationic polymers.
Katia R. Ávila Gutiérrez
División de Ciencias Naturales y Exactas. Universidad de Guanajuato

17:05 – 19:00 **Poster Session I (Even numbers)**

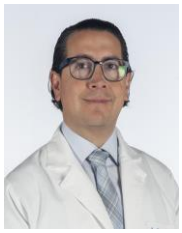
20:00 - **"Callejoneada", Guanajuato sightseeing**

9:00 – 11:00 **Symposium III**

TUESDAY, SEPTEMBER 24

CEREBRAL TUMORS



Chair: Dr. Liliana Quintanar
Departamento de Química, CINVESTAV, México
Coordinator: Dra. Aliesha González Arenas
Instituto de Investigaciones Biomédicas, UNAM, México

III.1 The role of renin-angiotensin in gliomas
Dr. Talia Wegman
Instituto Nacional de Cancerología, México
III.2 The important role of tumor microenvironment in medulloblastoma progression
Dr. Zeng-jie Yang
Philadelphia Fox Chase Cancer Center, USA
III.3 Gas1 as a tool for experimental glioma therapy
Dr. José Segovia
CINVESTAV, México
III.4 From neurology to neuro-oncology
Dr. Bernardo Cacho Díaz
Instituto Nacional de Cancerología, México

11:00 – 11:20 *Discover ANY maze to make easier your life as behavioral neuroscientist*
Dr. Sylvia Ortega Martínez. Scientific manager Neuroscience & ANY-maze™ Divisions. STOELTING Co

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11:00 – 11:30 **coffee break**

11.30 – 12:30 **Plenary Lecture II**

Dissociable dopamine dynamics for learning and motivation
Dr. Joshua Berke
UCSF Center for Integrative Neuroscience, USA

Chair: Dr. Hugo Merchant
Instituto de Neurobiología, UNAM

Oral Presentations II

12:30 – 13:30
Chair: Dr. Julio Morán Andrade
Instituto de Fisiología Celular, UNAM. Ciudad Universitaria. México

12:30 – 12:45 *TrkB-mediated LTP at Hippocampal Mossy Fiber Synapses on CA3 Interneurons.*
Ernesto Griego Melo
CINVESTAV Sur, México
12:45 – 13:00 *Comparison of actions between L-DOPA and different dopamine agonists in striatal DA-depleted microcircuits in vitro: pre-clinical insights*
Esther Lara González E.
Instituto de Fisiología Celular, UNAM, México
13:00 – 13:15 *Integrated single-cell analysis reveals coupled molecular gradient and functional subnetworks in the thalamic reticular nucleus*
Violeta Gisselle López-Huerta
Instituto de Fisiología Celular, UNAM, México
13:15 – 13:30 *Amyloid plaques: Friends or Foes? Exploring the association between Aβ plaques and soluble Aβ aggregates using the FAD4-42 mouse model*
José Sócrates López Noguerola. ICS, Universidad Autónoma del Estado de Hidalgo, México

13:30 - 15:00 **Lunch**

15:00 – 17:00 **Symposium IV**

"Symposium financed by CONACyT 2016 CB 282470 and PAEP-PMDCBQ"
PAPIIT IN208518

NEURAL NETWORKS




Chair: Dr. Silvia Solís Ortiz
Universidad de Guanajuato, México
Coordinator: Dr. Angélica Zepeda
Instituto de Investigaciones Biomédicas, UNAM, México

IV.1 Imprinting and recalling cortical ensembles
Dr. Luis Carrillo Reid
Instituto de Neurobiología, UNAM, campus Juriquilla, México
IV.2 Heterosynaptic structural plasticity of adult born granule cells
Dr. Stephan Schwarzacher
Goethe-Universität, Frankfurt am Main, Germany
IV.3 The influence of spatial learning on the integration of adult-born granule neurons.
Dr. Nora Abrous
Neurocentre Megendie, Bordeaux, France
IV.4 Intracortical and corticostriatal circuits for sensory processing and behavior
Dr. David Margolis
Department of Cell Biology and Neuroscience, Rutgers University, USA

17:00 – 17:05 **1 min talks for poster advertisings**

Chair: Dr. Diana Escalante
Instituto de Fisiología Celular, UNAM, México

Is peripheral thyrotropin-releasing hormone-degrading ectoenzyme a therapeutic target for diet-induced obesity?
Karina Hernández Ortega
Instituto de Biotecnología, UNAM
Evaluation of 25-OH Vitamin D levels in multiple sclerosis: association with clinical and hematological parameters in Mexican patients.
Andrea Michel Arellano-Pliego
Universidad Autónoma de Guerrero
Chronic administration of glutamate decarboxylase inhibitors in the rat spinal cord induces motor alterations and motor neuron death
Diana Elizabeth Colín Martínez
Instituto de Fisiología Celular, UNAM

Autophagy inducers trehalose and metformin prevent dopaminergic cell death
Yareth Gopar Cuevas
Facultad de Medicina, Universidad Autónoma de Nuevo Léon
Reactive astrogliosis is exacerbated after spinal cord injury in diabetic rats.
Adriana Domínguez-Vázquez
Departamento de Ciencias Naturales e Ingeniería, UAM Cuajimalpa

17:05 – 19:00 **Poster Session II (Odd numbers)**

WEDNESDAY, SEPTEMBER 25

9:00 – 11:00 **Symposium V**

COGNITIVE NEUROBIOLOGY




Chair: Dr. Adán Domínguez Vargas
Escuela Nacional de Estudios Superiores Unidad León, UNAM, México
Coordinador: Dr. Francisco Sotres Bayón
Instituto de Fisiología Celular, UNAM, México

V.1 Brainstem-to-amygdala control of emotional associative learning
Dr. Joshua Johansen
RIKEN Center for Brain Science, Japan
V.2 Perturbations in the Activity of Cholinergic Interneurons in the Dorsomedial Striatum Impairs the Encoding of an Instrumental Contingency Change
Dr. Fatuel Tecuapetla
Instituto de Fisiología Celular, UNAM, México
V.3 Neural basis of bilaterally coordinated actions
Dr. Pavel Rueda-Orozco
Instituto de Neurobiología, UNAM, campus Juriquilla, México
V.4 Prefrontal control of conflict choice behavior
Dr. Francisco Sotres Bayón
Instituto de Fisiología Celular, UNAM, México

11:00 – 11:30 **coffee break**

11.30 – 12:30 **Plenary Lecture III**

Transcription factor-dependent control of adult hippocampal neurogenesis
Dr. Chichung Lie
Institut für Biochemie, Friedrich-Alexander Universität Erlangen-Nürnberg, Germany

Chair: Dr. Susana Castro Obregón
Instituto de Fisiología Celular, UNAM

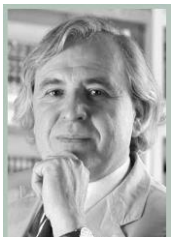
12:30 – 13:30 **Oral Presentations III**

Chair: Dr. Clorinda Arias Álvarez
Instituto de Investigaciones Biomédicas, UNAM

12:30 – 12:45 *FeRIC: a magnetogenetic technique to control neuronal excitability with no depth limitation*
Miriam Hernández-Morales
University of California Berkeley, USA
12:45 – 13:00 *Characterization of cortical dysplasias epileptogenicity in animal model*
Ana Itzel Aquiles Reyes
Instituto de Neurobiología, UNAM, México
13:00 – 13:15 *Long-term copper exposure induces autophagy upregulation and the loss of dopaminergic neurons in vivo*
Alfredo González Alcocer
Facultad de Medicina, Universidad Autónoma de Nuevo Léon, México
13:15 – 13:30 Krüppel-like Factors 9 and 13 Block Neurite Outgrowth Induced by cAMP Pathway Activation
José Avila-Mendoza
University of Michigan, USA

13:30 - 15:00 **Lunch**

15:00 – 16:00 **Closure Lecture**



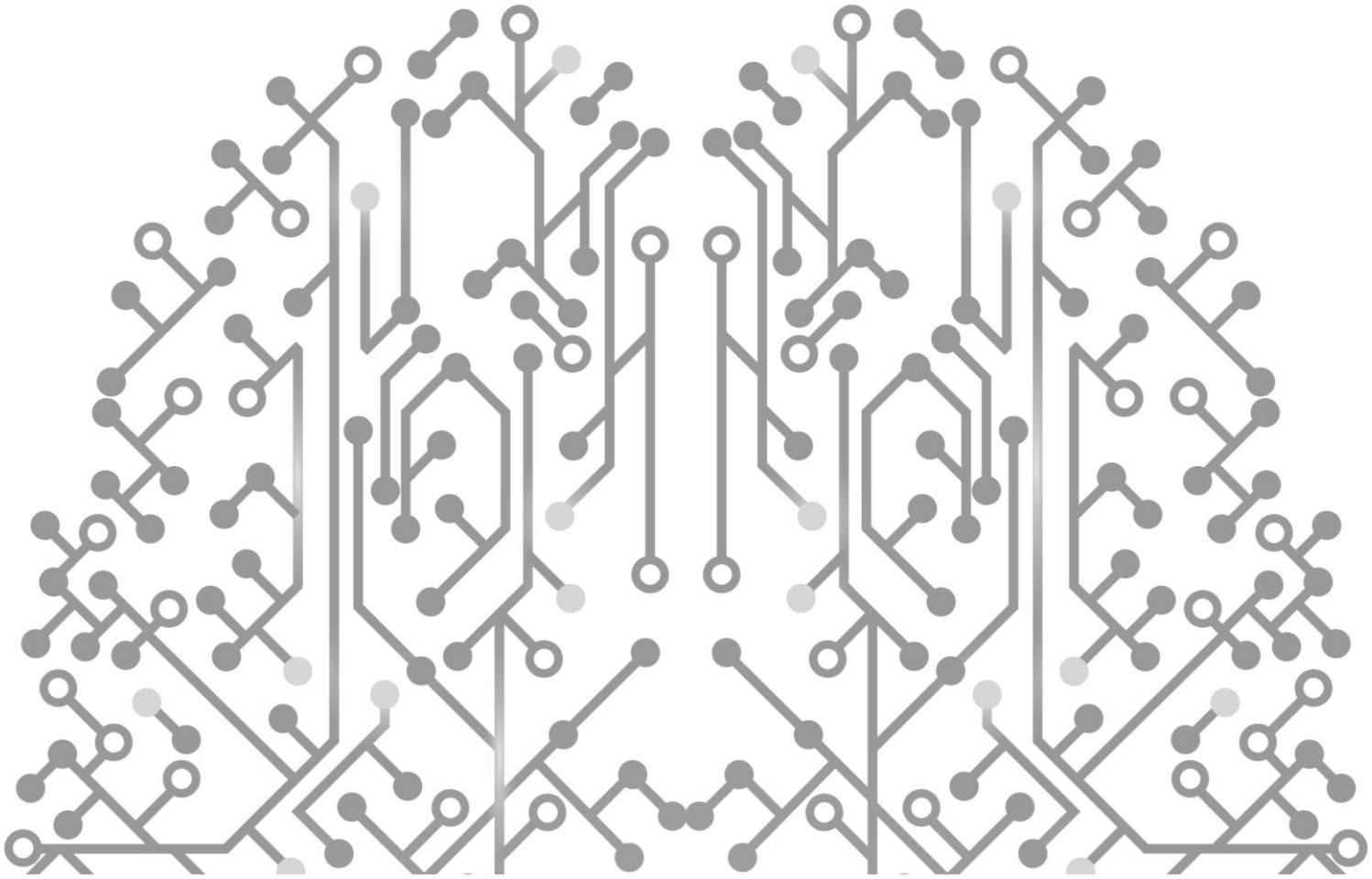
The neural code
Dr. Ranulfo Romo
Instituto de Fisiología Celular, UNAM
El Colegio Nacional de México
USA National Academy of Sciences

Chair: Dr. Hugo Merchant
Instituto de Neurobiología, UNAM

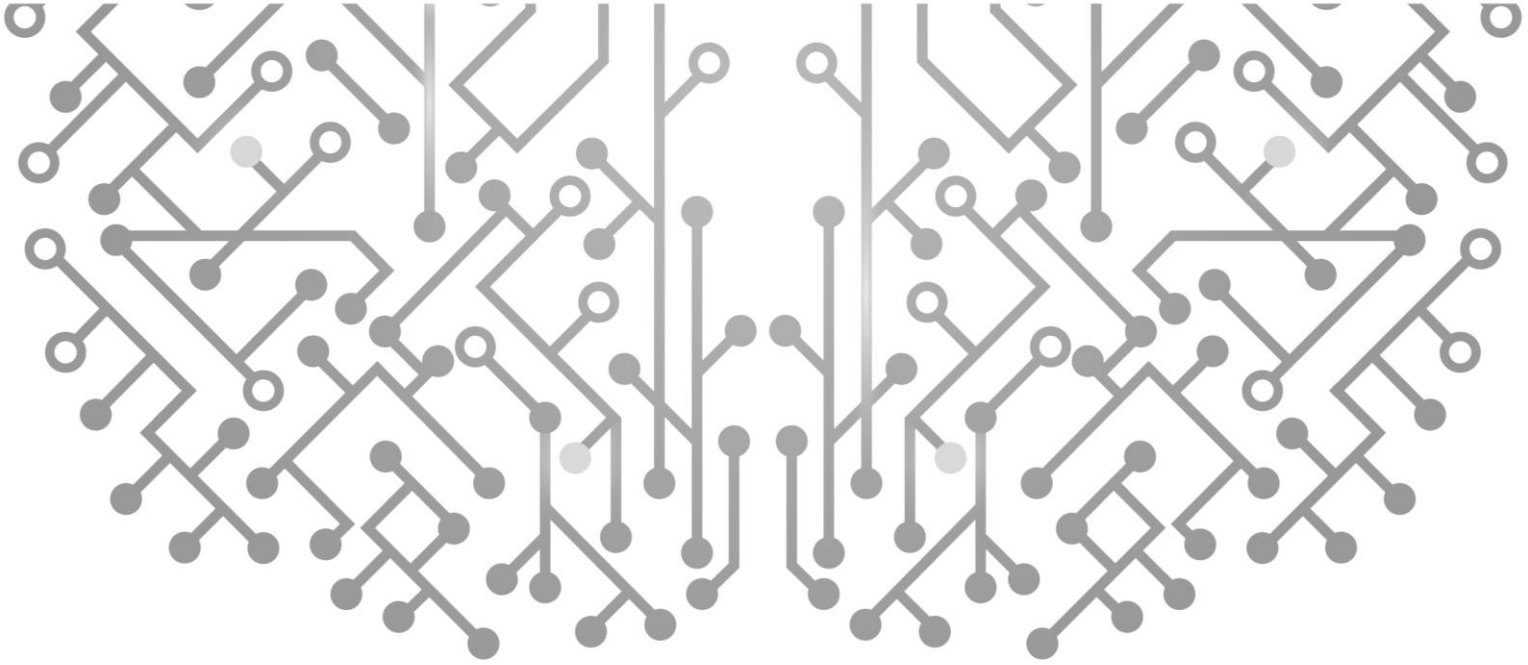
16:00 - 16:30	**Closing Ceremony**
17:00 - 18:00	**Having a beer with…**
18:00 – 18:30	Business meeting
20:00 -	**Farewell Dinner**

THURSDAY, SEPTEMBER 26

9:00 - 11:00	**Breakfast** Talks with Speakers
12:00	**Departure**



Poster Sessions



Posters Session I. Even numbers

Monday September 23, 2019.

COGNITION AND BEHAVIOR

2	Hippocampal functional connectivity associations with cognitive skills in temporal lobe epilepsy. **Alfonso Fajardo-Valdez**, Raúl Rodriguez-Cruces, Luis Concha. Instituto de Neurobiología, UNAM, Campus Juriquilla, Querétaro, México
4	Enrichment environment acts proneurogenic but induces social aggression behavior in male- but not in female- GFAP-EGFP mice: relevance of sex. **Cabrera-Muñoz Edith Araceli**, Olvera-Hernández Sandra, Ortiz-López Leonardo, Reyes-Haro Daniel and Ramírez-Rodríguez Gerardo Bernabé. Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"
6	Litter size effect on vulnerability and resilience. **Maritza Montserrat Cervantes Palacios**, Marcel Pérez Morales, Kurt Hoffman, Beatriz Gómez González, Emilio Domínguez Salazar. Universidad Autónoma Metropolitana - Iztapalapa
8	Predictive rhythmic tapping to auditory metronomes in the nonhuman primate. **Yaneri A. Ayala**, Luis Prado, Hugo Merchant. Instituto de Neurobiología, UNAM Campus Juriquilla
10	Sucrose intensity percept and decision-making coding in the rat anterior insular and orbitofrontal cortex. **Esmeralda G. Fonseca de la Cruz**, Vicente Sandoval Hernández, Silvia Mejía Ortiz, Francisco Zepeda Arias, Sidney A. Simon and Ranier Gutiérrez Mendoza Department of Pharmacology, CINVESTAV
12	Social Interaction: Adjustment to interdependent contingencies in a competition task with Long Evans rats. **Diana Laura Jacobo Godínez**, Alejandro Segura Beltrán & Oscar Zamora Arévalo. Facultad de Psicología. UNAM
14	Hippocampal Neurons in a Visual Metronome Task. **Ana María Malagón**, Karla Mercado, and Victor de Lafuente. Institute of Neurobiology, UNAM
16	Vulnerability and resistance to ketamine in an animal model of schizophrenia depend of litter size. **Ariel Miravete Gutiérrez**, Maritza Montserrat Cervantes Palacios, Kurt Hoffman, Emilio Domínguez Salazar. Departamento de Biología de la Reproducción, Universidad Autónoma Metropolitana- Iztapalapa
18	Cannabis use alters the advantage given by the cannabinoid receptor 1 gene genotype on selective attention performance. **Ivett E, Ortega-Mora**, Ulises Caballero-Sánchez, Talía V. Román-López, Cintia B. Rosas-Escobar, Sandra Romero-Hidalgo, Juan Antonio González-Barrios, Mónica Méndez-Díaz, Oscar E. Prospéro-García, Alejandra E. Ruiz-Contreras. Lab. Neurogenómica Cognitiva, Coord. Psicobiología y Neurociencias, Fac. Psicología, UNAM
20	Assessing Retrospective Memory: Temporal Sequences and Delays. **Mario Pérez Calzada**, Adriana Felisa Chávez de la Peña, Manuel Alejandro García Martínez, Montserrat Vanegas Chavarría & Oscar Zamora Arévalo. Facultad de Psicología, UNAM
22	Brain electrical differences during working memory retrieval are related with maintenance or manipulation processes and task difficulty. **Talía Vianney Román-López**, Ulises Caballero-Sánchez, Silvia Anali Cisneros-Luna, Carlos Sánchez-Gachuz, Jesús Antonio Franco-Rodríguez, Mónica Méndez-Diaz, Oscar Prospéro-García, Alejandra Evelyn Ruiz-Contreras. Coordinación de Psicogiología y Neurociencias, Facultad de Psicología, UNAM

DEVELOPMENT & AGING

24	Progesterone promotes the proliferation, differentiation and maturation of oligodendroglial progenitor cells from the mouse embryonic spinal cord. **Juan Carlos González-Orozco**, Aylin Del Moral-Morales & Ignacio Camacho Arroyo. Facultad de Química, Departamento de Biología, Universidad Nacional Autónoma de México
26	Demyelination associated to chronic arsenic exposure in Wistar rats. **Sandra A. Niño**, Erika Chi, Juan Ortiz, Sergio Zarazúa, Luis Concha, Ma. Esther Jiménez. Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí
28	Autophagy induction reduces features of cellular senescence in the hippocampus of old rats. **Elisa Gorostieta-Salas**, Daniel Moreno-Blas, Jorge Domínguez-Bautista, Bulmaro Cisneros-Vega, Federico Bermudez-Rattoni, Susana Castro-Obregón. Instituto de Fisiología Celular, UNAM
30	Distribution of mitochondria in cells of Medial Nucleus of Trapezoid Body from rat. **Hernández-Santos José Antonio,** Fernández-Valverde Francisca, Orozco-Ibarra Marisol. Laboratorio de Neurobiología Celular y Molecular, Instituto Nacional de Neurología y Neurocirugía "Manuel Velasco Suárez"
32	Analysis of expression of single exon genes in the mouse embryonic telencephalon. **Katia Aviña-Padilla**, Andrés García-García, Jose Antonio Ramírez Rafael, Emilio Gabriel Herrera-Oropeza, Maribel Hernández-Rosales, VijayKumar Muley and Alfredo Varela-Echavarría. Instituto de Neurobiología UNAM- Campus Juriquilla
34	Neuronal Senescence is promoted by Dysfunctional Autophagy. **Daniel Moreno-Blas**, Elisa G. Gorostieta-Salas, Gabriel Muciño-Hernández, Alexander M. Pommer-Alba & Susana Castro-Obregón. Departamento de Neurodesarrollo y Fisiología, División de Neurociencias, Instituto de Fisiología Celular, UNAM
36	Cortical Neurons from Human Embryonic Stem Cells Derived and Maintained on the Human Amniotic Epithelium. Ávila González Daniela, Portillo Martínez Wendy, Molina Hernández Anayansi, García López Guadalupe, **Díaz Martínez Néstor Fabián**. Departamento de Fisiología y Desarrollo Celular, Instituto Nacional de Perinatología

TEACHING & SCIENCE COMMUNICATION

38	The fascinating effects of music on the brain. **Miguel Ángel Mayoral-Chávez**, María del Pilar Gabriel-de la Torre, Jael López-Martínez. Centro de investigación Facultad de Medicina UNAM-UABJO

STRESS

40	Oseltamivir and Bezafibrate Induce Synergic Effect Decreasing Oxidative Damage in Rat Brain Regions. **David Calderón Guzmán**, Norma Osnaya Brizuela , Maribel Ortiz Herrera, Hugo Juárez Olguín, Armando Valenzuela Peraza, Ernestina Hernández García, Gerardo Barragán Mejía, Francisca Trujillo Jiménez. Lab. Neuroscience. UNAM. National Institute of Pediatrics. Mexico
42	Systemic administration of fractalkine affects hippocampal neurogenesis and induces depression like-behavior in female Balb/C mice. **Ramírez-Rodríguez Gerardo Bernabé**, Lugo-Hernández Enrique, Vega-Rivera Nelly Martiza, Ortiz-López Leonardo. Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"

GLIA

44	Evaluation of glial cells at the hippocampus of brain autistic-like mice C58/J. **De La Fuente-Granada Marisol**, Duarte-Campos Juan F, Barón-Mendoza Isabel C, González-Arenas Aliesha. Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, UNAM
46	Modulation of the response to an obesogenic diet by the astrocytic molecular clock. **Lucía Mendoza Viveros**, Clarisa Marmolejo Gutiérrez, Lorena Aguilar Arnal, Ricardo Orozco Solis. Instituto de Investigaciones Biomédicas, UNAM. INMEGEN
48	Combined early life stress and neonatal lipopolysaccharide affect hippocampal glial cells and induce long term behavioral alterations. **Saavedra Pimentel Luis Miguel,** Ochoa Zarzosa Alejandra, Torner Luz. Universidad Michoacana de San Nicolás de Hidalgo, (CMEB)

METABOLISM

50	Sucralose increases levels of oxidative stress in the brain of C57BL6 mice. **Cristina Doriany Balcón Pacheco**, Joel Ramírez Emiliano, César Ozuna, Elena Franco-Robles. Division of Life Sciences, University of Guanajuato Campus Irapuato-Salamanca
52	Neuroprotector effect of nicotinamide via colinergic in a model of cognitive deficit-induced by hypercaloric diet in rats. **Ramírez-Cruz Armando,** Ángeles-Mejía Selene, Benitez-García Gabriela Sugey**,** Romero-Vázquez Fernando Alfonso**,** Gómez-Olivares José Luis, Díaz-Flores Margarita. Unidad de Investigación Médica en Bioquímica. Hospital de Especialidades CMN Siglo XXI. IMSS
54	Fasting regulates markers of activity of thyrotropin-releasing hormone neurons in the dorsomedial nucleus and lateral hypothalamus of adult rats. Sex similarities and differences. **Karla Yamili Vargas Orihuela**, Lorraine Jaimes-Hoy, Fidelia Romero Arteaga, Arlene García-Vázquez, Patricia Joseph-Bravo, and Jean-Louis Charli**.** Departamento de Genética del Desarrollo y Fisiología Molecular, Instituto de Biotecnología, UNAM

NEUROENDOCRINOLOGY

56	Central estradiol protects the female brain against sleep loss related changes in blood-brain barrier function. **Enriquez Zamudio Mariely**, Medina-Flores Fernanda, González-Flores Óscar, Domínguez-Salazar Emilio, Velázquez-Moctezuma Javier, Gómez González Beatriz. Area of Neurosciences. Dept. Biology of Reproduction. Universidad Autónoma Metropolitana, Unidad Iztapalapa
58	Functional Electroencephalographic Connectivity and its Relationship with Hormones in Premenopause and Early Postmenopause. **Erika Guadalupe González-Pérez**, Markus Müller-Bender, Nicté Figueroa-Vega, Wady Ríos-Herrera, Martha Silvia Solís-Ortiz. Medical Sciences Department. University of Guanajuato
60	Neuro-immuno-endocrine changes induced by high- fat diet are associated with increased anxiety- like behavior in Wistar rats. **Hernández-Mondragón Juan Carlos,** Crespo-Ramírez Minerva, Apolinar-Manuel Leticia, Tesoro-Cruz Emiliano, Pérez de la Mora Miguel. Division of Neurosciences, Instituto de Fisiología Celular, UNAM
62	Sexual motivation is diminished in diabetic female rat. **Abigail Karina Hernández Munive**, Daniela Rebolledo Solleiro, Alonso Fernández Guasti. Centro de Investigación y de Estudios Avanzados

64	Effects of progesterone on the expression profile of miRNAs in human glioblastoma cells. **Diana Elisa Velázquez Vázquez**, Ignacio Camacho Arroyo. Unidad de Investigación en Reproducción Humana, Instituto Nacional de Perinatología-Facultad de Química, Universidad Nacional Autónoma de México
66	Evaluation of the proteomic profile of brain´s mouse by the effect of pharmacological regulatory compounds of cholecystokinin as a therapeutic alternative against overweight and obesity. **Vique-Sánchez JL,** Galíndez-Fuentes AI, Jiménez-Pineda A, Cruz-Aguirre AS and Benítez-Cardoza CG. Escuela Nacional de Medicina y Homeopatía – IPN
68	Transcriptional networks induced by prolactin in the hippocampus. **Erika Alejandra Cabrera-Reyes**, América Vanoye–Carlo, Edgar Ricardo Vázquez-Martínez and Marco Cerbón. Unidad de Investigación en Reproducción Humana, Instituto Nacional de Perinatología-Facultad de Química, Universidad Nacional Autónoma de México

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70	Effects of clonidine and oxytocin in the modulation of anxiety in rat. **Hernández-Mondragón Juan Carlos,** Crespo-Ramírez Minerva, Borroto-Escuela Dasiel, Fuxe, Kjell, Pérez de la Mora Miguel. Division of Neurosciences, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México
72	The combination of fluoxetine-tramadol inhibits generalized seizures caused by pentylenetetrazole. **Sánchez Hernández Josué Denichi** and Manjarrez Marmolejo Joaquín. Laboratory of Physiology of the Reticular Formation, National Institute of Neurology and Neurosurgery MVS
74	Exosomes of depression diagnosed-patients as a source of potential biomarkers**. Vásquez-Pérez Jorge Manuel,** Flores-Ramos Mónica, Ortiz-López Leonardo, Ramírez-Rodríguez Gerardo Bernabé. Laboratorio de Neurogénesis, Subdirección de investigaciones clínicas, Instituto Nacional De Psiquiatría Ramón De La Fuente Muñiz

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76	Integration of the direct and indirect pathway in the substantia nigra reticulata and its modulation by cannabinoids. **Báez-Cordero Ana Silvia**, Pimentel-Farfán Ana Karen, González-Pereyra Perla, Peña-Rangel María Teresa, Rueda-Orozco Pavel Ernesto. Department of Neurobiology of Development and Neurophysiology, Institute of Neurobiology, UNAM
78	Neuronal plasticity evoked by somatosensensory stimulation in the cortico-thalamus-striatal circuits. **Hidalgo-Balbuena Ana Elizabeth**, Luma Annie Yolene, Pimentel-Farfán Ana Karen, Peña-Rangel María Teresa, Rueda-Orozco Pavel Ernesto. Departamento de Neurobiología del Desarrollo y Neurofisiología. Instituto de Neurobiología, UNAM
80	Investigating the role of the pallidal cannabinergic system in the control of speed. **Martínez-Montalvo Mario Gabriel**, Ortega-Romero Diana Itzel, Peña-Rangel María Teresa, Rueda-Orozco Pavel Ernesto. Departamento de neurobiología del desarrollo y neurofisiología, Instituto de Neurobiología. UNAM
82	Exploring the role of dorsolateral striatum in bimanually coordinated movements in rats. **Pimentel-Farfan Ana Karen,** Báez-Cordero Ana Silvia, Peña-Rangel Maria Teresa & Rueda-Orozco Pavel Ernesto. Laboratorio de Neurofisiología de los Hábitos, Departamento de Neurobiología del Desarrollo y Neurofisiología, Instituto de Neurobiología. UNAM

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84	Activation of TLR9 with a synthetic ligand in a murine medulloblastoma xenograft. **Abarca-Merlín Daniela Melissa**, Maldonado-Bernal Carmen, Álvarez-Arellano Lourdes. Laboratorio de Investigación en Neurociencias, Hospital Infantil de México Federico Gómez
86	Increase of TNF alpha plasmatic concentrations is associated to depressive symptoms in residents from central zone in Veracruz. **Balderas-Vazquez Cecilia Luz**, Valenzuela Limón Olga Lidia, Rodríguez-Landa Juan Francisco, Garcia-Montalvo Eliud Alfredo, Bernal-Morales Blandina. UV-Xalapa, Veracruz, México
88	Role of NADPH oxidase-2 in the progression of the inflammatory response secondary to striatum excitotoxic damage. **Diego Rolando Hernández Espinosa**, Lourdes Massieu Trigo y Julio Morán Andrade. División de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México
90	Effects of Anti-NMDA receptor antibodies on NMDA-induced intracellular Ca^{2+} rise: possible implications for anti-NMDAR encephalitis. **Montes Oca Balderas, Pavel**, Gómora García Juan Carlos, Massieu Trigo Lourdes, Hernández-Cruz, Arturo. Unidad de Neurobiología Dinámica, Departamento de Neuroquímica, INNN
92	Evaluation of the protein expression the Neurotrophic factors in rats with chronic spinal cord injury immunized with the A91 peptide. **Thalía Rodríguez-Barrera**, Julián García-Sánchez, Adrián Flores-Romero, Elisa García-Vences, Antonio Ibarra and Roxana Rodríguez-Barrera. Facultad de Ciencias de la Salud, Universidad Anáhuac

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94	Content and colocalization of progesterone receptor and protein kinase c alpha increased according to malignancy grade in biopsies of mexican patients. **Arcos-Montoya Denisse**, Mejía-Pérez Sonia, Wegman-Ostrosky Talia, González-Arenas Aliesha. Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México
96	The proliferation of neural progenitor cells in the adult mouse hippocampus depends on the duration of the proinflammatory profile induced by LPS. **Ávila-Muñoz Evangelina**, Pérez-Domínguez Martha, Domínguez-Rivas Eduardo and Zepeda Angélica. Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México
98	Tau hyperphosphorylation in mouse brain during diabetic ketoacidosis. **Jorge Andrés Cázares Preciado**, Elizabeth Mata Villegas, Argelia Rosillo de la Torre, Gustavo Basurto Islas. División de Ciencias e Ingenierías, Universidad de Guanajuato, Campus León
100	LPS-induced neuroinflammation promotes distinct effects on the proliferation of defined subpopulations of neural progenitor cells in the adult dentate gyrus. **Eduardo Domínguez-Rivas**, Martha Pérez-Domínguez, Evangelina Ávila-Muñoz, Angélica Zepeda. Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México
102	A New Murine Model Of H-ABC Human Tubulinopathy. **Ángeles Garduño Robles**, Valeria Piazza, José Ramón Eguíbar Cuenca, Ma. Del Carmen Cortés, Sergio Pantano, Silvia Alejandra López Juárez, Victor H. Hernández González. División de Ciencias e Ingenierías, Universidad de Guanajuato
104	Friend or Foe? Participation of IRE1 in the unfolded protein response induced by glucose deprivation in cortical neurons. **Juan Carlos Gomora-Garcia**, Lourdes Massieu Trigo Instituto de Fisiología Celular, Universidad Nacional Autónoma de México

106	Estrogen receptor beta activation induces medulloblastoma cells proliferation whereas PKCs activation blocks it. **Hernández-Rojas Rubí**, De la fuente-Granada Marisol, González-Arenas Aliesha. Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México
108	Estradiol induces epithelial-to-mesenchymal transition on human glioblastoma cells. **Ana María Hernández-Vega**, Ignacio Camacho-Arroyo. Unidad de investigación en Reproducción Humana, Instituto Nacional de Perinatología-Facultad de Química, UNAM
110	Olfactory alterations in a *Drosophila* Parkinson´s disease model expressing α-synuclein**. Estefanía De Allende Becerra**, Enrique Alejandro Reynaud Garza. Instituto de Biotecnología, UNAM
112	Calorie restriction modify stroke outcome in a mice model. **M. Xóchitl Mendoza-Rojas**, Hilda Martínez-Coria and Héctor E. López-Valdés. Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez
114	Longitudinal evaluation of bundle-wise water diffusion changes following axonal degeneration in a region of fiber crossing. **Omar Narvaez-Delgado**, Ricardo Coronado-Leija, Gilberto Rojas-Vite, Marcos Aranda, Alonso Ramirez-Manzanares, José Luis Marroquin, Jorge Larriva-Sahd, and Luis Concha. Instituto de Neurobiología, UNAM
116	Non-evoked electroretinogram reveals slow oscillatory activity that is altered in obese mice. **Noguez Imm Ramsés**, Martínez-Torres Ataúlfo, Thébault Stéphanie. Instituto de Neurobiología, Campus UNAM-Juriquilla
118	Effect of a high-fiber diet on amyloid aggregation and memory performance of APP/PS1 transgenic mouse. **Hernández-Acosta Julieta**, Cuervo-Zanatta Daniel, Pérez-Grijalva Brenda, Reyes-Chávez Ricardo M, Sánchez-Valle Vicente and Perez-Cruz Claudia. Instituto de Neurobiología, UNAM
120	Inhibition of HDAC4 with sodium butyrate does not prevent AMPA-induced excitotoxic degeneration of spinal motoneurons in vivo. **Prior-González Mara**, Lazo-Gomez Rafael, Tapia Ricardo. División de Neurociencias, Instituto de Fisiología Celular, UNAM
122	The Ketone body beta-hydroxybutyrate restores autophagic degradation in the brain of hypoglycemic rats. **Carmen Torres-Esquivel,** Teresa Montiel-Montes, Marco Flores-Méndez, and Lourdes Massieu-Trigo. Departamento de Neuropatología Molecular, División de Neurociencias, Instituto de Fisiología Celular, UNAM
124	The mRVG29 peptide as vehicle for delivery of the CDNF gene in an animal model of Parkinson's disease. **Sheila Adela Villa Cedillo**, Daniel Matta Yee Chig, Humberto Rodríguez Rocha, Aracely García García, María de Jesús Loera Arias, Adolfo Soto Dominguez, Roberto Montes de Oca Luna, Odila Saucedo Cárdenas. Universidad Autónoma de Nuevo León, Facultad de Medicina, Departamento de Histología

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126	Effect of nicotine abstinence on both the anxiolytic-like behavior and synaptic transmission of the ventral hippocampus in young rats. **Varela Correa María Berenice**, Ayala Rodríguez Jesús David & García Colunga Jesús. Instituto de Neurobiología, UNAM campus Juriquilla

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128	Dendritic complexity in prefrontal cortex and hippocampus of the autistic-like mice C58/J. **Barón-Mendoza Isabel**, Del Moral-Sánchez Ireri, Martínez-Marcial Mónica, García-

	Rebollar Jorge Omar, García Octavio, Garzón-Cortés Daniel, González-Arenas Aliesha. Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México
130	Connectivity in the auditory and premotor cortex in the rat brain. **De León Andrez Cynthia Ivette**, García Saldivar Pamela, Aguilar Ayala Yaneri, Rojas Piloni Gerardo, Concha Loyola, Luis Merchant Hugo. Instituto de Neurobiología, UNAM campus Juriquilla, Querétaro
132	The improvement of living conditions increases the effects of Citalopram at the level of neuroplasticity and behaviors associated with depression. **Domínguez-Flores Betsabé**, Ortíz-López Leonardo, Vega-Rivera Nelly M., Flores-Ramos Mónica and Ramírez-Rodríguez Gerardo Bernabé Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"
134	Long-lasting effects of environmental enrichment on behavior: implications of neuroplasticity in male Balb/C mice**. Granados-Juárez Andrea,** Cabrera-Muñoz Edith, Ortiz-López L, and Ramírez Rodríguez Gerardo Bernabé. Laboratorio de Neurogénesis. Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz
136	Analysis of the multineuronal activity patterns in the respiratory rhythm generator and its reconfiguration during hypoxia. **Juárez Vidales Josué de Jesús,** Pérez Ortega Jesús, Loera Hernández Jonathan Julio, Méndez Salcido Felipe, Peña Ortega José Fernando. Instituto de Fisiología Celular, UNAM
138	Repetitive transcranial magnetic stimulation induces antidepressant like effects and modifies cellular populations involved in the generation of new neurons. **Meneses-San Juan David**, Ortiz-López Leonardo, González-Olvera Jorge Julio and Ramírez-Rodríguez Gerardo Bernabé. Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz
140	Striatal Parvoalbumin expressing neurons activate the striatal microcircuit and switch between different network states. **Mariana Duhne**, Esther Lara-González, Antonio Laville, and José Bargas. División Neurociencias, Instituto de Fisiología Celular, UNAM
142	Alterations in dendritic spine density and morphology correlate with an abnormal BDNF content in the prefrontal cortex of the autistic-like mice C58/J. **Maqueda-Martínez Emely** and González-Arenas Aliesha. Instituto de Investigaciones Biomédicas, UNAM

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144	Plasmid Transfection in mouse brain using cationic polymers. **Katia R. Ávila Gutierrez**, Vania Martínez Godínez, Sylvie Remaud, Víctor H. Hernández González, Alejandra López-Juárez. División de Ciencias Naturales y Exactas. Universidad de Guanajuato

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146	Arsenic alters the expression but not the function of P2X7 and P2Y2 purinergic receptors in Neuro2a cells: implications for Alzheimer Disease. **Marcos Santiago Nava**, Mayra Delgado Ramírez, Rainald P. Ordaz Ramos, Aldo Rodríguez Menchaca, Rogelio Arellano Ostoa, Sergio Zarazúa Guzmán, Guadalupe Martel Gallegos. Laboratorio de Biomedicina, UAMZM-Universidad Autónoma de San Luis Potosí
148	GPR40 and GPR120 receptors activation with DHA and its implication in cytoskeleton rearrangement in hippocampal neurons of an autistic-like mouse. **Guzmán-Vázquez Sandra,** Barón-Mendoza Isabel, Flores-León Manuel, González-Arenas Aliesha. Instituto de Investigaciones Biomédicas, UNAM

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COGNITION AND BEHAVIOR

1	Nucleus accumbens shell single-unit activity encoding of reward probability estimation. **Jorge Benjamín Arroyo Casillas**, Esmeralda G. Fonseca de la Cruz, and Ranier Gutiérrez Mendoza. Department of Pharmacology, CINVESTAV
3	Differential patterns of Evoked Related Events of the retrieval of spatial and temporal contexts. **Ulises Caballero-Sánchez**, TV. Román-López, AY. Polo-Romero, AE. Ruiz-Contreras. Universidad Nacional Autónoma de México
5	Neuroprotective effects of Adiponectin in an Amyloid Beta1-42 model. **Sergio Alan Candelas Juárez**, Amor Herrera González, Carlos Beltrán Mondragón, Mara Guzmán Ruiz, Rosalinda Guevara Guzmán. Departamento de Fisiología, Facultad de Medicina, UNAM
7	Evidence-Integration Mechanisms of Rhythmic Stimuli Discrimination. **Espinoza Monroy Marisol** and de Lafuente Flores Victor Hugo Institute of Neurobiology, National Autonomous University of Mexico
9	Perceptual decision making in the intraparietal sulcus: Implications in the modulation of local field potential. **Flores Alonso Santiago I**. and De Lafuente-Flores V. Department of Neurobiology of Development and Neurophysiology, Institute of Neurobiology, UNAM Campus Juriquilla
11	Decision-making process in areas of sensory integration. **Goyri-Aguirre Miriam**, Rojas-Hortelano, Eduardo and De Lafuente-Flores, Victor Hugo. Department of Neurobiology of Development and Neurophysiology, Institute of Neurobiology, UNAM Campus Juriquilla
13	Optogenetic inhibition of the Dorsomedial versus Dorsolateral Striatum. **Llanos Moreno Argelia**, Cuevas-Vicente Nisa, Alatriste-León Hector, Valdez-Fernandez Yiatziry, Ramirez-Jarquín Josué Orlando & Tecuapetla Fatuel. Instituto de Fisiología Celular, UNAM
15	High-Fat and High-Fructose Diet-Induced Obesity Impair Recognition Memory in C57BL/6 Adult Mice. **Humberto Martínez Orozco**, Sofía Yolanda Díaz Miranda, Cuauhtémoc Sandoval Salazar, Joel Ramírez Emiliano, Luis Antonio Reyes Castro, Martha Silvia Solís Ortiz. Departamento de Ciencias Médicas, División de Ciencias de la Salud, Campus León, Universidad de Guanajuato
17	Association of Adiposity with Inhibitory Control and Prefrontal Symptoms in Women with Excess Body Weight. **María de los Remedios Moreno Frías**, Martha Silvia Solís Ortiz. Departamento de Ciencias Médicas, División Ciencias de la Salud Campus León, Universidad de Guanajuato.
19	Repetitive transcranial magnetic stimulacion (5 Hz) promotes learning and memory processes, increases the number of doublecortin associated cells and the axons of granule cells in Swiss-Webster female mice. **Palacios-Cabriales Diana M**, Meneses-San Juan David, Ortiz-López L and Ramírez-Rodríguez Gerardo Bernabé. Instituto Nacional de Psiquiatría "Ramón de la Fuente Muñiz"
21	Cortico-strital contribution to execution of a chain of sequences. **Sánchez-Fuentes Asai**, Ramírez-Armenta Kathia Itzel, Diaz-Hernandez Edgar, Ramirez-Jarquín Josué Orlando & Tecuapetla Fatuel. Instituto de Fisiología Celular, UNAM

DEVELOPMENT & AGING

23	An approach to the study of linguistic deficiencies in Alzheimer's patients through words association norms. **Luna-Umanzor Diana Iris**, Minto-García Aline, Ríos-Ponce Alma Esperanza, Jiménez-Flores Dania, Flores-Coronado Marco Antonio, Arias-Trejo Natalia. Facultad de Psicología, Universidad Nacional Autónoma de México
25	Relation of animal protein intake and brain dynamics in indigenous infants of an Isolated Me'phaa community. **Rosa María De la Fuente Rodríguez**, Olga Araceli Rojas Ramos, Ariatna Hernández Catillo, Rodolfo Solís Vivanco, Javier Nieto-Gutiérrez, Isaac González-Santoyo. Neuroecology Lab, Faculty of Psychology, National Autonomous University of Mexico
27	Regulation of actin cytoskeleton by p47 overexpression in cerebellar granule neurons. **Medina Ruiz Gabriela Itzetl** y Morán Julio. División de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México
29	Relation between the intake of lipids and the brain dynamics on indigenous children from a Me'phaa community**. Ariatna Hernández Castillo**, Olga Araceli Rojas Ramos, Rosa María de la Fuente Rodríguez, Rodolfo Solís Vivanco, Javier Nieto Gutierrez, Isaac González Santoyo. Neuroecology Laboratory, Facultad de Psicología, UNAM
31	The role of the autophagy during the early nervous system development. **Pilar Sarah Acevo-Rodríguez**, Sandra Cabrera-Benítez, Diana Escalante-Alcalde and Susana Castro-Obregón. Departamento de Neurodesarrollo y Fisiología, División de Neurociencias, Instituto de Fisiología Celular, UNAM
33	Development and validation of a biophysical mathematical model for studying aging in three types of hippocampal neuron. **Parra-Reyes J. Alejandra**, McKiernan Erin C. Department of Physics, Faculty of Science, UNAM
35	Effect of prolactin on the process of differentiation of mouse embryonic stem cells to cortical neurons. **Omar Martinez-Alarcon**, G. Madai Castillo-Villalon, Daniela Avila-Gonzalez, Guadalupe Garcia-Lopez, Anayansi Molina-Hernandez & N. Fabian Diaz. Departamento de Fisiología y Desarrollo Celular**.** Instituto Nacional de Perinatologia

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37	Early life stress, epigenetics and resilience, and their influence on the development of psychiatric illnesses. **Jael López-Martínez** , María del Pilar Gabriel-de la Torre, Miguel-Ángel Mayoral-Chávez. Centro de Investigación UNAM-UABJO
39	Bachelor's program on Neuroscience: UNAM. **Camila del Rio Castro**, Xarenny Jazmín Díaz Zarate, Allan Irasek Rico Becerra & Diana Monserrat Silvas Baltazar. Instituto de Fisiología Celular, UNAM

STRESS

41	Evaluation of the protective effect of resveratrol on behavioral alterations and oxidative stress in prenatally stressed rats. **Edith Zugaide-García**, Margarita López-Martínez, Alberto M. Guzmán-Grenfell, Philippe Leff-Gelman, Carlos Z. Gómez-Castro. Instituto Nacional de Perinatología
43	Effects of curcumin on oxidative damage in brain of mice fed a high fructose diet. **María C. León-García,** Joel Ramírez-Emiliano, Luz A. Ortega-Hernández, Martha S. Solís-Ortiz, Victoriano Pérez-Vázquez and Elena Franco-Robles. Departamento de Ciencias Médicas, División de Ciencias de la Salud, Campus León. Universidad de Guanajuato

GLIA

45	Reactive astrogliosis is exacerbated after spinal cord injury in diabetic rats**. Adriana Domínguez-Vázquez**, Pedro Medina-Granados, Cynthia Sámano-Salazar. Depto. de Ciencias Naturales e Ingeniería, UAM-Cuajimalpa
47	Translational control by silica nanoparticles exposure in glial cells. **Rodríguez-Campuzano Ada Génesis**, De Vizcaya- Ruiz Andrea, López-Bayghen Esther, and Ortega Arturo. Laboratorio de Neurotoxicología, Departamento de Toxicología, CINVESTAV-IPN
49	Rotenone damages cytoskeleton and reduces glutamine synthetase and GSH in rat astrocyte primary cultures. **María Fernanda Tovar-González**, Omar Fuentes-Lugo, Norma Serrano-García Marisol Orozco-Ibarra. Laboratorio de Neurobiología Molecular y Celular, Instituto Nacional de Neurología y Neurocirugía, "Manuel Velasco Suárez"

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51	Role of Palmitic Acid in the hyperphosphorylated state of tau protein. **Valeria Melissa García-Cruz**, Karina Sánchez-Alegría, Patricia Ferrera and Clorinda Arias. Departamento de Medicina Genómica y Toxicología Ambiental, Instituto de Investigaciones Biomédicas, UNAM
53	High fat diet-induced obesity development modulates thyrotropin releasing hormone biosynthesis in the juxtaparaventricular perifornical lateral nucleus of the hypothalamus in male rats. **Rosa María Uribe Villegas**, Oscar Eduardo Bastida Salazar, Marlen Asucena Ramírez Busto, Miguel Cisneros Ramírez, Patricia Joseph-Bravo, Jean-Louis Charli Casalonga. Instituto de Biotecnología, Universidad Nacional Autónoma de México

NEUROENDOCRINOLOGY

55	Thyrotropin-releasing hormone-degrading ectoenzyme null male mice are resistant to diet-induced obesity. **Cote-Vélez, Antonieta,** Hernández-Ortega, Karina, Aguilar-Vargas, Gabriela, Uribe, Rosa María, Joseph-Bravo, Patricia and Charli, Jean-Louis. Instituto de Biotecnología, Universidad Nacional Autónoma de México
57	Expression and hormonal regulation of mPRδ and mPRε in human glioblastoma cells. **Aylin Del Moral-Morales**, Juan Carlos González-Orozco, Ana Gabriela Medina Piña, Jose Moises Capetillo-Velázquez & Ignacio Camacho-Arroyo. Unidad de Investigación en Reproducción Humana, Instituto Nacional de Perinatología-Facultad de Química, UNAM
59	Stressed female rats during adolescence have a deficient response of HPT axis to energy demands. **Angélica Gutiérrez Mata**, Andrea Castillo Campos, Miguel Cisneros, Jean-Louis Charli, Patricia Joseph-Bravo. Departamento de Genética del Desarrollo y Fisiología Molecular, Instituto de Biotecnología, UNAM
61	Is peripheral thyrotropin-releasing hormone-degrading ectoenzyme a therapeutic target for diet-induced obesity? **Hernández-Ortega, Karina,** Anaya Mitzi Lucero, Uribe, Rosa María, Cote Vélez Antonieta, Parra-Montes de Oca Marco Antonio, Pérez Estrada José Raul, Joseph-Bravo Patricia and Charli Jean Louis. Instituto de Biotecnología, Universidad Nacional Autónoma de México
63	Stress during rat adolescence modifies the thyroid axis response to voluntary exercise. **Parra-Montes de Oca Marco Antonio**, Charli Jean-Louis, Joseph-Bravo Patricia.

	Departamento de Genética del Desarrollo y Fisiología Molecular, Instituto de Biotecnología, UNAM
65	β2-tanycytes thyrotropin-releasing hormone-degrading ectoenzyme regulates thyrotropin secretion. **Adair Rodríguez-Rodríguez**, Rosa María Uribe, Patricia Joseph-Bravo and Jean-Louis Charli. Instituto de Biotecnología, UNAM
67	Progesterone metabolite, allopregnanolone, promotes migration and invasion of human glioblastoma cells. **Carmen J Zamora-Sánchez**, Ignacio Camacho-Arroyo. Unidad de Investigación en Reproducción Humana, Instituto Nacional de Perinatología-Facultad de Química, Universidad Nacional Autónoma de México

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69	Anticonvulsive and Neuroprotective effect of Scammonin 1 and Tyrianthin C on cortex and hippocampus in mouse brain. **José Manuel Castro G**, Juana Villeda H, Ismael León R, María del Carmen Gutiérrez V. Laboratorio de Neurofarmacología, Centro de Investigación en Biotecnología. UAEM
71	Pioglitazone favors neurogenesis and increases dendrite spines in the hippocampus without affect learning and memory processes or depressive-like behavior in female Balb/C mice. **Hernández-Velasco Natalia**, Vega-Rivera Nelly M, Reyes-Haro Daniel and Ramírez-Rodríguez Gerardo Bernabé. Laboratory of Neurogenesis, Division of Clinical Research, National Institute of Psychiatry "Ramón de la Fuente Muñiz"
73	Influence of mental health and the use of antidepressant during pregnancy and its effect on the neurological development of Mexican children. **Meza-Rodríguez María del Pilar**, Garza-Morales Saúl Jesús, Fuentes-Medina Diana, Zorrilla-Dosal José Antonio, Farfán-Labonne Blanca, Padilla-García Manuel Alejandro, Leff-Gelman Felipe, Belmont-Gómez Aurora, Camacho-Arroyo Ignacio. Departamento de Neurociencias, Instituto Nacional de Perinatología

INTEGRATIVE PHYSIOLOGY

75	Changes in the functional coupling between mPFC and BLA associated with reversal learning of spatial memory task. **Estrada Reyes Yoana**, Olvera Cortés María Esther, Cervantes Alfaro José Miguel, López Vázquez Miguel Ángel. Laboratorio de Neurociencias, Facultad de Ciencias Médicas y Biológicas "Dr. Ignacio Chávez" UMSNH.
77	Pharmacological manipulation of the cannabinoid receptor type I in the basal ganglia output nuclei in a model of Parkinson's disease in mice. **González-Pereyra Perla**, Báez-Cordero Ana Silvia, Peña-Rangel Maria Teresa, Rueda-Orozco Pavel E. Departamento de Neurobiología del Desarrollo y Neurofisiología, Instituto de Neurobiología, UNAM
79	Evaluation of the participation of the central medial nucleus of the thalamus in a bimanual task and in the interhemispheric activity of the cortico-striatal circuitry. **Luma Annie Yolene**, Pimentel-Farfán Ana Karen, Peña-Rangel María Teresa, Rueda-Orozco Pavel E. Department of Neurobiology of Development and Neurophysiology, Institute of Neurobiology, UNAM
81	Role of the direct and indirect pathway of the basal ganglia in the adjustment of speed during the execution of motor sequences. **Ortega-Romero Diana Itzel**, Peña-Rangel María Teresa, Rueda-Orozco Pavel Ernesto. Departamento de Neurobiología del Desarrollo y Neurofisiología, Instituto de Neurobiología, UNAM

83	Pallidal GATs modulate cortical oscillations by inhibition of reticular neurons. **Villalobos Vásquez Nelson**, Ortiz Zárate Mindrid Ireri, Acosta Mejía Martha Teresa, Magdaleno Madrigal Víctor Manuel. Academia de Fisiología, Escuela Superior de Medicina, Instituto Politécnico Nacional
85	Sensory and Motor Cortical Input to Dorsal Striatum: Differences in Microcircuitry, Synaptic Physiology and Behavioral Effects. **Alex J. Yonk*, Branden D. Sanabria*, Sindhuja S. Baskar***, Christian R. Lee, David J. Margolis. *Equal contribution. Department of Cell Biology and Neuroscience, Rutgers, The State University of New Jersey

NEUROIMMUNOLOGY

87	The role of KChIP3 in the development of Alzheimer's disease. **Bolivar Jesus Arcos-Encarnación**, Eladio Cortes-Flores, Leopoldo Goméz-Caudillo, Sergio Manuel Encarnación-Guevara, Maribel Herrera-Ruiz, Gustavo Pedraza-Alva and Leonor Peréz-Martínez. Laboratorio de Neuroinmunobiología. Departamento de Medicina Molecular y Bioprocesos, Instituto de Biotecnología. UNAM
89	Evaluation of the expression of genes associated with inflammation and regeneration in rats immunized with the A91 peptide before a chronic spinal cord injury. **Juan Francisco-Márquez**, Marcela Garibay López, Adrián Flores-Romero, Elisa García-Vences, Antonio Ibarra and Roxana Rodríguez-Barrera. Facultad de Ciencias de la Salud, Universidad Anáhuac México
91	Pericyte detachment during sleep loss disrupts blood-brain barrier. **Fernanda Medina-Flores**, Gabriela Hurtado-Alvarado, Maria A. Deli, Beatriz Gómez-González. Posgrado en Biología Experimental, CBS, UAM-Iztapalapa
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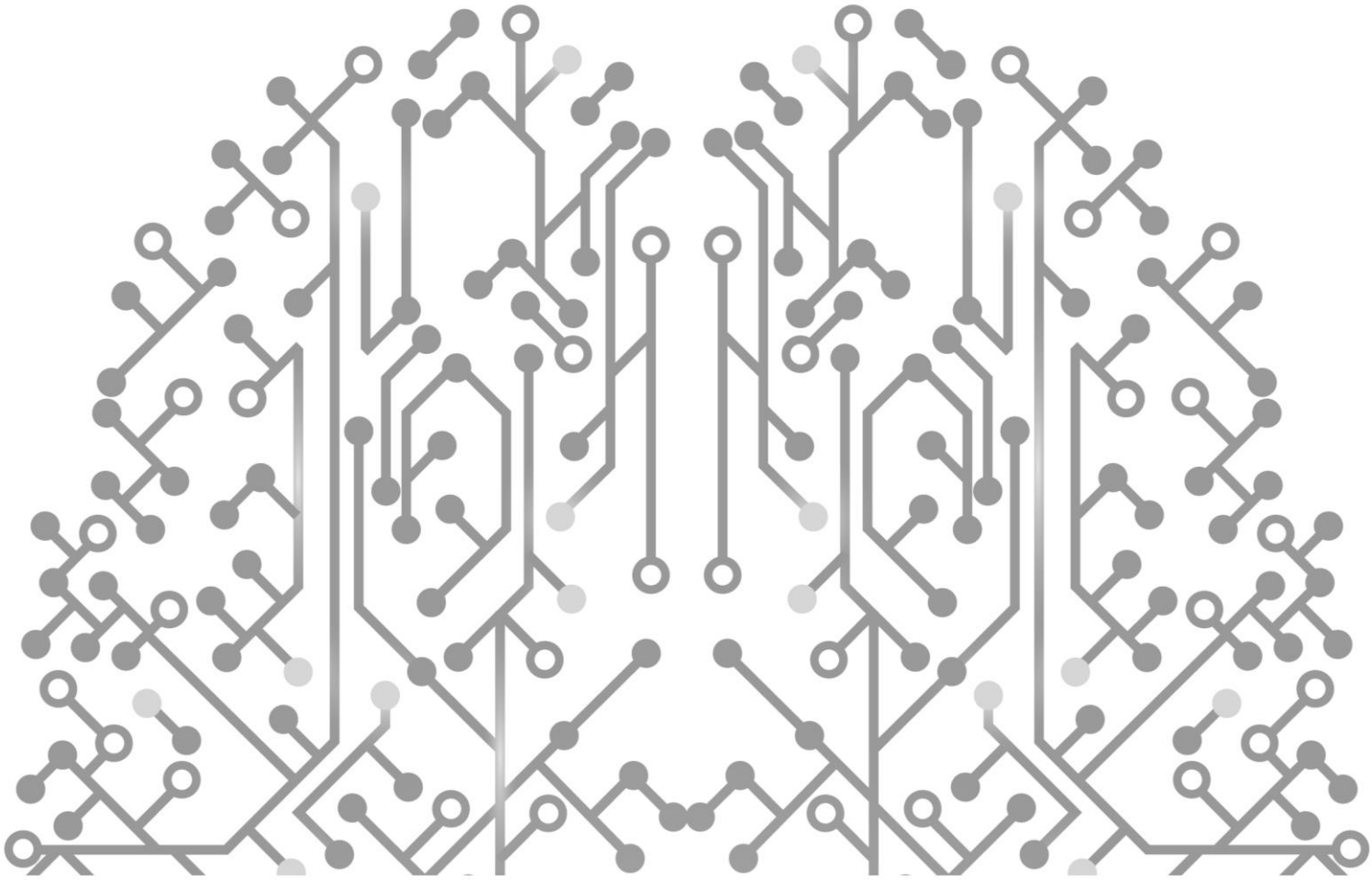
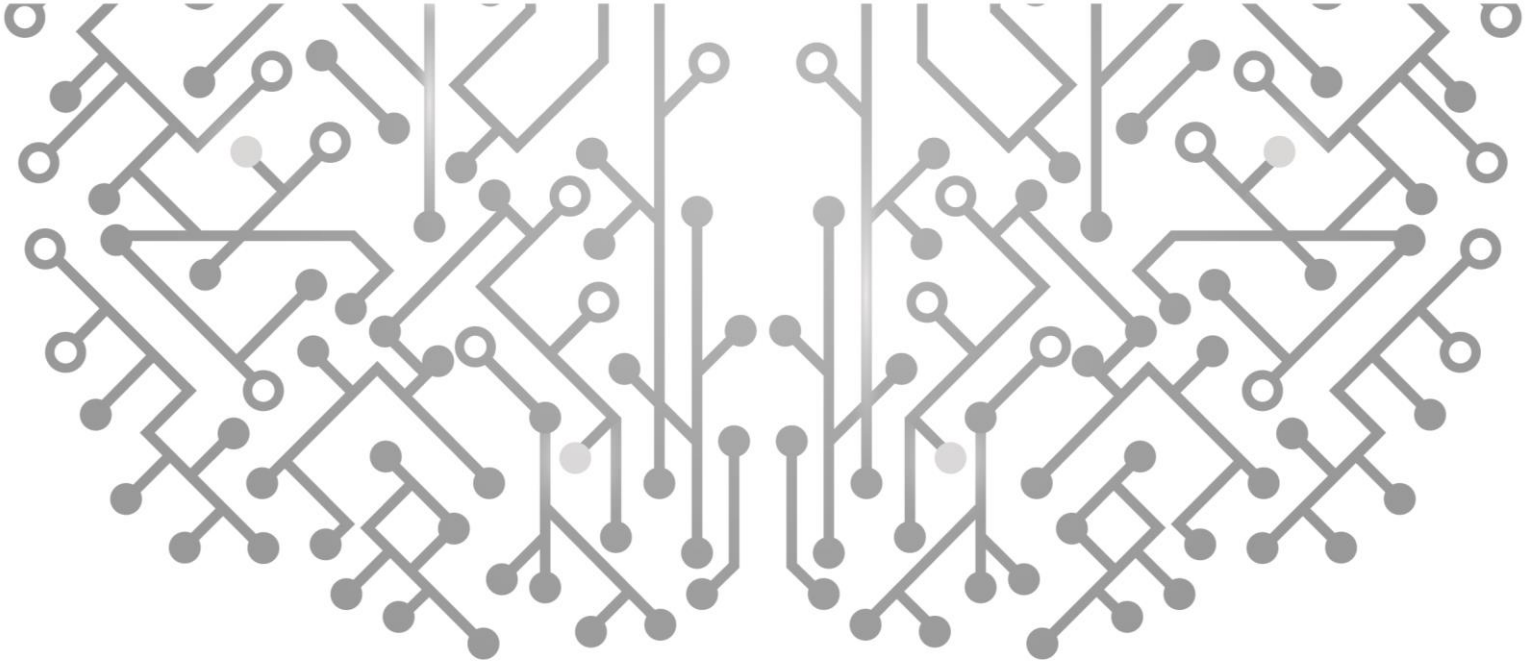


Oral Sessions



Movement dynamics in the motor cortex

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Columbia University Medical Center, USA

Primary motor cortex was the first brain area to be studied electro-physiologically, and the first to be recorded from in a behaving animal. Yet the relationship between motor cortex activity and movement has remained controversial. Primate motor cortex projects to spinal interneurons and motoneurons, suggesting that activity should be dominated by muscle-like commands. An alternative hypothesis is that activity encodes high-level movement commands. The debate over whether motor cortex encodes 'muscles' versus 'movements' has proved nearly intractable. The fundamental hurdle is that neural activity contains features incompatible with either view. To provide a different perspective, we employed a novel behavioral paradigm that facilitates comparison between time-evolving neural and muscle activity. We found that single motor cortex neurons displayed many muscle-like properties, yet the structure of population activity was not muscle-like. Unlike muscle activity, neural activity was structured to avoid 'tangling': moments where similar activity patterns led to dissimilar future patterns. Avoidance of tangling was present across tasks and species. Network models revealed a reason for this consistent feature: low tangling confers noise robustness. The need to avoid tangling explains the major features of the motor cortex response. Indeed, we could quantitatively predict motor cortex population activity by leveraging the hypothesis that muscle-like commands are embedded in additional structure that yields low tangling. Thus, although motor cortex activity initially appears confusing, its major properties are easily understood in terms of a simple computational goal: robustly generating descending motor commands.

Epigenetic Instructions for Building the Cerebral Cortex

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The coordinated activities of transcriptional enhancers in neural stem cells (NSCs) regulate gene expression programs that produce a vast diversity of cell types in the mammalian brain. In the developing cerebral cortex, neurogenesis is accompanied by dynamic changes in chromatin accessibility and histone modifications within enhancer regions. However, the mechanisms by which epigenetic modifications in NSCs determine the complex architecture of the cerebral cortex are mostly unknown. We report that in mouse embryonic cortex, the activity of the histone methyl-transferase PRDM16 in NSCs determines the final position of cortical neurons. PRDM16 regulates the epigenetic state of transcriptional enhancers in NSCs, thereby presetting the gene expression programs that control the organization of excitatory neurons into distinct cortical layers. Our work provides insights into how the epigenetic landscape in NSCs defines a pattern of neuronal positioning within the Neocortex.

"Phospholipid phosphatase-3, a novel marker of neural stem cells, participates in the ventricular system remodeling and adult neurogenesis in mice"

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Neurogenesis is the process during which new functional neurons are formed from progenitor cells. In the adult brain, this process is mainly restricted to the ventricular-subventricular zone (V-SVZ) of the lateral ventricles and dentate gyrus' subgranular zone (SGZ) of the hippocampus. Recent single-cell RNAseq transcriptomic analyses have associated sphingolipid metabolism and/or signaling to the maintenance of neural stem cells quiescence, making these processes a key point in the regulation of neurogenesis in these niches.

The phospholipid phosphatase-3 (PLPP3) is an integral membrane enzyme with the ability of regulating the concentration and signaling activities of several bioactive lipids, including sphingosine-1-phosphate (S1P). In the adult brain, PLPP3 and some S1P G protein-coupled receptors (GPCRs) are highly expressed in neurogenic areas. This suggested that PLPP3 could participate in regulating the concentration and biological activity of this lipid in both neurogenic niches.

In this work we show that PLPP3 expresses in astroglial cells including radial and non-radial neural stem cells (NSCs) in the V-SVZ and SGZ. Using the Cre/*loxP* system to conditionally inactivate *Plpp3* in the neural lineage, we analyzed the consequences of the lack of PLPP3 during brain development and in both adult neurogenic niches.

Nestin::cre mediated ablation of *Plpp3* in the brain renders defects in olfactory ventricle regression and an olfaction deficit without modification of the number of incorporated interneurons in the OB by 12-weeks of age, suggesting that astrocyte mediated alterations of neurotransmission could be involved. In addition, *Plpp3* deactivation in the brain uncovered a role for PLPP3 in regulating the mitotic activity of NSCs and neural progenitors in both neurogenic niches.

Ablation of *Plpp3* also produced a strong down-regulation of the type 1 receptor of S1P ($S1P_1$) in hippocampus, SVZ and derived neurospheres. Our data indicate that PLPP3 has an important role in regulating neural progenitor cell proliferation and differentiation, in part through regulating $S1P_1$ receptor signaling.

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Development of large-scale brain networks from infancy to adulthood.

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The human brain is a complex network of neurons interconnected in a modular and hierarchical organization. Although this organization is evident at multiple levels, magnetic resonance imaging (MRI) allows the exploration of the whole brain structure and function at large scales, with a resolution in the order of hundreds of micrometers and hundreds of milliseconds in the spatial and temporal domains, respectively. The exploration of the functional organization with MRI, based on the correlation of the spontaneous physiological signals between regions, has revealed the integration of brain regions into specialized functional networks. These so called “resting state functional networks” are segregated into specialized modules, including sensory, motor and associative networks. Using this technique and mathematical models for network analyses, it has been suggested that such functional organization enables the efficient processing of information and supports complex brain functions. Given the feasibility to explore such resting state networks in less cooperative subjects, including infants, recent studies have characterized the functional organization of the brain across development, evidencing increased long distance functional integration and increased functional segregation with age. In this talk, we will discuss the main principles of the functional organization of the brain, its maturation across development and its relation to complex brain functions.

Engineering neurogenesis for the postnatal brain

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We explore the possibilities of generating new neurons where natural neurogenesis has ceased to occur, such as the postnatal or adult cerebral cortex. The approach we have taken is of lineage reprogramming glia or other brain-resident cells into induced neurons. Toward this end, we force the expression of developmentally relevant transcription factors such as Ascl2 and Neurog2 to induce a neurogenic program. Here, I will discuss our efforts (1) to induce neurogenesis from glial cells in the postnatal mouse cortex *in vivo*, and (2) to decipher the molecular and cellular trajectory of adult human brain pericytes undergoing conversion into neurons.

From hidden to overt: uncovering the roles of glia in hearing and hearing loss

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Hearing and balance are mediated by the function of inner ear hair cells and neurons. Therefore, these cells have been the focus of many studies. However, like in other parts of the nervous system, these excitable cells are surrounded by glial cells. Until recently, these non-neuronal cells were viewed as serving primarily structural and homeostatic functions. During my talk I will discuss the growing information about the roles that inner ear glial cells play in the development, function and maintenance of the inner ear and their activities in pathological states, including overt and hidden hearing loss, a recently described auditory disorder that affects temporal processing and hearing acuity in subjects with normal audiometric thresholds, particularly in noisy environments.

Keywords: synapse, myelin, noise-induced hearing loss

Area: cellular and molecular neuroscience, development, hearing.

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Social behavior in ants relies on a specialized olfactory system

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Social insects display fascinating behaviors including parental care, nest defense, collective foraging, and division of labor. Ants rely on chemical communication mediated by pheromones to coordinate these behaviors. To sense these molecules the ant olfactory system possesses an expanded repertoire of odorant receptors that are expressed by olfactory sensory neurons in the antenna. These neurons send their axons to the brain, where they are segregated by odor specificity and form an odotopic map by synapsing with projection neurons in discrete glomeruli.

Here we use the clonal raider ant, *Ooceraea biroi*, to describe the neurobiology of olfaction and the way that perception of chemical signals affects ant social behavior. We established a protocol for gene editing that allowed us to generate odorant receptor co-receptor (*orco*) mutant ants. Lack of the Orco protein impairs the function of all odorant receptors and disrupts basic social behaviors: *orco* mutants cannot follow pheromone trails or nest with other ants and have reduced fitness. Surprisingly, *orco* mutants also have a dramatic brain phenotype: due to the lack of sensory innervation from the olfactory sensory neurons, *orco* deficient ants have smaller antennal lobes with 80% fewer glomeruli than wild types.

We further characterized the development of the ant olfactory system to understand how the glomerular map is established. We detected *orco* expression in the sensory neuron axons before they reach the brain. Using transcriptome analysis, we observed an early onset of odorant receptor expression in the developing antenna that coincides with the arrival of the sensory innervation to the antennal lobe and the formation of glomeruli; therefore, it is possible that neuronal activity *orco*-dependent is required for the map formation. Early mechanical ablation of olfactory sensory neurons retards the establishment of the glomerular map and recapitulates the *orco* mutant phenotype, indicating that innervation is required for proper antennal lobe development. Later removal of the antenna results in immediate arrest of glomeruli formation but the glomeruli that were already established are maintained, suggesting that once specified, the glomerular map in the antennal lobe is stable. This developmental mechanism with a stereotyped and a sensory-dependent patterning has not been described in other insects, reinforcing the functional significance of olfaction for the ant social behavior.

Social behavior; Olfaction; Odorant receptors

Effects of maternal conditions on sexual preference of the male progeny

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Area: Neuroendocrinology

Sexual preference is expressed in a different way depending on sex. Males prefer sexual interaction with females and females with males. However, there is a population of males that spontaneously prefer to interact with other males. There are several hypotheses proposed to explain the causes of this behavior in rats. The endocrine theory proposes that alterations in the brain aromatization of testosterone to estradiol during a specific developmental window affects sex preference in adults; however, other factors are contributing. Here we examined the effect of multiparity, gestational stress and inhibition of aromatase on sexual preference of the male progeny. We evaluated the role of these factors individually and their putative interaction.

Young adult males, whose mothers were primiparous or multiparous (4 or more deliveries); stressed (restriction stress for 10 days) or treated with the aromatase inhibitor, letrozole (0.56µg/kg/from G10 to delivery), were tested for sexual preference and sexual behavior. Sexual preference was evaluated using a three-compartment cage, where animals could choose between a sexually experienced male and a receptive female. Additionally, we evaluated their male and female sexual behavior determining the percentage of males displaying the behavior.

We found that letrozole treatment induces a 40% of males with preference for another male, 30% of males with a stressed mother presented same sex preference, but there was a lack of interaction between letrozole treatment and gestational stress (50%). When mothers were multiparous, 34% of the male progeny showed sexual preference for the sexually active male.

Feminine sexual behavior was increased in males with same sex preference in different maternal conditions (gestational stress or multiparity), additionally, in males whose mothers where stressed and administered with letrozole there was a reduction of male sexual behavior. These results indicate an effect of these treatments on the brain defeminization and masculinization processes during development.

These data reveal that sex preference is influenced prenatally by several factors, which do not seem to interact, additionally multiparity seems to be important to induce a change on sex preference in the male progeny.

Key words: Sexual preference, male rats, brain differentiation.

Dual NMDAR signaling in cultured astrocytes: flux-independent pH sensor and flux-dependent regulator of mitochondrial membrane potential (mΔψ) through cell membrane-mitochondria communication.

Montes Oca Balderas, Pavel*#@ and Hernández-Cruz, Arturo#.

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Glutamate N-methyl-D-aspartate (NMDA) receptor (NMDAR) is critical for neurotransmission as a Ca2+ channel. Nonetheless, several reports have demonstrated also flux-independent signaling. Astrocytes express NMDAR distinct from its neuronal counterpart, but cultured astrocytes have no electrophysiological response and controversial findings have questioned NMDAR function. We recently demonstrated that in cultured astrocytes NMDA at pH6 (NMDA/pH6) elicits flux-independent Ca2+ release from the Endoplasmic Reticulum (ER) and depletes mitochondrial membrane potential (mΔψ). Here we show that flux-independent Ca2+ release is mainly due to pH6, whereas mΔψ depletion requires both pH6 and flux-dependent NMDAR signaling. Immunofluorescence exhibited that plasma membrane (PM) NMDAR is apposed or surrounds ER and mitochondria. Moreover, NMDA/pH6 treatment generated ER stress, increased endocytosis, mitochondria-ER and -nuclear contacts and strikingly, PM invaginations near mitochondria along with electrodense structures referred here as PM-mitochondrial bridges (PM-m-br). Our data and earlier observations strongly suggest PM-mitochondria communication, as a proof of concept of this notion, NMDA/pH6 provoked mitochondria labeling by the PM dye FM-4-64FX. Finally, we analyzed by WB NMDAR subunit GluN1 to explore putative causes of NMDAR dual function, we found fragments with M.W. consistent with previously identified cleavage sites. Accordingly, GluN1 intracellular and extracellular domains presented little colocalization. Our findings demonstrate that NMDAR plays a dual function: a flux-independent pH sensor and a flux-dependent regulator of mΔψ. More importantly, mΔψ depletion seems to be mediated by PM-mitochondria communication. Finally, we found different GluN1 fragments that could be involved in NMDAR dual signaling, although causality awaits demonstration (submitted to JBC).

KEYWORDS: NMDAR; signaling; mitochondria

AREA: Glia/Transducción de señales

Th1/Th17 and Th2 Cytokines in Women with Severe Anxiety and Depression during late pregnancy

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Instituto Nacional de Perinatologia Isidro Espinosa de los Reyes

Background: Controversial findings regarding the association between pro-inflammatory cytokines and depression have been reported in pregnant subjects. Scarce data about anxiety and its relationships with cytokines are available in pregnant women. In order to understand the association between anxiety and cytokines during pregnancy, we conducted the present study in women with or without depression.
Methods: Women exhibiting severe depression (SD) and severe anxiety (SA) during the 3rd trimester of pregnancy (n = 139) and control subjects exhibiting neither depression nor anxiety (n = 40) were assessed through the Hamilton Depression Rating Scale (HDRS) and the Hamilton Anxiety Rating Scale (HARS). Serum cytokines were measured by a multiplex bead-based assay. Correlation tests were used to analyze the data and comparisons between groups were performed.
Results: The highest levels of Th1- (IL-6, TNF-alpha, IL-2, IFN-gamma), Th17- (IL-17A, IL-22), and Th2- (IL-9, IL-10, and IL-13) related cytokines were observed in women with SD+SA. The SA group showed higher concentrations of Th1- (IL-6, TNF-alpha, IL-2, IFN-gamma) and Th2- (IL-4, and IL-10) related cytokines than the controls. Positive correlations were found between HDRS and IL-2, IL-6, and TNF-alpha n the SA group ($p<0.03$), and between HDRS and Th1- (IL-2, IL-6, TNF-alpha), Th2- (IL-9, IL-10, IL-13) and Th17- (IL-17A) cytokines ($p<0.05$) in the SD+SA group. After adjusting the correlation analysis by gestational weeks, the correlations that remained significant were: HDRS and IL-2, IL-6, IL-9, and IL 17-A in the SD+SA group ($p<0.03$). HARS scores correlated with IL-17A in the SA group and with IL-17A, IL-17F, and IL-2 in the SD+SA group ($p<0.02$). A linear model of analysis of variance showed that HDRS and HARS scores influenced cytokine concentrations, such as IL-6 and TNF-alpha.
Conclusions: The cytokine profile differ after comparing pregnant subjects exhibiting SA with comorbid SD against those displaying SA without depression.

Keywords: Cytokines, inflammation, pregnancy, depression, anxiety

Striatal integration of food reward and satiety

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During feeding, dopamine activity in the brain reflects the gustatory and nutritive qualities of the food being ingested. Food-derived signals make use of the dopamine system to gain access to the striatal circuits that ultimately control the decision to continue or stop eating. However, the molecular identities of the neural effectors downstream to dopamine release remain to be determined. This talk will review emerging evidence suggesting that separate basal ganglia neuronal streams encode food preferences *vs*. satiation. These findings provide novel insights into the neural mechanisms underlying unhealthy feeding behaviors.

Visceral Control of Brain Reward Systems

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Friedman Brain Institute
Diabetes, Obesity and Metabolism Institute
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The presentation will discuss recent evidence supporting a role for the gut-brain axis in controlling brain circuits involved in reward, emotion and motivation. It will be argued in particular that gut-innervating vagal sensory neurons function as reward neurons. Via asymmetric ascending pathways of vagal origin, gut signals reach brain reward regions via dedicated visceral nuclei in pons. More generally, a topographic sensory organization for food reward appears to exist throughout the striatum, with gastrointestinal *vs*. orosensory rewarding signals causing dopamine release into different striatal sectors. The extent to which these findings relate to human neuroimaging findings will be also discussed. In sum, the gut-innervating vagal neurons have sensory-specific control over dopamine reward neurons, and may constitute a novel target for stimulation therapies for eating and affective disorders.

A hypothalamic-BNST circuit regulates delay discounting in decision making

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Duke University

Choice behavior is characterized by temporal discounting, i.e., preference for immediate rewards over delayed rewards. Temporal discounting is often dysfunctional in psychiatric disorders, addiction, and eating disorders. However, the underlying neural mechanisms governing temporal discounting are still poorly understood. We found that food deprivation resulted in steep temporal discounting of food rewards, whereas satiation abolished discounting. In addition, optogenetic activation of AgRP-expressing neurons in the arcuate nucleus or their axon terminals in the posterior bed nucleus of stria terminalis (BNST) restored temporal discounting in sated mice. Activation of postsynaptic neuropeptide Y receptors (Y1Rs) within the BNST, which is influenced by neuropeptide released by AgRP neurons, was sufficient to restore temporal discounting. These results demonstrate for the first time a profound effect of motivational signals from hypothalamic feeding circuits on temporal discounting and reveal a novel neural circuit that regulates choice behavior.

Lateral hypothalamus GABAergic neurons encode sucrose's palatability

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Hedonic value or palatability of sucrose is one contributing factor for overconsumption of high calorie foods and the development of obesity. However, the neuronal circuits by which the brain assign or enhance palatability to gustatory stimuli is not known. Recently, it was uncovered that optogenetic stimulation of Lateral Hypothalamus GABAergic neurons triggers a positive valance signal that promotes appetitive and consummatory behavior to the nearest stimuli, regardless of their nutritional value. We reasoned that an additional function of these neurons could be to assign or enhance palatability to gustatory stimuli. To test this idea, we used a Vgat- transgenic mice constitutively expressing ChR2 in GABAergic neurons (Vgat-ChR2 mice) and multiple behavioral assays. First, we show that open-loop stimulation of LH GABA neurons in a box with three simultaneously available solutions (water, 3, and 18% sucrose) promotes consumption but towards the most palatable stimuli available (i.e., 18% sucrose). To further test, whether LH GABA neurons promoted ingestion of the most palatable stimulus or the nearest-although less palatable, the same animals were trained in a similar task, but this time the laser was activated that is each time they made a head entry (closed-loop) in the central port (where water is the nearest stimuli). Surprisingly, in some Vgat-ChR2 mice increased water intake to similar levels than 18% sucrose. We then replaced the water in central port for either no solution (dry licks), quinine, or airpuffs. After stimulation, mice gave dry licks but ceased licking for bitter and punishment, although, they continued self-stimulating in all three conditions, showing that is rewarding. However, if photostimulation was delivered after the first lick given to the central sipper rather than with the head-entry (i.e., the airpuff is now unavoidable), the transgenic mice completely stopped self-stimulation. Thus, LH GABAergic neurons activation does not override aversive stimuli. Finally, when 18% sucrose was put in the central sipper, transgenic mice drastically overconsumed it. Finally, by using a brief access test. We then show that paring LH GABA neurons stimulation selectively with the intake of water or 3% could actually enhance the hedonic value of the normally less palatable stimulus. We concluded that activation of LH GABAergic neurons is highly rewarding and could enhance the hedonic value of stimuli, thereby promoting approach consummatory behavior to the nearest and most palatable gustatory stimuli.

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The role of renin-angiotensin in gliomas

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Gliomas are the most common primary malignant tumors of the central nervous system (CNS) in the adult population worldwide, representing approximately 27% of all CNS tumors and 80% of CNS malignant tumors in the United States. Several biochemical networks are involved in gliomatogenesis, and many of them are obvious targets of study because of their roles in the cell cycle and in maintaining the integrity of the genome. But others, such as the renin-angiotensin system (RAS), which is known for controlling the cardiovascular function of the human organism, are now being added to the complex networks of carcinogenesis. The RAS has been involved in several hallmarks of cancer including proliferative signaling, evading growth suppressors, resisting cell death, inducing angiogenesis, reprogramming of energy metabolism, inflammation, cell migration, invasion and metastasis

RAS includes several peptides and proteins with paracrine functions in the brain, which are under study as part of gliomatogenesis and biomarkers for gliomas.

Drugs that target the RAS are widely used in the treatment of hypertension, their side effects are well known and have relatively low costs; thus, they could be good coadjuvants in the treatment of cancer.

In this talk we will review the current information about the role of RAS in gliomas and the potential use in the clinical setting.

The important role of tumor microenvironment in medulloblastoma progression

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Astrocytes, the most abundant type of glial cells in the brain, play critical roles in supporting neuronal development and brain function. Although astrocytes have been frequently detected in brain tumors, including medulloblastoma (MB), their functions in tumorigenesis are not clear. Recently, we demonstrate that astrocytes are essential components of the MB tumor microenvironment.Tumor-associated astrocytes (TAA) secrete the ligand sonic hedgehog (Shh), which is required for maintaining MB cell proliferation despite the absence of its primary receptor
Patched-1 (Ptch1). Shh drives expression of Nestin in MB cells through a smoothened-dependent, but Gli1-independent mechanism. Ablation of TAA dramatically suppresses Nestin expression and blocks tumor growth. These findings reveal an indispensable role for astrocytes in MB tumorigenesis and reveal a novel Ptch1-independent Shh pathway involved in MB progression.

Gas1 as a tool for experimental glioma therapy

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Cinvestav

Gas1 (Growth Arrest Specific1) is a pleiotropic protein widely expressed in the organism, particularly in the Central Nervous System (CNS). The *gas*1 gene was originally isolated in NIH-3T3 cells arrested by withdrawing serum from the culture medium. Thus, the protein was associated with growth arrest and cell death. Early investigations suggested that Gas1 inhibited the Shh-mediated intracellular cell signaling, however, using bioinformatics techniques, we predicted the similarity among Gas1 and the receptors of the GDNF family (GDNFRαs), and postulated that the effects of Gas1 inhibiting cell cycle and inducing cell death were caused by its capacity blocking the intracellular pathways mediated by GDNF and other members of this family of neurotrophic factors. Then, we were able to molecularly dissect the pathway by which Gas1 induces an intrinsic apoptotic process when it is overexpressed in cancer cells. Gas1 reduces Ret phosphorylation and inhibits the activity of Akt, triggering the dephosphorylation of Bad, which, in turn, provokes the release of Cytochrome-c from the mitochondria to the cytosol, activating caspase-9, prompting the activity of caspase-3 and resulting in apoptosis of the cells. The apoptotic process is intrinsic, because there is no activation of caspase-8, thus this is consistent with apoptosis induced by lack of trophic support. Interestingly in cells where Gas1 has been silenced there is a significant delay in the onset of apoptosis. This information allowed us to understand the inhibitory effect of Gas1 in experimental models of glioma and other types of cancer. On the other hand, to increase the therapeutic range of Gas1, we obtained a mutant form of the protein (tGas1) that is released from producer cells, allowing it to act both in autocrine and paracrine manners eliminating not only tGas1-producing cells, but other neighboring cells. With the goal of improving gene therapy approaches, we have genetically engineered neural stem cells (NSCs), which can track and localize tumors in the organism, so they can overexpress tGas1 in a doxycycline-induced manner. Using this system we have generated Gas1-producing NSCs capable of targeting experimental intracerebral gliomas, which by secreting tGas1 inhibit glioma growth and increase the survival of treated mice. Moreover, when these engineered NSCs, are systemically administered (iv) they track and inhibit the growth of orthotopically implanted breast tumors in female mice, and completely prevent the formation of lung metastases.

The data presented here support the use of Gas1 as an adjuvant for the treatment of cancer.

From neurology to neuro-oncology

Bernardo Cacho-Díaz MD, MSc
Instituto Nacional de Cancerología

The evolution of the human species is genetic, epigenetic, environmental, stochastic and scientific. Information has become more specialized, narrowing the aim of the training. In the case of medicine, it has brought two specialized areas: neurology and oncology in to a new expertise area: Neuro-oncology. Clinicians should complete their formation from the source: the basic areas (neuroscience) and try to foment translational research. During this talk, it will be reviewed how neurology and oncology came together and the consequences of such bonds. Finalizing with an update of the current research in high grade gliomas involving the progesterone receptors in cell lines, preclinical models and the first clinical trial ever to aim at this potential therapy. In this clinical trial, patients with high grade glioma, who were candidates to conventional therapy with chemoradiation received RU486, security of this combination has been stablished and the preliminary data show this combination (chemoradiation/RU486) improves health related quality of life, progression free survival and overall survival.

Dissociable dopamine dynamics for learning and motivation.

Joshua Berke
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The dopamine projection from ventral tegmental area (VTA) to nucleus accumbens (NAc) is critical for motivation to work for rewards, and reward-driven learning. How dopamine supports both functions is unclear. Dopamine spiking can encode prediction errors, vital learning signals in computational theories of adaptive behavior. By contrast, dopamine release ramps up as animals approach rewards, mirroring reward expectation. This mismatch might reflect differences in behavioral tasks, slower changes in dopamine cell spiking, or spike-independent modulation of dopamine release. Here we compare spiking of identified VTA dopamine cells with NAc dopamine release in the same decision-making task. Cues indicating upcoming reward increased both spiking and release. Yet NAc core dopamine release also covaried with dynamically-evolving reward expectations, without corresponding changes in VTA dopamine cell spiking. Our results suggest a fundamental difference in how dopamine release is regulated to achieve distinct functions: broadcast burst signals promote learning, while local control drives motivation. I will further present initial results that cholinergic interneurons are responsible for the local control of motivation-related dopamine release.

TrkB-mediated LTP at Hippocampal Mossy Fiber Synapses on CA3 Interneurons

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Area: Synaptic Transmission

We examined the role of the tropomyosin-related kinase B (TrkB) receptor on the induction of synaptic plasticity of interneurons somatically located in the S. Lucidum of hippocampal area CA3. Confocal imaging analyses revealed in GAD-67 immunoreactive neurons, the combined expression of TrkB with the calcium-binding proteins parvalbumin, calbindin, or calretenin. Whole cell recordings in acute brain slice revealed that perfusion of 7,8-DHF, the specific agonist of TrkB, increases the rate of fast, spontaneous synaptic currents impinging on S. Lucidum interneurons, suggesting modulation of the AMPAR-mediated transmission. In another group of cells, we stimulate Mossy Fibers (MF) and recorded the evoked excitatory postsynaptic currents. MF-mediated potentiation was observed in interneurons, predominantly expressing calcium impermeable AMPA receptors (CI-AMPARs), whereas cells mainly expressing calcium-permeable AMPA synapses exhibited inconsistent responses to 7,8-DHF stimulation. Remarkably, we found that expression of the CI-AMPARs occurred on regular spiking, but not fast spiking interneurons, suggesting that TrkB-mediated potentiation at the MF synapse, occurs on selected subpopulations of hippocampal interneurons. This form of synaptic potentiation was abolished when 7,8-DHF was perfused in combination with ANA-12, a TrkB ligand that prevents activation of the receptor by BDNF. Our data show that S. Lucidum interneurons express a novel mechanism of input-specific MF LTP restricted to regular spiking interneurons.

Key words: CA3, Interneurons, TrkB.

Comparison of actions between L-DOPA and different dopamine agonists in striatal DA-depleted microcircuits *in vitro*: pre-clinical insights

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Área: Neurofarmacología

Parkinson's disease is a neurodegenerative illness presenting motor and non-motor symptoms due to the loss of dopaminergic terminals in basal ganglia, most importantly, the striatum. L-DOPA relieves many motor signs. Unfortunately, in the long term, L-DOPA use causes motor disabilities by itself and does not act in comorbid conditions such as depression. These deficiencies have led to search for drugs such as dopamine (DA) receptor agonists (DA-agonists) that allow the reduction of L-DOPA dose. Previously, we have identified the attributes of non-stimulated (resting) and cortical stimulated (active) striatal microcircuits following the activity of dozens of neurons simultaneously using calcium imaging in brain slices. We also have characterized the changes that take place in DA-depleted microcircuits *in vitro*. In control conditions, there is *low* spontaneous activity. After cortical stimulation (CtxS) sequences and alternation of neuronal ensembles activity occur, including reverberations. In contrast, DA-deprived circuits exhibit *high* spontaneous activity at rest, and a highly recurrent ensemble curtails alternation. Interestingly, CtxS briefly relieves these Parkinsonian signs in DA-depleted tissue. Here we compare the actions of some DA-agonists used in PD therapeutics on the pathological dynamics of DA-depleted microcircuits at rest and with CtxS; taking L-DOPA as reference. D_2-class agonists better reduce the excessive spontaneous activity of DA-depleted microcircuits. All DA-agonists tend to maintain ensemble alternation seen in control circuits after CtxS. However, quantitative analyses suggest differences in their actions: in general, DA-agonists only approximate L-DOPA actions. Nonetheless no treatment, including L-DOPA, completely restores microcircuit dynamics to control conditions.

Key words: Parkinson's Disease, Dopaminergic agonists, Calcium imaging.

Integrated single-cell analysis reveals coupled molecular gradient and functional subnetworks in the thalamic reticular nucleus

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Abstract. The thalamic reticular nucleus (TRN), the major source of thalamic inhibition, is known to regulate thalamocortical interactions relevant for sensory processing, attention and cognition. Recent studies have suggested that TRN dysfunction may contribute to sensory abnormalities, attention deficit and sleep disturbances across multiple neurodevelopmental disorders. Despite this importance, little is known about the molecular, anatomical and functional organization of the TRN at the single-cell resolution, and how such organization relates to divergent functions of the TRN, hindering both the basic understanding of the circuit and its therapeutic targeting in disorders. To address this challenge, we performed an integrative study linking single-cell molecular and electrophysiological features of the mouse TRN to connectivity and systems-level function. We found that TRN cellular heterogeneity formed a continuum of gradient expression of hundreds of genes that, nonetheless, co-varied with well-defined anatomical and electrophysiological profiles. Extremes of this molecular gradient predicted distinct TRN anatomical types that arranged in a shell/core like structure and preferentially projected to first order (FO) and higher order (HO) thalamic nuclei, respectively. These anatomical types exhibited distinct electrophysiological properties including propensities to generate rebound burst firing, and showed differential impact on sleep rhythms *in vivo*. Furthermore, using an *in vivo* CRISPR/Cas9 approach we identified genetic mediators that link TRN gene expression to these distinct electrophysiological profiles. Altogether, by generating a detailed molecular and functional atlas of the TRN at single-cell resolution, we revealed distinct subnetworks in the TRN, and thus provide a foundation to dissect diverse thalamo-cortical circuit function as well as its dysfunction in brain disorders.

Key words. RNAseq, TRN, circuits

Amyloid plaques: Friends or Foes?
Exploring the association between Aβ plaques and soluble Aβ aggregates using the FAD4-42 mouse model

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One of the key pathological hallmarks of AD is the extracellular aggregation and deposition of Aβ in the form of plaques. However, the presence of Aβ plaques has also been found in cognitively normal subjects. Additionally, accumulated evidence from AD brains suggests that the levels of soluble Aβ oligomers correlate better with the risk and severity of the disease than insoluble amyloid plaques. In order to study the association between soluble Aβ oligomers and insoluble fibrillar plaques *in vivo*, the 5XFAD and the Tg4-42 mouse models were crossed to produce the novel FAD4-42 model. The 5XFAD model exhibits early and aggressive amyloid pathology, while the Tg4-42 develops age-dependent CA1 neuron loss and does not develop amyloid plaques. FAD4-42 mice showed an increased amyloid burden compared to 5XFAD mice at 3 months of age. However, at 12 months of age, no differences could be detected between 5XFAD and FAD4-42 mice. Furthermore, no neuron loss in the CA1 region of the hippocampus was observed in the FAD4-42 model at 3 or 12 months of age. These results indicate that soluble $A\beta_{4-42}$ binds to amyloid plaques resulting in a reduction of $A\beta_{4-42}$ toxicity, suggesting a potential protective effect of amyloid plaques against soluble toxic Aβ oligomers.

Keywords

Alzheimer's disease, amyloid plaques, soluble Aβ oligomers.

Área:

Neuropatología

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Imprinting and recalling cortical ensembles

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Cortical ensembles in primary visual cortex are groups of neurons with coordinated activity. The functional connectivity of these ensembles gives rise to activity patterns that generate an internal representation of the surrounding world. In this way neuronal ensembles recalled by sensory stimulation make use of imprinted patterns of activity stored in the cortical circuitry. However, whether it is possible to imprint and recall artificially created neuronal ensembles has been difficult to investigate. We used simultaneous two-photon optogenetics and imaging of neuronal populations in vivo to activate artificial ensembles whose members can be identified and manipulated with single cell resolution. Recurrent activation of the same ensembles imprinted them in cortical microcircuits. Artificially imprinted ensembles alternate their activity with visually evoked ensembles without interfering with endogenous circuitry. Moreover, imprinted ensembles remained coactive on consecutive days and single neuron photostimulation is able to recall a complete ensemble. Our findings demonstrate the possibility to reprogram neuronal ensembles and observe behavioral correlates of cortical manipulation.

Heterosynaptic structural plasticity of adult born granule cells

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Abstract

Adult neurogenesis of dentate gyrus granule cells (GCs) is present in mammals, including humans, an d has been implicated in hippocampal forms of learning and memory. Adult newborn GCs (abGCs) ha ve been shown to exert enhanced synaptic plasticity and to survive and functionally integrate into th e existing mature hippocampal network. Here, we ask, which structural processes underlie a successf ul synaptic integration of abGCs and which forms of synaptic plasticity are developed during maturati on of abGCs. Specifically, we present in vivo evidence for a gradual emergence of homosynaptic longt erm potentiation (homLTP) at stimulated perforant path-GC synapses, followed by a concurrent hete rosynaptic longterm depression (hetLTD) at non-stimulated perforant path-GC synapses of the same abGC, identified by retroviral labelling. Interestingly, hetLTD was accompagnied by dendritic pruning i n synaptically activated abGCs during a critical cell age of 28 – 35 days, but did not appear in mature GCs. This evidences an enhanced structural dendritic plasticity in abGCs.

Our results in vivo and in vitro indicate, that dendritic structural maturation precedes functional integration. AbGCs stayed structurally distinct from mature GCs. Structural spine plasticity (Spine enlargement and shrinkage) occurred in parallel on dendritic segments of the same neuron located within or outside the layer of stimulation and appeared gradually from 21 dpi on, with a sharp increase between 28 dpi and 35 dpi.

In summary, abGCs stay structurally distinct from mGCs even after long maturation times and abGCs undergo a critical period between 28 dpi and 35 dpi during their dendritic arbor is shaped and their ability to express heterosynaptic plasticity emerges.

This work was supported by DFG and LOEWE.

Influence of spatial learning on the integration of adult-born granule neurons

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Neurogenesis in the dentate gyrus of the hippocampus is characterized by the daily birth of thousands of new cells throughout life – the fate of which depends on life experiences. Spatial learning promotes the survival of newborn neurons generated a week before learning at the expenses of youngest ones that are eliminated from the network. Spatial learning also increases the dendritic arbor of newborn neurons that were generated one week before learning. We have demonstrated that these learning effects on the dendritic arbor are homeostatically regulated and last for several months. This dendritic shaping is governed by the cognitive demand and depends on glutamatergic NMDA receptors. By using a retrovirus PSD-95:GFP that allows the visualization of PSD-95, a scaffolding protein that localizes to the postsynaptic density of glutamatergic synapses, we recently found that spatial learning increases the density of glutamatergic inputs in new neurons. By using a monosynaptic retrograde viral approach, identified different areas of the brain projecting onto neurons that 'learned to survive'. We have shown how spatial learning remodels not only new neurons but also creates new networks that extend beyond the hippocampus itself.

Intracortical and corticostriatal circuits for sensory processing and behavior

David Margolis.

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The rodent whisker-to-barrel system is a classic model system for the study of sensory processing in neuroscience. Recent work has revealed close links between early somatosensory processing and motor control. This talk will highlight recent and ongoing experiments that investigate the function of projections from primary somatosensory cortex (S1) to the dorsal striatum using projection-specific optogenetic stimulation and electrophysiological recordings of identified cell types. We find that corticostriatal inputs from S1 and primary motor cortex (M1) differentially innervate spiny projection neurons and interneurons in the dorsal striatum, and exert opposing effects on sensory-guided behavior. Parvalbumin-expressing (PV) interneurons play a prominent role in mediating these effects. Ongoing experiments aim to determine the innervation pattern of cortical and thalamic inputs on a subcellular scale and to reveal the cellular dynamics of striatal population activity during learning, with the goal of understanding the opposing influences of sensory and motor inputs on striatal circuitry and sensory-guided behaviors.

Brainstem-to-amygdala control of emotional associative learning

Joshua Johansen
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Aversive experiences are powerful triggers for memory formation and alter neural circuits to adaptively shape behavior. The lateral amygdala (LA) is a critical site of neural plasticity mediating aversive memory formation, but how aversive experiences are transduced by the nervous system into neural signals which produce learning and memory is not well understood. I will discuss our recent studies examining how aversive sensory and bodily state information reaches the LA through parallel brainstem neural circuits to trigger aversive associative learning. Using cell type specific optogenetic, neural recording and anatomical tracing approaches, we examined potential aversive glutamatergic projections to the LA during fear learning. We identified a specific glutamatergic mesencephalic reticular formation pathway which integrates aversive sensory and defensive behavioral response information and triggers fear learning through a direct projection to the LA. This pathway makes synaptic connections with a specific population of LA neurons which receive convergent synaptic inputs from auditory thalamus and cortex. Inactivation of this pathway abolishes fear learning and reduces shock evoked responding in LA neurons. Furthermore, stimulation of this pathway is sufficient to produce fear learning as well as defensive behaviors. Together, these findings reveal a potential neural mechanism through which neural circuits transduce aversive external sensory and internal bodily experiences into neural signals which trigger emotional memories.

Perturbations in the Activity of Cholinergic Interneurons in the Dorsomedial Striatum Impairs the Encoding of an Instrumental Contingency Change

Hector Alatriste-León, Anil K. Verma, Josué O. Ramírez-Jarquín & Fatuel Tecuapetla

Summary

The striatal cholinergic system is key in detecting changes in instrumental contingencies. While recent evidence supports this vision, cell type-specific online control on the activity of the cholinergic striatal neurons is necessary to empirically test it. During this presentation I will present ongoing work in which we performed optogenetic manipulations of the activity of striatal cholinergic interneurons (CINs) to evaluate their contribution to the updating of a previously learned instrumental contingency. By modulating the activity of CINs, we identified that the inhibition of CINs impairs the encoding of the contingency change. Remarkably, a manipulation that perturbs the activity of CINs, rather than inhibiting them also impaired the encoding of the change in contingency. These results emphasize that beyond an increase in the activity of CINs, the proper activity of these cells is required for the identification of an instrumental contingency change.

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Neural basis of bilaterally coordinated actions

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Bilateral coordinated movements are indispensable for our everyday activities and are severely affected during pathological conditions such as Parkinson's disease. Previous literature implicates multiple cortical and subcortical regions, including sensorimotor cortices and striatum in bimanual coordination in humans and non-human primates. However, the exact contributions of specific regions and their interactions are still to be fully understood. In this context, we have developed a bimanual coordination protocol for rats, our model provides enough resolution to precisely reconstruct bimanual movement trajectories and evaluate their spatiotemporal coupling and synchronization. We combined this strategy with structural lesions and pharmacological and optogenetic manipulations. Currently we are exploring the role of sensory and non-sensory cortical and thalamic inputs to the basal ganglia and their implications during learning and expert execution of bimanually coordinated movements. Our preliminary data suggest that subcortical regions are mainly implicated in the modulation of kinematic parameters of bilaterally coordinated movements.

Prefrontal control of conflict choice behavior

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Imagine a thirsty zebra that in order to obtain water from a river must overcome the threat of a crocodile. Such situations challenge animals to choose between conflicting behavioral responses (avoid vs approach) guided by opposing motivational stimuli (threat vs reward, respectively). While the prelimbic cortex (PL) has been widely implicated in signaling threat-related responses as well as reward-seeking behavior, it is not known whether this prefrontal region is critical to choose between competing motivations during conflict, to be able to obtain a reward despite the threat. To address this, we combine the use of local pharmacological inactivations, immunocytochemistry and optogenetic manipulations in rats that learned to obtain a reward despite the threat. We found that PL inactivation in well-trained rats decreases the time to obtain a reward despite the threat, while leaving threat memory retrieval and reward-seeking responses intact. Preliminary findings indicate that PL optogenetic stimulation increases the time to obtain a reward despite the threat. Consistently, we found that PL activity increases in rats that were unsuccessful at overcoming threat to obtain a reward, compared to those that were successful in such challenge. Together, these preliminary findings suggest that PL controls choice behavior when threat- and reward-related stimuli are presented simultaneously (motivational conflict) and not simply, as originally thought, to regulate threat-related responses or reward-seeking behavior separately (no motivational conflict). Because we previously found that, like PL inactivation, ventral striatum (VS) inactivation decreases the time to obtain a reward despite the threat, currently we are using optogenetic manipulations to examine the contribution of PL-VS pathway in conflict choice behavior.

Transcription Factor-dependent Control of Adult Hippocampal Neurogenesis

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Adult hippocampal neurogenesis, i.e., the generation of dentate granule neurons from stem cells throughout life, is an essential contributor to hippocampal-plasticity. There is growing evidence that disruption of adult neurogenesis contributes to cognitive and behavioral impairment in neurodegenerative and neuropsychiatric diseases. In adult neurogenesis, new neurons are generated from neural stem cells through a complex sequence of proliferation, differentiation, and maturation steps. Development of the new neuron is dependent upon the precise temporal activity of stage-specific genetic programs. Understanding the genetic control of neuronal development will provide new insights into the mechanisms underlying neurogenesis-dependent plasticity in health and disease. Here, I will provide an overview on the current understanding of transcription factor-mediated regulation of mammalian neural stem cells and will present new data on how transcription factor networks regulate essential steps in adult neurogenesis.

FeRIC: a magnetogenetic technique to control neuronal excitability with no depth limitation

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The ability to control neuronal excitability with high spatial and temporal resolution is essential to understanding the complex circuitry of the brain. We have devised a technique termed “FeRIC” (Ferritin-iron Redistribution to Ion Channels) to remotely control neuronal excitability with non-invasive radio-frequency (RF) magnetic fields. FeRIC technology couples modified membrane ion channels with ferritin. Specifically, the intracellular domain of the transient receptor potential vanilloid 1 and 4 (TRPV1 and TRPV4), and the Ca^{2+}-activated Cl^- channel Anoctamin 1 (Ano1 or TMEM16A) were fused with the ferritin-binding region (domain 5) of Kininogen. The resulting FeRIC channels redistribute endogenous ferritin to their proximity and could be activated with RF. Here we show that RF activates cultured hippocampal and cortical neurons expressing $TRPV1^{FeRIC}$ and $TRPV4^{FeRIC}$ channels. In those neurons, RF depolarizes the membrane potential, triggers Ca^{2+} transients, and increases the firing rate. Conversely, RF inhibits neurons expressing $TMEM16A^{FeRIC}$ via membrane hyperpolarization. To conclude, present work shows the feasibility of FeRIC technology to remotely control the neuronal excitability with spatiotemporal resolution.

Keywords: magnetic fields, neuronal excitability, ion channels

Area: Technology and innovation

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What makes a malformed cortical circuit epileptogenic?

Characterization of cortical dysplasias epileptogenicity in animal model

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Research Area - Neuropathology

Several biological processes are involved in the morphological development of the cortex during early stages of gestation. Neuronal migration and the organization of the layered neocortex occurs in a series of orchestrated events that occur over a specific time window. Genetic and epigenetic factors can alter cortical development and lead to morphological abnormalities collectively known as malformations of cortical development (MCD). One of those are the focal cortical dysplasias (FCD), characterized by dyslaminated cortex, blurring of the gray/white matter interface and variable architectural abnormalities (Guerrini *et al.,* 2015). Currently, their characterization and classification are limited, as they are often underdiagnosed, and may even go undetected for years. High-resolution neuroimaging has greatly improved the early detection of large to moderate malformations in patients, but it is still difficult to detect FCDs, as they are often subtle, variable in extension, cell morphology and localization. Their clinical importance is striking: approximately 27% of those malformations generate chronic and medically refractory epilepsy (Rakhade & Jensen, 2009) yet, when amenable to surgical resection, have excellent prognosis.

It is unknown, however, how these relatively subtle morphological abnormalities can lead to epilepsy. If function follows form, then epileptogenesis can be the consequence of neural network rearrangement (Rakhade & Jensen, 2009). This, however, has been extremely difficult to study in humans and requires animal models.

In our work we use the BCNU model of cortical dysplasia one of those models. BCNU, an anti-neoplastic agent, is injected in pregnant rats precisely during cortical genesis of the embryo. This results in a cortical morphology that resembles many features of FCD. The aim of this study is to characterize the anatomical and functional differences between dysplasias and healthy cortex, and their susceptibility to generate epileptic seizures in response to an exogenous stimulus. Calcium imaging of live sections of the cortex of BCNU and control rats at P30 was performed before, during, and after the introduction of pilocarpine. Large field-of-view imaging allowed us to monitor the signal time series of several hundred neurons. Their network topology was investigated through graph-theoretical analyses of adjacency matrices built from the correlation of their time series. Although the number of neurons was not greatly reduced in BCNU rats, their network response to pilocarpine was greatly different than healthy rats, and their cortical circuit activity did not return to baseline conditions after the pilocarpine challenge. Our work aids in the identification of network abnormalities that result in chronic epilepsy.

Key words: Epileptogenesis, Neural Network, Cortical Dysplasia

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Long-term copper exposure induces autophagy upregulation and the loss of dopaminergic neurons *in vivo*

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Area: Neuropathology

α-Synuclein gene multiplication and point mutation are associated with familial and sporadic Parkinson's disease (PD). In addition, the cerebrospinal fluid and blood of PD patients have shown an increase in copper (Cu) levels. Likewise, occupational exposure to Cu is related to a high risk to develop PD. Recently, it has been demonstrated that α-Synuclein, wildtype or mutated, requires an environmental factor, such as exposure to copper, to increase its cytotoxicity. Therefore, we aimed to elucidate the mechanisms by which Cu regulates dopaminergic cell death in an *in vivo* model. Mice were treated with $CuSO_4$ at 100, 250, and 500 ppm in tap water to drink *ad libitum* for ten months. Since the motor function is affected in PD, we evaluated whether exposure to Cu has an effect on mice. Gait analysis was performed in mice, and no difference was observed in response to Cu. However, a decrease of neuronal population in the midbrain was observed in response to increasing concentrations of Cu with an anti-TH antibody by immunofluorescence and corroborated by western blot. The loss of dopaminergic neurons was correlated with an increased expression level of the autophagy marker LC3-II and mTOR, in the midbrain. Besides, α-Synuclein protein, which is associated with PD pathogenesis, was also increased in response to Cu. Taken together, these results show that Cu has a neurotoxic effect and upregulates autophagy in midbrain dopaminergic neurons.

Keywords: *Parkinson's disease, autophagy, copper*

Krüppel-like Factors 9 and 13 Block Neurite Outgrowth Induced by cAMP Pathway Activation

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Area: Signal Transduction

The ability of neurons to elaborate projections declines during postnatal development, both by the formation of an inhibitory extracellular environment and by the establishment of a new genetic program. Krüppel-like factors (KLFs) have been identified as important regulators of neuronal differentiation and regeneration. They comprise a family of 17 zinc finger transcription factors grouped into 3 subfamilies based on the sequences of their N-terminal domains. In our previous work, we found that the expression of *Klf9* and *Klf13*, members of subfamily 3, increases in hippocampus during postnatal development. In addition, by RNA sequencing, we discovered that KLF9 and KLF13 work predominantly as transcriptional repressors in the adult mouse hippocampus-derived cell line HT22. This suggest that these KLFs could contribute, as intrinsic factors, to the establishment of the inhibitory environment. In order to describe the action mechanisms of these transcription factors, here we analyzed and compared the cellular functions, and genomic targets of KLF13 and KLF9 to test the hypothesis that these two closely related Klfs inhibit neurite outgrowth by similar mechanisms. We engineered the adult mouse hippocampus-derived cell line HT22 to control *Klf9* or *Klf13* expression by addition of doxycycline. We also used CRISPR/Cas9 genome editing to generate *Klf9, Klf13* knock out (KO) and *Klf9/Klf13* double KO HT22 cell lines.To induce neurite outgrowth, we treated cells with forskolin (FK)+IBMX, which increases cAMP; elevated cAMP is a hallmark of regenerative responses of neurons to injury. Our results show that, although the KO cells maintain the response to FK, the main effect is observed in the basal length of the neurites, which is larger in *Klf9* and *Klf13* single KOs and even larger in doble KO in comparison with the parental line. Conversely, the stimulatory effect of FK+IBMX on neurite outgrowth was blocked by simultaneous forced expression of *Klf9* or *Klf13*. This effect on neurite outgrowth was confirmed in primary hippocampal neurons where electroporation of *Klf9* or *Klf13* expression plasmids resulted in significantly shorter neurite length compared with control transfected cells. Analysis of RNAseq data obtained from HT22 cells following 8 hr of induced *Klf9* or *Klf13* expression showed that both proteins perturb the cAMP signaling pathway, suggesting that, in part, these transcription factors inhibit neurite outgrowth by inhibiting this pathway. Our results support that cAMP-dependent neurite outgrowth in hippocampal neurons can be blocked by KLf9 and KLF13.

Keywords: Kruppel-like factors; Neurite outgrowth; cAMP pathway

The neural code

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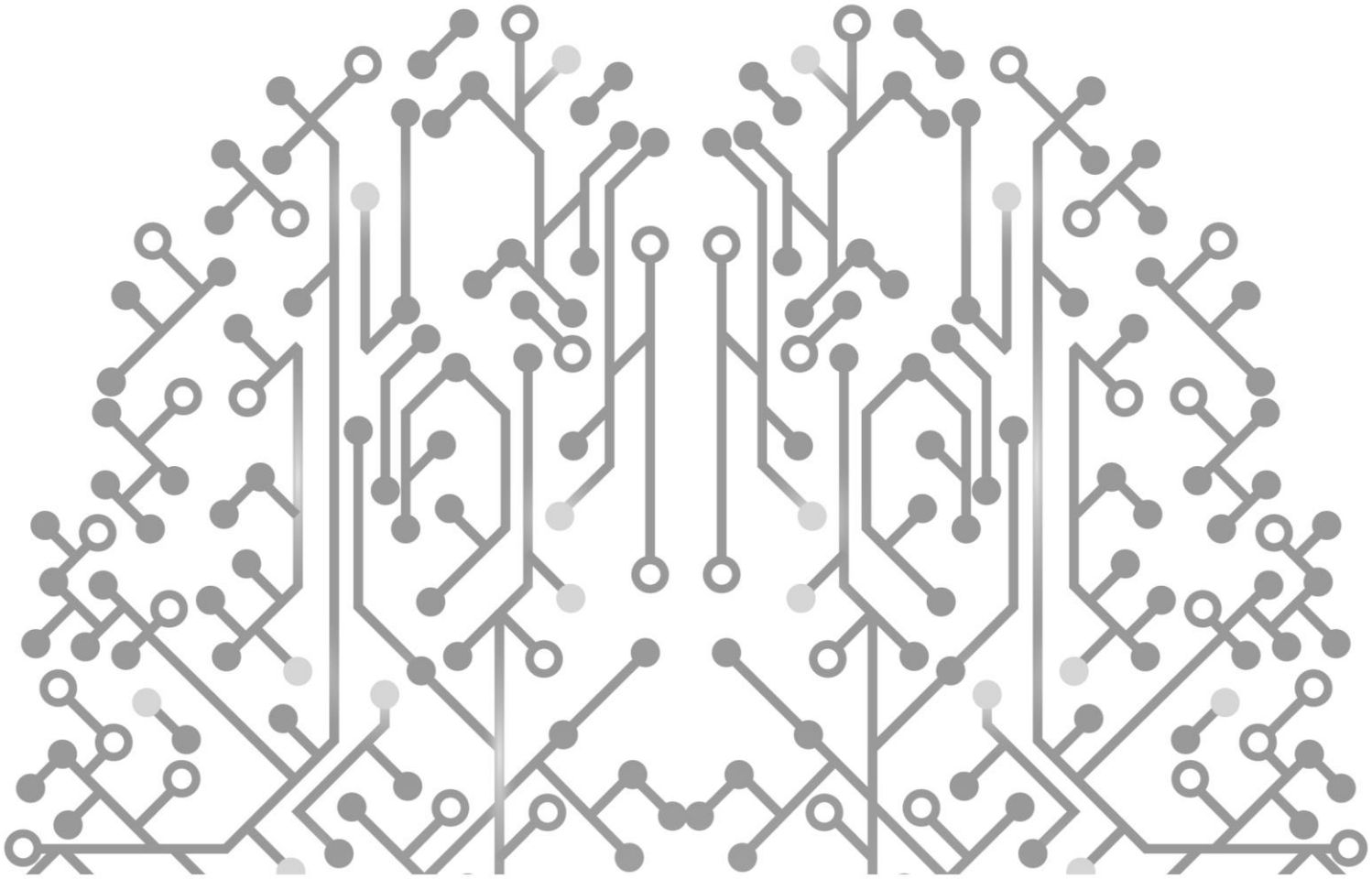
The problem of neural coding has stimulated a large amount of research in Neuroscience. The underlying belief is that unravelling the neural representations of sensory stimuli from the periphery to early stages of cortical processing is key to addressing brain function, be it local or distributed. Investigations in several systems have shown how neural activity represents the physical parameters of sensory stimuli in both the periphery and central areas. These results have paved the way for new questions that are more closely related to cognitive processing. For example, how are the neural representations of sensory stimuli related to perception? What attributes of the observed neural responses are relevant for downstream networks and how do these responses influence decision-making and behavior? Here, I will speak on these topics.



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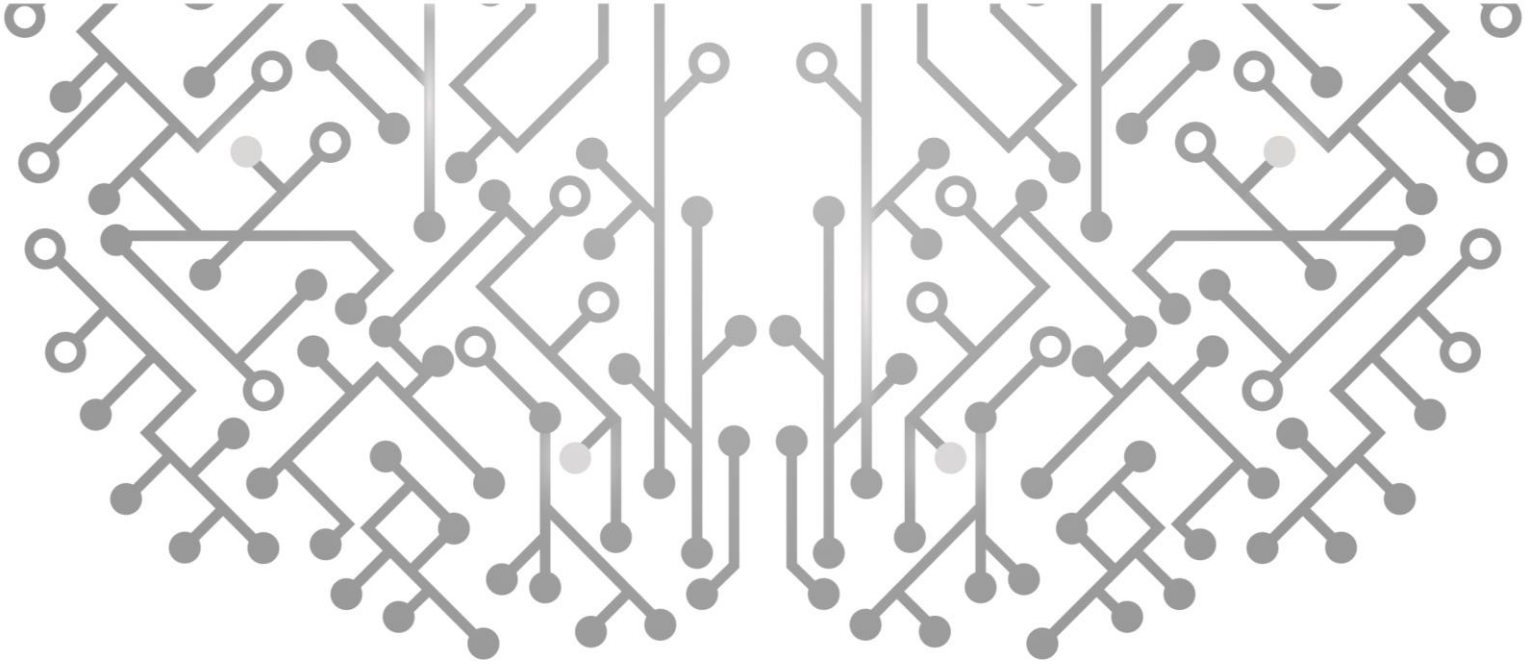

Hippocampal functional connectivity associations with cognitive skills in temporal lobe epilepsy

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Research area: Cognition and behavior

Introduction: Many patients with temporal lobe epilepsy (TLE) present deficits in cognitive skills that involve network participation and recruitment of brain regions that are far-distant from temporal lobe. Therefore TLE may cause alterations in functional connectivity (FC). Default mode network (DMN) is one of the most studied resting state (RS) networks and although it deactivates during execution of resource demanding cognitive tasks, alterations in DMN have been associated to cognitive decline. In fact, DMN activity is negatively correlated to task positive activated networks (TPN), and it is believed that this interaction may be crucial to maintain intact cognitive skills. The aim of this work was to assess integrity of DMN and TPN, and its relationship with cognition in TLE patients with different characteristics.

Methods: 25 healthy controls and 21 TLE patients were included. Cognitive skills indexes were obtained though WAIS-IV & WMS Assessment from which specific cognitive domain indexes were derived. Functional fMRI RS volumes were acquired in 3T Philips Achiva Tx scanner. Images were preprocessed using CPAC software pipeline. In order to analyze FC a DMN and TPN region of interest (ROI) template was created in Neurosynth.org resulting in 21 clusters. Spherical ROIs (4mm radius) at the centers of this clusters were created. Right TLE patient images were flipped on the X axis to increase sensitivity of analysis. Correlation matrices (Pearson coefficient) of pairs of ROIS were computed to model FC. Familywise error was controlled using false discovery rate (FDR) correction. Simple linear regressions were used to model association between FC and Cognition. Analysis of Covariance (ANCOVA) was used to test group interactions.

Results : TLE patients had on average lower cognitive scores than controls. FC analysis showed that TLE patients have a signtificant loss of inter-hippocampalconnectivity and also a detrimental effect on TPN, observed in insular- paracingulate FC.Patients with abnormal cognition showed reduced FC between C.MTG and l.PRG. Thus,cognitive impairment in TLE may underly a blunted interaction between DMN and TPN as well as hippocampal dysfunction. TLE patients have significant associations of FC with processing speed index. Hippocampus, Insula and temporal regions are frequently involved, maybe due to dysfunction of this structures. We found a strong interaction between FC and verbal coefficient in non hipoccampal sclerosis patients.

Keywords: Epilepsy, Cognition, Brain connectivity.

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Enrichment environment acts proneurogenic but induces social aggression behavior in male- but not in female- GFAP-EGFP mice: relevance of sex

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Abstract

Neurogenesis in the dentate gyrus of the hippocampus (GD) during adulthood has been amply demonstrated. Several studies indicate that neurogenesis can be modified by multiple factor including environmental cues, such as voluntary exercise, learning paradigms and the exposure to enriched environment (EE). Interestingly, environmental cues positively modify neuroplasticity-related processes including the generation of new neurons in the dentate gyrus of the hippocampus. . Moreover, some studies have indicated that the environmental cues along development can influence the capability of mice to cope with stress and its possible psychosocial consequences in adulthood (for example, aggression and/or violence). Also, it has been suggested that the beneficial effects of AEnr on behavior and plasticity are dependent of sex differences. Based on these evidences, we thus here investigated the effects of EE on sociability, aggression and/or violence behavior, neurogenesis in the dentate gyrus of the hippocampus and neuronal activity in the regions of the limbic system of male and female adult mice. Female and male GFAP-EGFP transgenic mice were used to perform the present study. At postnatal day 21 (PD21), mice were separated according to their sex and assigned into two groups: 1) Standard condition (SC) or 2) EE. Mice were injected with BrdU at PN37 and at PD53 rodents were exposed to the open field test followed by the intruder-resident test to evaluate social behaviors. Two-hours after the behavioral test mice were euthanized to dissect out the brain from the skull to further perform the histological analysis of some events of the neurogenic process (proliferation, Ki67; survival, BrdU; intermediate stages of neuronal development, doublecortin) and neuronal activation (ARC). Results confirmed that the exposure to an EE increased the events of the neurogenic process in the DG of both females and males mice. At the behavioral level, sexual differences were presented, since the sustained EE modified the exploratory behavior only in females, while males did not present significant differences compared to the SC group. However, EE male mice showed higher levels of aggression-related behavior than EE female mice. Finally, the data of this study confirmed that EE acts proneurogenic and suggest that EE exposure promotes social behavior in females but in males it increases aggression. Thus, our results are in the direction to the effects of EE on social behavior are dependent of the sexual dimorphism.

Key words: Adult hippocampal neurogenesis, enriched environment, sexual dimorphism.

Área: Plasticidad Celular y Circuitos Neurales, Cognición y Comportamiento,

Litter size effect on vulnerability and resilience

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Área: Cognición y comportamiento

Some individuals show resistance to diseases and disorders even in adversity (resilience), and others are more susceptible (vulnerability). Modifying litter size is a common method to study obesity, malnutrition and its effects. Previous studies in our laboratory suggested that litter size modify sexual behavior, memory, and learning. Therefore, we analyzed if vulnerability and resilience depended on litter size, making this manipulation a suitable model to study them.

Method

The large litters (LL) were formed by 16 pups, control litters (CL) by 9 pups and small litters (SL) by 3 offsprings. Object recognition and elevated plus maze tests were performed at 2, 4 and 6 months of age. Sleep restriction was performance at 3 months of age.

Object recognition: Each subject was placed in a box with 2 different objects, allowing it to explore them for 10min. At the next day, the process was repeated with a familiar and a new object.

Elevated plus maze: During 10 min the time spend in open or close arms was evaluated

Sleep restriction effects on BBB integrity: Males spend 20h per day during 8, 10 and 12 days on a cage with platforms surrounded by water, at the last day, tracers of low and high molecular weight were i.v. administrated and several brain regions were obtained. Concentration of tracer was evaluated by spectrophotometry.

Results

We observed that LL animals had better declarative memory than SL and less anxiety than CL and SL. The effect on permeability was dependent of brain region, however, the BBB permeability was higher in LL and the recovery of permeability was faster in SL.

Conclusion

Predictive rhythmic tapping to auditory metronomes in the nonhuman primate

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Cognición y comportamiento

Beat entrainment is the ability to entrain one's movements to a perceived periodic sequence, such as a metronome in music. Previous studies have shown that Rhesus monkeys share some of the human capabilities for rhythmic entrainment, such as tapping regularly at the period of isochronous stimuli. Regardless, monkeys tend to tap hundreds of milliseconds after stimulus onsets and exhibit a preference for visual metronomes in contrast to humans, who tap slightly ahead of the stimulus onsets and are more sensitive in detecting and synchronizing to auditory metronomes. To test the predictive and flexibility nature of rhythmic entrainment to auditory rhythms in nonhuman primates, we trained two Rhesus monkeys to perform fast hand movements in phase to the seven stimuli of an isochronous metronome (stimulus onset intervals: 550, 650, 750, 850 ms). Monkeys were also trained to maintain their rhythmic movements when the last two stimuli of the metronome were omitted or when only one stimulus was omitted at random positions (4-6) within the metronome. First, we found that monkeys could predictively entrain to the trained and novel isochronous auditory rhythms, generating movements in anticipation of the stimulus onset, i.e., negative asynchronies. This predictive behavior also occurred when the animals synchronized their movements to metronomes with stimulus omissions at expected and unexpected positions for the largest interval (850 ms). Notably, the asynchronies at the random omitted positions were similar to the asynchronies at the same positions from trials with no stimulus omissions as also observed in humans (n=11). Second, we found that monkeys entrained to the isochronous beat using an error-correction mechanism to compensate for prior stimulus-movement phase variability: the inter-movement interval was inversely dependent on the duration of the preceding movement. Important for archiving prediction and error correction in the monkeys' performance was to provide immediate feedback about the timing of each movement during the training period. Overall, results show that monkeys are capable of predictive and flexible entrainment to auditory rhythms even with stimulus omissions and that generalize this ability to novel untrained tempos. Our findings shift the limits of beat entrainment in nonhuman primates and advance our knowledge on the evolutionary origins of beat entrainment.

Keywords: beat entrainment, predictive tapping, Rhesus monkey

Acknowledgments

Sucrose intensity percept and decision-making coding in the rat anterior insular and orbitofrontal cortex

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Taste is essential for survival since it promotes consumption of food that signals immediate energy and rejection of potentially noxious stimuli. A stable representation of the same taste quality (bitter, sweet), despite intensity/concentration variations, might be essential for an animal in order to detect these nutrients or poisonous foods. It has been reported that sweet intensity is encoded by a similar proportion of neurons in the anterior Insular Cortex (aIC) and Orbitofrontal Cortex (OFC), which are also known as primary and secondary gustatory cortices. However, it remains unexplored if aIC and OFC neurons could detect a taste quality over a variety of intensities: Intensity-invariant cells. To address this question, we recorded single-unit activity from the aIC and OFC while rats performed a sucrose detection task (Non-sucrose 0% vs Sucrose 0.5, 1.3, 3.2, 7.9, 20%). We found that more than half of neurons recorded, in both cortices, were responsive to cue delivery. Although, at the population level, different modulatory patterns were displayed: aIC responded earlier and with a strong phasic component, whereas OFC neurons exhibited a late tonic response. Only a small (~16.6%) subpopulation of Quality-selective (QS) neurons responded differentially to sucrose in comparison to water. This group contained more information -in the firing rate and spike timing- about the intensity in comparison to Non-selective. Furthermore, QS could respond differently to at least two of sucrose intensities (Intensity-Variant, Var) or very similar to all sucrose intensities (Intensity-Invariant, Inv). The proportion of the Inv neurons was higher in the aIC in comparison to OFC, while Var neurons prevailed in the OFC. We propose that Inv neurons could be important to detect sucrose regardless of its sweetness. In both cortices, a subset of Var neurons linearly modulated their firing rate as a function of intensities. These data confirm that both regions represented sucrose quality and intensity physical dimension: responses covaried with stimulus. On the other hand, we confirmed that the psychological dimension of the sweet taste detection can be encoded in both regions: responses covaried with the animal choice. Finally, other decision-variables such as movement direction and outcome omission were encoded by these two regions. Thus, the taste system uses a compact and distributed code to detect and represent the perceived quality and intensity of sucrose. Moreover, the decision variables, as opposed to other sensory systems, are encoded by both cortices demonstrating they served as multimodal areas. Importantly, we describe for the first time the existence of concentration invariant neurons in the taste field.

Áreas: Cognición y Comportamiento.

Key words: taste, electrophysiology, perception.

Social Interaction: Adjustment to interdependent contingencies in a competition task with Long Evans rats.

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Área: Cognición y Comportamiento

The importance of studying behavioral patterns generated from the interaction among organisms with interdependent payments comes from the way a specie organizes their activities into an environment, and how those activities have consequences in their social structure if they share time and space and can be performed in coordination. One of the possible patterns is competition; which is defined by Schmitt (1968) as a contingency in which reinforcement is delivered depending on the relative performance of the organism.

With the intention to explore which variable has more weight in defying competition, 2 groups of 14 rats each, were used in 2 different experiments. The task consisted in moving a small ball across a rail in a choice paradigm with Interaction experimental box. Where the subjects could choose between an individual response versus an interdependent one, that required the coordination of the 2 subjects working on the task and an evaluation of their relative performance was conducted within the session to determine a winner in each round. In both groups, the manipulation consisted in varying the contingencies experimented in the interdependent trail. The first group was exposed to 3 levels of magnitudes of reinforcement (5-0,5-2,5-4). The second group undergo 3 levels of amount of work that each individual had to do in order to become the winner of the round (0.51, 0.67, 0.81).

The results showed in both groups an overall preference for the individual response measured by the total time spent in any of the options during the experimental sessions. The subjects were more sensitive to the restrictions in the amount of work condition. Also, both groups displayed big difficulties to coordinate at the more extreme levels of the manipulation (magnitude: 5-0 & work: 0.81).

Hippocampal Neurons in a Visual Metronome Task

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Neural activity encoding temporal information has been found across cortical and subcortical structures. Recently, the hippocampus has been shown to contain so called “time-cells” that represent elapsed time in the context of spatial tasks in rodents. In addition to this in primates, rodents and bats have been found cells that encode different types of spatial information and share similar characteristics. However, it is not clear whether these time cells can be found in the primate brain in a behavioral task that does not involve spatial displacement. To address this issue, we recorded the activity of single neurons in the hippocampus in rhesus monkeys performing a visual metronome task in which the animals learned to track a circle that appeared alternately on the left and right sides of a touchscreen with a regular tempo. Our preliminary results show neurons that oscillate in synchrony with the stimulus, even when this stimulus is no longer visible, and the subjects had to maintain the rhythm internally.

Keywords: rhesus monkey, hippocampus, time perception.

Vulnerability and resistance to ketamine in an animal model of schizophrenia depend of litter size.

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Área: Cognición y comportamiento

Subjects from small litter (SL) are used as an obesity model, whereas males from large litter (LL) are a common model of postnatal malnutrition. However, some results show that males from SL are more susceptible to stress and have poor memory and more anxiety, and animals from LL show a better performance in memory tasks and they are more resistant to stress. We are using those subjects like a model of vulnerability and resiliency. Schizophrenia is a mental disorder very complex to study in animals. An animal model for this disease consists of the administration of a low dose of ketamine. Then, in order to evaluate the ability of this model to discriminate between susceptibility of animals, we used resilient and vulnerable males from LL and SL, respectively.

We used Wistar rats from vivarium of UAM-Iztapalapa. LL males were obtained from litters of 17 offspring, control litter (CL) subjects are from litters of 9 pups, and SL males, from 3 pups' litters. Subjects were used at 6-7 months of age. Locomotor activity was evaluated during 10 min in an acrylic box, and the behavior was recorder with Ethovision system. Eight males from each group were used and behavior was evaluated in a Latin square design every 2-3 days. During the first 3 tests, habituation was done. During the next 4 tests, a dose of 0, 5, 10 and 20 mg/Kg of ketamine was administrated 5 min before test. Three more tests were performed after ketamine administration without any treatment.

Result showed that ketamine induces an increase in locomotor activity in males from SL faster and with higher duration than males from CL. Males from LL exhibited a short duration/intensity increase in locomotor activity only with dose of 10 and 20 mg/Kg.

We conclude that Ketamine model of schizophrenia showed to be sensitive to males with different characteristic of vulnerability and resilience, supporting both the face validity and construct validity of this animal model of schizophrenia.

Keywords: schizophrenia, ketamine, locomotor

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Cannabis use alters the advantage given by the cannabinoid receptor 1 gene genotype on selective attention performance

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Área: Cognición y Comportamiento

Assessing Retrospective Memory: Temporal Sequences and Delays

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An adequate integration of information from different temporal events is fundamental for organisms to adapt optimally into the environment. There are processes related to memory which consider the integration of temporal sequences, specifically, processes related to retrospective memory. In this paper, it was evaluated the role of retrospective memory when it was used a delayed symbolic matching to sample task with two temporal sequences. This paper had two aims. First aim was to know whether rodents could learn to discriminate three-stimuli-sequences such as a short or a long sequence. Second aim was to test the learning of organisms when different delays were presented (0", 5", 15" and 30"), either between the presentation of the stimuli or at the end of the presentation of the stimuli. For these purposes, four Wistar rats performed a delayed symbolic matching to sample task where 1", 2" and 4" durations were associated to a short sequence while 2", 4" and 8" durations were associated to a long sequence. Results analysis was conducted by two ways: percent correct responses and signal detection theory. Results of index correct responses showed that the correct responses decrease when the delays increase either between the presentation of the stimuli or at the end of the presentation of the stimuli. Furthermore, results of signal detection analysis showed that the hits rates, the false alarms rates, the bias parameter, and the sensitivity parameter varied as a function of the delays.

Keywords: delayed symbolic to matching to sample tasks; signal detection, rats

12. Cognition and behavior.

Brain electrical differences during working memory retrieval are related with maintenance or manipulation processes and task difficulty

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Cognición y comportamiento

Working memory (WM) requires the ability to maintain (Mt) and manipulate (Mp) information. Differences between both processes are evidenced behaviorally and by means of the Event-related potentials (ERPs) at the delay period. We previously have showed changes in ERPs between both processes at the retrieval phase. However, the effect of difficulty on each process at the retrieval is less known. We evaluated ERPs during the retrieval of information as a function of the WM process (Mt or Mp) and its task-demand (low and high). ERPs were recorded to 38 subjects, while they solved two independent Delay Match-to-Sample Tasks. In Mt task, they indicated if the test stimulus matched in color, or color and shape (target stimuli; low and high difficulty, respectively) or not (non-target) to the encoded stimulus. In Mp task, participants indicated if the encoded shape was rotated 90° or 180° (target stimuli Tgt; low and high difficulty, respectively) or not (non-target; Ntgt). Higher percentage of correct responses and shorter reaction times were observed for Mt than for Mp; target trials were faster than non-target. P300 latency at the retrieval phase was shorter for low (vs. high) difficulty trials, for both Mt and Mp. Also, target trials had shorter latency in both Mt and Mp than non-target trials. An interaction was observed by task x difficulty, Mt-low difficulty condition had shorter latency than Mp-Low, both were shorter than Mt-high and this one also was shorter than Mp-High. Additionally, a scaffolding effect was observed between task, difficulty and type of trial on the latency of P3: first, the Mt and Mp-Low-Tgt trials, then Mt and Mp-High-Tgt trials and finally, Mt and Mp-High-Ntgt trials. These results suggest that mechanisms in recognition during retrieval in WM depends on the type of processing required (Mt or Mp), the task demand and the type of trial.

Keywords: Working memory, retrieval, difficulty

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Progesterone promotes the proliferation, differentiation and maturation of oligodendroglial progenitor cells from the mouse embryonic spinal cord

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Area: Development & Aging

Abstract

Oligodendrocytes are the myelinating cells of the central nervous system (CNS). These cells arise during the mouse embryonic development by the specification of the neural stem cells (NSC) to oligodendroglial progenitor cells (OPC) at the developmental stage E12.5; once this cell fate is acquired, the OPC proliferate to achieve a homogeneous distribution throughout the developing CNS. The subsequent differentiation and maturation of OPC to myelinating oligodendrocytes occurs shortly a few days before birth, thus myelination occurs very actively over the first week of mouse postnatal life.

Some of the molecular factors that regulate the specification and differentiation of OPC during prenatal neurodevelopment have been identified. For example, the morphogen Shh is indispensable for the specification of the NSC to OPC, while the growth factors PDGF and FGF2 are essential to maintain the self-renewal of these cells. Finally, differentiation is promoted by hormones such as the thyroid hormone T3. Along with these molecules, there are studies that have shown that the steroid hormone progesterone promotes the proliferation and differentiation of OPC during early postnatal life, while it also promotes nerve myelination during adult life. However, until now it is unknown whether progesterone also has effects on OPC during prenatal development.

In this study we investigated the effects of progesterone on OPC primary cultures derived from the spinal cord of mouse E14.5 embryos. For the first time, we detected the expression of the intracellular progesterone receptor (PR) in embryonic OPC; moreover, we found that progesterone (10 nM) increased the proliferation of OPC in co-treatment with t PDGF and FGF2 (10 ng/mL), whereas the treatment with progesterone without growth factors stimulated the differentiation of OPC into myelinating oligodendrocytes. These effects were mediated by the PR since the treatment with the pharmacological PR antagonist RU486 (1 μM) blocked them. Finally, trough RT-qPCR experiments we observed that progesterone upregulated the expression of key genes for the self-renewal and differentiation of OPC. Our results suggest that progesterone through the activation of the PR participates in the oligodendrogenesis during prenatal mouse neurodevelopment.

Keywords

Oligodendrocyte progenitor cells; progesterone; myelination.

Demyelination associated to chronic arsenic exposure in Wistar rats

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Inorganic arsenic (iAs) is among the major contaminants of ground water in the world. It is widely recognized that it produces deleterious effects in the brain. Worldwide population-based studies demonstrate that chronic iAs exposure is inversely associated with cognitive function among children and adults, while research in animal models confirms learning and memory deficits after arsenic exposure. At cellular level, iAs affects energy generation, neurotransmitter synthesis and release, intracellular signaling and promotes the generation of oxidative stress and DNA damage. In addition, current research supports that long-term exposure to iAs favors molecular changes resembling the functional and pathologic features of Alzheimer disease (AD). In this respect, iAs may subtly affect developmental processes such as synaptic plasticity and myelination along years of exposure, whose final outcome would be neurodegeneration. To investigate the long term effects of low level iAs in the myelination process, we undertook a longitudinal study with repeated follow-up assessments. In this work, male Wistar rats were divided into 2 groups: 1) control without arsenic; and 2) exposed to 3 ppm sodium arsenite in drinking water. Animals received the treatment from gestation until 2, 4, 6, 12 months of postnatal age. To assess associations between morphology and myelin, levels of myelin basic protein (MBP) by immunohistochemistry/histology and immunoblot from frontal cortex and corpus callosum (CC) were evaluated. In order to analyze the microstructure from CC *in vivo,* we employed diffusion tensor imaging (DTI) and determined fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) at the same ages. According to our hypothesis of As-induced demyelination, we analyzed mitochondrial mass (VDAC) by western blot as an essential adaptive/stress response designed to maintain the function of demyelinated axons. Since early impairments in demyelination from frontal lobe are components of AD, in parallel with neurodegeneration, we also measured amyloid precursor protein (APP) level in frontal cortex. Ultrastructural imaging demonstrated iAs-associated decreases in FA and AD, and increases in MD and RD. This result is in agreement with decreased levels of MBP and immunohistochemistry images, together with significant increases of mitochondrial and APP markers. This study indicates that iAs-exposure is associated with a significant and persistent impact on white matter tracts. Future research should explore preventative strategies for the protection from the detrimental health endpoints associated with prolonged iAs exposure.

Keywords: arsenic; demyelination; mitochondria
Área: 4-Desarrollo y Envejecimiento

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SMB

Autophagy induction reduces features of cellular senescence in the hippocampus of old rats.

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Aging is defined as a time-dependent loss of physiological function that increases the likelihood to die. Some of the molecular and cellular changes associated with aging are the loss of functional autophagy and the persistence of senescent cells. Autophagy, is an important mechanism involved in cellular homeostasis and their biological functions include starvation adaptation and the clearance of misfolded proteins and damaged organelles. On the other hand, cellular senescence is a phenotype characterized by a perdurable cell cycle arrest that functions for example as a tumor-suppresor mechanism. Even though there is no single marker of cellular senescence, those cells show several common features such as an increase of a lysosomal enzyme with β-galactosidase activity, expression of tumor suppressors like $p21^{CIP1/WAF1}$ and $p16^{INK4A}$, lipofuscin accumulation and nuclear envelop deformation, among others. Of most importance is the development of a senescence associated secretory phenotype (SASP). In *in vitro* studies, dysfunctional autophagy correlates with an increase of cellular senescence. In this work, we investigated if the loss of autophagy function during aging favors the establishment of cellular senescence in the brain. We observed that a dysfunctional autophagic flux in the hippocampus of old rats correlated with the presence of senescent cells. Interestingly, when we restored the autophagic flux in the hippocampus of old rats we observed a reduction in several markers of cellular senescence. A hippocampal-dependent learning and memory test was performed in order to evaluated if the induction of autophagy and the downregulation in the SASP components were able to improve cognitive performance. The results obtained will be discuss.

Key words: Autophagy, Senescence, Aging, Hippocampus

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Distribution of mitochondria in cells of Medial Nucleus of Trapezoid Body from rat.

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4. Development and Aging.

Introduction: Mitochondria is the primary energy source in the cell, across the ATP synthesis. This organelle has a significant association with high-efficiency synaptic regions, in particular, those related to sensorial processing, like the Medial Nucleus of Trapezoid Body (MNTB) synapsis, into the auditory brainstem. This nucleus has a specialized terminal (calyx of Held) with a lot of synaptic vesicles and associated mitochondrion as crucial energetic support. This information is knowing only in adulthood stage, in contrast with what could be happening in the ultrastructure previous to the ear opening, which occurs at postnatal day 13 (P13) in the rat. This stage includes relevant changes in the auditory circuit: apoptosis, cell proliferation, synaptogenesis, and calyx growing. ***Aim:*** This work aimed to describe the mitochondrial distribution in principal cells of the Medial Nucleus of Trapezoid Body previous the ear opening. ***Methods:*** Male rats (postnatal day 9, P9) were used for this work. Brains were fixed with paraformaldehyde (4%) for immunofluorescence assays, that were cut in coronal slices (40µm) that contained MNTB, incubated with Anti-ATP5a antibody [1:250]. Other brains (auditory brainstems) were dissected in 1 mm cubes of MNTB for Transmission Electron Microscopy (TEM) processing to obtain ultrathin sections (60–90 nm). Sections were contrasted with uranyl acetate (4%) and lead citrate (1%) for TEM observation. ***Results:*** Immunofluorescence assays shown a tubular network around the cellular nucleus and in the axonal cone of principal cells–like. This information was confirmed with TEM observations, that shown mitochondria close to the cellular nucleus and around the active zones (pre- and post– synapsis sites). Neuronal mitochondria had more cristae that glial mitochondria. ***Discussion:*** In the present work results shown mitochondria close to pre- and post– synapsis, that is different in contrast with posterior ages (>P13) reported previously, where mitochondria are close only to the presynaptic terminal, forming Mitochondria Associated Complexes (MACs), that were not seen yet in P9 stage. This distribution could be related to plastic processes that occur in MNTB, in particular, those about protein related to the development and strengthening of synapses. Posterior studies could relate with more precision the relevance of distribution of mitochondria with development of auditory brainstem across different stages of postnatal life. **Keywords:** *Mitochondria, MNTB, TEM.*

"Analysis of Expression of Single Exon Genes in the Mouse Embryonic Telencephalon"

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Area: Desarrollo y Envejecimiento

Eukaryotic genes without introns in their coding sequence are known as "single exon genes" (SEGs), in contrast to "multiple exon genes" (MEGs). Several SEGs have been demonstrated to be expressed in a tissue-specific manner mainly in brain and testis tissues, which raises questions about their origin, evolution, and function. Among SEGs, there are multiple genes encoding histones, G protein-coupled and olfactory receptors, transcription factors, and proteins involved in the regulation of development, growth, and proliferation. The aim of this work was to determine the occurrence, ontology, and differential expression of SEGs in the mouse telencephalon during embryonic development. Mouse SEG and MEG datasets were obtained from the Ensembl database according to their exon count and classified into two groups: 1) genes with more or equal to three exons were labeled as multi-exon genes (MEGs). 2) genes with one exon and one transcript count were labeled as SEGs. PFAM and SUPERFAMILY functional predictions showed that SEGs in the mouse genome are mainly transmembrane proteins including receptors of the seven transmembrane domain G protein-coupled receptor class, TAS2Rs (taste receptor proteins), vomeronasal receptors (receptors for pheromones), cadherins (class of type-1 transmembrane proteins), claudins (small transmembrane proteins), and adams cysteine rich. Datasets were examined for differential expression in the embryonic telencephalon in stages E9.5 and E10.5. This study revealed that up-regulated SEGs during telencephalic development are mainly HMG box domain transcription factors and protocadherins.

Keywords: *Intronless gene*, *telencephalon development, mouse genome*

Neuronal Senescence is promoted by Dysfunctional Autophagy

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Cellular senescence is a state of cell cycle arrest induced by different stimuli, including telomere shortening, reactive oxygen species, DNA damage, oncogene activation and developmental cues. In aging, senescent cells are not efficiently cleared by the immune system leading to their accumulation in old tissues, where they can modify the microenvironment, promote local inflammation and induce paracrine senescence, spreading the senescent phenotype along old tissues. Persistent senescent cells contribute to aging and age-related diseases; therefore, it is fundamental to understand the molecular mechanisms of cellular senescence establishment and maintenance. To date, most of the knowledge related to cellular senescence has been collected through the study of mitotic cells, and it has been theorized that post-mitotic cells are incapable of entering into a senescent state. Nevertheless, neurons with several senescent features have been observed in old mice and human brain, although the molecular mechanisms to induce neuronal senescence are unknown. Since alterations in autophagic flux have been observed during brain aging and neurodegenerative disorders, we hypothesized that autophagy dysfunction could contribute to neuronal senescence establishment.

In this study, we developed an *in vitro* model of neuronal senescence in long-term primary culture of rat cortical cells, in which we observed neurons with several senescence-related features, together with a deficient autophagic degradation noticed by the accumulation of autophagosomes and p62/SQTSM. In addition, we found that autophagy induction decreased the number of senescent neurons, whereas autophagy inhibition increased them, indicating autophagy dysfunction as a possible inductor of neuronal senescence.

Key words: Neurons; Autophagy; Cellular senescence; Aging

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Cortical Neurons from Human Embryonic Stem Cells Derived and Maintained on the Human Amniotic Epithelium

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Human embryonic stem cells (HESC) are derived from the epiblast and have a pluripotent potential (ability to differentiate into all the cell types that conform an organism). However, the conventional culture of HESC using a feeder layer of mouse embryonic fibroblasts (MEF) for their derivation and maintenance has several drawbacks, including the risk of xeno-contamination. Also, it has been suggested that the culture of HESC in this standard condition is an artifact and does not correspond to the *in vitro* counterpart of the epiblast during human embryonic development. Besides, our previous studies demonstrated the use of an alternative feeder layer of human amniotic epithelial cells (HAEC) to derive and maintain HESC. In recent years, different research groups have demonstrated that HAEC are specified from the epiblast before implantation, so the culture of HESC on HAEC could represent a different pluripotent stage, being more suitable to recapitulate development early processes, such as neural induction and formation of cortical layers of the forebrain. Here, we differentiated HESC on HAEC or standard conditions (on MEF) to derive cortical neurons. For neural induction, we used a dual SMAD signaling inhibition protocol during 12 days (D12); subsequently, the cells were detached and cultured in N2B27 medium. At the end of the neural induction stage, we found neural rosettes constituted by $SOX2^+/PAX6^+$ and $NESTIN^+$ neural stem cells (NSC). From D16 to D30, the first $TUJ1^+$ immature and $MAP2^+$ mature neurons were detected. Later, the cortical phenotypes of deep layers were identified at D40 using the specific markers CTIP2 and FOXP2; while from D50, $GAD67^+$ and $CALRETININ^+$ interneurons emerged. Interestingly, there was an increase in all the neural markers evaluated when HESC were induced to form neural lineage under the condition of HAEC as feeder layer, in contrast when were maintained on MEF. These data suggest that HESC maintained on the alternative feeder layer of HAEC are able to derive NSC and differentiate towards cortical neuronal phenotypes. GRANTS: INPER 212250-3230-21214-01-16, CONACYT 272968.

Area: 4. Development and aging

Key words: human embryonic stem cells, neural induction, human cortical neurons.

Oseltamivir and Bezafibrate Induce Synergic Effect Decreasing Oxidative Damage in Rat Brain Regions

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Abstract

Background. Oseltamivir alter dopamine brain levels and Bezafibrate treatment is associated with neuroprotection. Bezafibrate significant risk reduction among coronary heart disease patients with elevated triglyceride levels that substantially reduced their triglyceride level with treatment, and the combination of both remain unknown. The aim of this study was to measure the effect of oseltamivir mixed with bezafibrate on biogenic amines and some oxidative biomarkers in brain regions of young rats. Methods. Male young Wistar rats grouped in 6 each, were treated as follow: group 1, NaCl 0.9%, (controls); group 2, oseltamivir (100 mg/kg); group 3, single dose of bezafibrate (150 mg/kg) (beza-1); group 4, four dose of bezafibrate (beza-4); group 5, single dose of bezafibrate + oseltamivir (beza + oselta-1) and group 6, four doses of bezafibrate + oseltamivir (beza + oselta-4). Drugs were given orally. Fresh blood was collected to measure triglycerides. Their brain was extracted and dissected in regions to measure the dopamine, 5-HIAA, GSH, H_2O_2 using fluorimetry and spectrophotometry methods.

Results. Dopamine concentrations decreased significantly in animal groups treated with the combination of oseltamivir and bezafibrate in cerebellum/medulla oblongata region. The levels of 5-HIAA, GSH and lipoperoxidation in the three regions were significantly less in the group that received only oseltamivir. H_2O_2 levels in the cortex of the group that was treated with only oseltamivir were significantly less.

Conclusion. In animals with hypo-triglyceridemia, the consumption of oseltamivir in single or repeated doses induces synergic changes in dopaminergic and serotonergic receptors and at the same time, provokes antioxidant effect in the brain.

Keywords: Bezafibrate, oxidative damage, oseltamivir.

Systemic administration of fractalkine affects hippocampal neurogenesis and induces depression like-behavior in female Balb/C mice

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Abstract

Adult hippocampal neurogenesis is regulated by several factors and its alteration has been involved in some neuropsychiatric disorders such as depression. Interestingly, recent studies have pointed to the direction of a relevant regulation of neurogenesis by systemic millieu. In this regard, some peripheral factors have shown deleterious effects on learnging and memory processes but also affect the generation of new neurons in the dentate gyrus. In addition, recent studies have revealed a relevant role of microglia on the generation of new neurons. Morevoer, microglia favor or affect the generation of new neurons depending on the cytokine profile or on its capability to sense the signal of soluble factors such as fractalkine (Cx3cl1). The receptor of this chemokine is important to control microglia and at least one study have shown alterations in the concentration of fractlakine in antenatal depression. Cx3cr1 knockout mice have shown that rodents may resist to the effects of stressful situations. However, it is not known whether systemic administration of fracktalkine can cause affectations at the behavioral level and on the neurogenic niche of the dentate gyrus in the hippocampus. Based on the above-mentioned antecedents, in this study we analyzed the effects of one single or seven administrations performed during 14 days of fracktalkine on depression-like behavior, on the number and morphology of dendrite spines of granule cells, cell proliferation, survival and on the intermediate stages of neuronal development. In addition, we analyzed the morphological changes of microglia cells and protein levels of some phosphoproteins were also analyzed. Two hours after the behavioral test, mice were sacrificed to dissect out the brain. Brains were used for immunohistochemistry to identify some protein markers involved in the hippocampal neurogenic process (proliferation, Ki67; proliferation or survival, BrdU; intermediate stages of neuronal development, doublecortin (DCX)). Also, we analyzed the morphological changes of microglial cells (Iba-1). In addition, we analyzed the hippocampal neuronal activation identifying ARC expression. Moreover, fracktalkine levels in serum of control, chronic mild stress with or without treatment with antidepressant drugs, acute stress alone or after ENR interventation. Also the levels of fracktalkine were determined in serum of depression diagnosed patients. Results were analyzed with one- or two- way ANOVA followed by the appropriate post-hoc test. The data indicate that fractalkine affects hippocampal neurogenesis, microglia morphology and induces depression-like effects. Finally, fracktalkine quantifiaction was also performed in serum of depression diagnosed patients and the results will be discussed.

Palabras clave: depression, glia, neurogenesis.

Area: Estrés

The fascinating effects of music on the brain

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Área: Divulgación

Abstract

The brain has been the most fascinating and mysterious organ, particularly the human brain, which has achieved the greatest functionality of this organ. Around the brain, the biggest problem at the present is the appearance of neurodegenerative events; although since we have managed to overcome early mortality and live longer, this has led us to observe more frequently various types of degenerative diseases, including neurodegenerative ones; also the current lifestyle, which not only surrounds us with environmental stressors, but in addition to toxic elements of the diet and environment, many of these with potential carcinogens or inducers of degenerative events, substrate for the appearance of chronic-degenerative diseases and cancer. Moreover, the current technological circumstances and sedentarism complicate the lifestyle and promote neurodegeneration.

In the search for elements that stop the progression of the inevitable neurodegeneration, or even reverse its effects by giving us better quality of life, at the same time as more years in good physical and intellectual conditions, have been analyzed various activities to which one can be exposed, and which could exert the beneficial effects of recovery from neurodegeneration, its slowing down or reversal. Although there are several activities that promote brain activity, music still has the most beneficial effects. Whether singing, listening to music, dancing, the effects on the brain and body are amazing. But executing a musical instrument offers greater advantages of neuroplasticity.

In this work we analyze the effects of music in all its forms, mainly when playing a musical instrument, on the brain and the body in general.

Key words: Music, neuroplasticity, brain

Evaluation of glial cells at the hippocampus of brain autistic-like mice C58/J.

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Area: Glia

Autism spectrum disorder (ASD) is a neurodevelopment disorder characterized by deficient social interaction, impaired communication as well as repetitive behaviors. Although the etiology of ASD remains unclear, increasing evidence indicates that astrocytes and microglial cells, which play a major role in synapse maturation, function and removal are deregulated in ASD, which could directly contribute to the pathophysiology of the disease. The formation of synapses and the modulation of synaptic activity and plasticity by astrocytes mainly take place as a result of the secretion of neuroactive substances, known as synaptogenic factors, such as throbospondin1-5, among others. Recent findings from our laboratory showed reduced content of TSP-1 protein in prefrontal cortex and hippocampus in the brain autistic-like mice C58/J, but not in the GFAP level, compared to wild type. C58/J inbred mouse strain has been used as an ASD animal model due to the high similarity between its behavior and that of people with ASD. Further, C58/J strain shows some genetic variants also present in ASD patients. Due to the importance of glial cells in autism we decided to evaluate the characteristics of glial populations (astrocytes and microglia) at the hippocampus of C58/J mice. Our data show that number of astrocytes (defined as GFAP+ cells) per area, as well as, mean fluorescence intensity of GFAP is reduced at CA1 hippocampus region, in 10-week-old autistic-like mice C58/J compared to wild type counterparts (C57BL/6). These findings could be related to changes in synapsis maturation and function within the hippocampus, which is an area involved in learning and memory formation. Nevertheless, it is necessary to evaluate also the microglial population within the same area, as well as the activation state of glial cells, in order to obtain a better understanding of these findings.

Key words: Autism spectrum disorder, Astrocytes, Hippocampus.

Modulation of the response to an obesogenic diet by the astrocytic molecular clock

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Áreas: Glia, Metabolismo.

The circadian clock is an endogenous timekeeping mechanism that allows organisms to synchronize their behavior and physiology to the cyclically changing conditions in the environment (i.e. day/night). The master clock in mammals is the suprachiasmatic nucleus in the hypothalamus, which communicates time-of-day information to other thalamic and hypothalamic brain regions. Temporal information is then spread to peripheral organs through synaptic and/or hormonal signals. Although the physiological processes involved in metabolism generally follow the endogenous circadian clock, some peripheral organs can also be synchronized to certain stimuli, for instance to food. The reciprocal influence between the circadian system and metabolism is further evidenced by the disruption of rhythmic patterns of feeding and energy expenditure by conditions such as obesity induced by a high fat diet (HFD). Furthermore, diet induced obesity (DIO) deeply affects the circadian transcriptome of tissues of metabolic importance, such as the liver.

Recently, glial cells in the central nervous system have been reported to be involved in systemic metabolic processes. Specifically, hypothalamic astrocytes express receptors to hormones related to food consumption and glucose regulation (leptin, ghrelin, insulin). Activation of hypothalamic astrocytes can also modulate feeding behavior. Additionally, signaling pathways in astrocytes related to inflammation seem to have a role in regulating weight gain in DIO paradigms.

To investigate the role of the astrocytic molecular clock in the response to a high fat diet, we used mice with a conditional deletion in astrocytes of *Bmal1*, a gene without which the molecular clock cannot function (*Bmal1* cKO). Preliminary results show that *Bmal1* cKO mice gain less weight when fed a HFD, compared to wild-type animals. Also, the deletion of the molecular clock in astrocytes under these conditions affects the circadian variation in body temperature, and glucose tolerance. We are currently exploring the mechanisms for these phenotypes, focusing on the potential role of astrocytes in regulating neuronal activity in hypothalamic nuclei in response to hormones of metabolic relevance, as well as on inflammation-relevant signaling pathways in the brain.

Key words: metabolism, circadian clock, astrocytes

Combined early life stress and neonatal lipopolysaccharide affect hippocampal glial cells and induce long term behavioral alterations

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Early life stress induces an immediate increase of the activation of glial cells and results in depressive behavior in adulthood. Severe infections at an early age also increase the activation of glial cells and could contribute to the development of depression and anxiety. Here we analyzed the long-term effects of a neonatal stress-immune challenge on the neuroimmune system of the hippocampus and on the emotional behavior. Four groups of male rats (Sprague Dawley) were used: 1) control group + vehicle, 2) control group + Lipopolysaccharide (LPS, 0.5mg / kg), 3) maternal separation group (MS, 3 h/day postnatal days (PN) 1 to 14 + vehicle, 4) group MS + LPS. LPS was administered at PN14. The animals remained undisturbed until the start of the behavioral tests on PN120. The emotional state of the animals was analyzed with the elevated plus maze, open field and forced swimming tests. Immediately after the behavioral tests the rats were sacrificed and the brains were collected and cut in 40 µm sections to perform immunohistochemistry. We observed the MS-vehicle and MS-LPS male rats showed depressive - like behavior in the forced swimming test as they displayed a greater immobility time and a lower latency than the other groups. The Control-LPS and MS-LPS groups performed less time and a lower percentage of entrances to the center of the open field indicating an anxious like behavior. In the elevated plus maze we observed a lower percentage of time and few entrance open arm. On the other hand, we observed an increase in the cellular density of astrocytes only in the group Cont-LPS probably related to reactive astrogliosis, the microglia did not present changes in the density but we observed an increase in the activation in the following groups Cont – LPS and MS -LPS in the hippocampal CA3 region. Exposure to LPS and early MS leads to long - term alterations in the neuroimmune system and emotionality.

Key words: emotional behavior, early life adversity, microglia

Sucralose increases levels of oxidative stress in the brain of C57BL6 mice

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Abstract: Low-calorie or artificial sweeteners are defined as a diverse chemical group with high sweetening power, which improve the flavor and palatability of foods (Pepino, 2015). The response after the ingestion of these sweeteners is carried out through the ventral tegmental area connected to the hypothalamus and other areas of the limbic system (amygdala, nucleus accumbens) are important parts of the mesolimbic pathway involved in the hedonic response, both areas generate signals homeostases that respond to glucose the main energy substrate for the brain (Opstal *et al.,* 2018). Previous studies indicate that the intake of sweeteners such as aspartame for long periods cause a direct impact on the hedonic response increasing its intake and therefore an imbalance of the antioxidant mechanism carried out in the brain thanks to the production of reactive oxygen species (ROS) originating in substrates proper to metabolism, which leads to various neurological diseases (Abhilash *et al.,* 2012, Onaolapo *et al.,* 2016). The aim of this study was to evaluate the level of oxidized lipids and carbonyls in the brain of mice fed with a diet supplemented with artificial sweeteners. Twelve mice of strain C57BL / 6 were divided into 3 treatment groups (T1 sucrose, T2 stevia and T3 sucralose) during 8 weeks, water and food were administered *ad libitum*. Then, cervical dislocation was applied and the brain was collected. The levels of species reactive to thiobarbituric acid (TBARS) (Sinha et al., 2001) and carbonyls (Levine et al., 1990) were evaluated. All the data were analyzed using one-way ANOVA with Tukey's poshoc and p values of <0.05. In T3 (1517.96 ± 38.9 nmol / mg of protein) TBARS levels were increased compared to T2 and T1 (148.11 ± 12.1, 66.69 ± 8.1 respectively, p <0.05). In the same way, the levels of carbonyls increased statistically significantly in the brain of the T3 (53643.55 ± 231.6 ng / mg of protein) compared to those of T1 and T2 (38285.47 ± 195.6, 2625.79 ± 51.2 Interestingly, between both treatments 1 and 2 a difference was observed in lipid levels (148.11 ± 12.1, 66.69 ± 8.1p <0.05) and at carbonyls levels (38285.47 ± 195.6, 2625.79 ± 51.2 nmol / mg of protein p <0.05) Our results show an increase of oxidative damage in the brain of mice by the administration of sucralose compared to mice supplemented with sucrose and stevia. The possible mechanism that creates this imbalance can be explained due to the high food intake with artificial sweeteners conditioned by the reward response, increasing metabolites that cause neurological damage.

Key words: oxidative damage, artificial sweeteners, brain.

NEUROPROTECTOR EFFECT OF NICOTINAMIDE VIA COLINERGIC IN A MODEL OF COGNITIVE DEFICIT-INDUCED BY HYPERCALORIC DIET IN RATS

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Area: Metabolism

Abstract. Excessive consumption of saturated fats and simple sugars is associated with learning and memory functions impairment, both dependent on the integrity of the hippocampus. This type of diet can produce several neurophysiological changes including neuroinflammation. High production of TNF α and IL-1 β can impair the metabolic pathways responsible for neural homeostasis. In this context, acetylcholine, the main parasympathetic neurotransmitter and inflammation regulator could be crucial. Acetylcholine is hydrolyzed by acetylcholinesterase and butyrylcholinesterase (AChE and BChE, respectively). Changes of these cholinesterases by the diet, maintains their functionality hydrolyzing to acetylcholine and increasing the inflammation. The use of vitamins as adjuvants to treat inflammatory diseases has increased. Nicotinamide is a vitamin that exerts antioxidant and anti-inflammatory effects. This study evaluated the cholinergic activity associated with antioxidant and anti-inflammatory effect of nicotinamide (NAM) in a model of cognitive deficit-induced by hypercaloric diet in rats.

Methods. Thirty animals were distributed into 6 groups and subjected to the following treatments: 1) Control; 2) High fat+sucrose (HFS; 18 % and 40%, respectively); 3) HFS+NAM 5mM; 4) HFS+NAM 10 mM; 5) HFS+NAM 15 mM for 12 weeks *ad libitum*. Cholinesterases activities, GSH and MDA levels; as well as Morris test were evaluated.

Results. The results showed that cognitive deficit induced by HFS consumption was associated with increased hippocampus AChE activity and MDA contents along with diminished GSH levels. NAM reduces cognitive deficit through the regulation of AChE activity by increasing GSH levels and decreasing MDA.

Conclusion. Therefore NAM is proposed as a good neuroprotector.

Keywords. Cognitive deficit, cholinesterases, nicotinamide.

Fasting regulates markers of activity of thyrotropin-releasing hormone neurons in the dorsomedial nucleus and lateral hypothalamus of adult rats. Sex similarities and differences

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Energy homeostasis clues control brain circuits involved in counterregulatory responses which include feeding. Although these circuits have been extensively mapped, there are still many unknown. For example, thyrotropin-releasing hormone (TRH) is a potent anorexic peptide whose mode of action is not yet fully understood. TRH neurons are present in various hypothalamic nuclei involved in energy homeostasis. A large group of TRH neurons is present in the dorsomedial nucleus of the hypothalamus (DMN), a nucleus fundamental for coordinating food entrainment of circadian rhythms and daily levels of feeding. About a third of the DMN neurons that project to the lateral hypothalamus (LH) express TRH. TRH type 1 receptors (TRH-R1) are expressed abundantly in the LH, but their precise distribution and functional relevance is not fully understood. However, based on in vitro studies it was suggested that DMN TRH neurons innervate and stimulate LH GABAergic neurons that are up-stream of LH MCH neurons, a peptide that promotes food intake. It was proposed that TRH effect on MCH neurons may account for its anorexic effect, but the relationship between DMN TRH neurons and sensing of energy clues is unsettled. To investigate whether energy cues control TRH neurons of the DMN, and sex-dependency, we probed in adult Wistar rats the effect of fasting (and refeeding) on the levels of proxies (TRH, TRH-R1 mRNA levels) of the activity of TRH neurons at soma and projection field levels and the distribution of TRH-R1 positive cells along the rostro-caudal extent of the LH. We observed that fasting induced a down regulation of DMH TRH mRNA levels in both sexes and in the LH an increase in TRH-R1 expression in male rats. TRH-R1 positive cells were distributed along the rostro-caudal extent of the LH, with a larger number per section in the anterior and medium peduncular zone than in the tuberal zone. In the posterior part of the LH TRH-R1 positive cell numbers were similar in the peduncular, tuberal and perifornical area. In conclusion, in male rats in both the DMN and LH the expression of biochemical markers of the activity of TRH neurons is altered by fasting. The data are consistent with the hypothesis that a TRH projection from the DMN into the LH is down regulated during fasting in male animals. This may lead to a reduction of the anorectic signal of TRH, facilitating downstream activities related to food seeking. In female animals we detected a similar response in the DMN, but not in the LH, suggesting that in female rats the DMN TRHergic projection into the LH is functionally distinct from that in male rats.

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Key words: dorsomedial nucleus, TRH, hypothalamus, fast, TRH-R1, lateral hypothalamus

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Central estradiol protects the female brain against sleep loss related changes in blood-brain barrier function

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Introduction. The maintenance of the blood-brain barrier is crucial to guarantee the homeostasis of the central nervous system. In previous experiments it has been shown that chronic sleep loss in male rats increases the permeability of the blood-brain barrier, by increasing the density of pinocytic vesicles in hippocampal endothelial cells and decreasing the tight junction protein expression. It has been found that in female rats, estrogen acts as protective agent in brain injury and stroke. In the case of the blood-brain barrier it is known that decrease of estradiol levels increases the permeability of the blood-brain barrier and the restitution of physiological levels recover the normal permeability. In female rats our previous data shown that chronic sleep loss did not modify the function of the blood-brain barrier, hence, in the present study we look to characterize the role of estrogens in the protection of the blood-brain barrier during chronic sleep loss in female rats.
Objective. To characterize the regulatory role of estrogens in the permeability of the blood-brain barrier during sleep loss in female rats.
Method. 3-month-old female Wistar rats were used. The control group slept *ad libitum* and the experimental group was sleep restricted (SR) during 20h for 10d using the multiple platform technique. *Experiment 1.* Effect of peripheral estrogen loss on blood-brain barrier function during sleep loss, the groups included virgin female controls (Ctrl and SR) and ovariectomized (OVX-Ctrl and OVX+SR, n=4 per group). Ovariectomy was performed 30d before blood-brain barrier permeability assays. *Experiment 2.* Effects of unspecific estradiol receptor antagonism on blood-brain barrier function during SR, groups included were Tamoxifen (Tam) or vehicle (Veh) treated female rats (Veh, Tam, Veh+SR, Tam+SR, n=4 per group). Tamoxifen was subcutaneously administered (1mg/Kg) 4d before blood-brain barrier permeability assay. *Experiment 3.* Effect of selective antagonism of alpha estradiol receptors on blood-brain barrier function, groups included were MPP or vehicle treated female rats (Veh, MPP, Veh+SR, MPP+SR, n=4 per group). MPP was subcutaneously administered for 10d (1ml/kg). *Experiment 4.* Effect of selective antagonism of beta estradiol receptors on blood-brain barrier function during SR, groups included were HTPP or vehicle treated (Veh, HTPP, Veh+SR, HTPP+SR, n=4 per group). HTPP was subcutaneously administered 4d before blood-brain barrier permeability assay. After 10 days of SR blood-brain barrier permeability assays were performed with a cocktail (0.2ml/100g body weight) containing Na-Fluorescein (10 mg/ml PBS) and Evans blue (1mg/ml PBS). Tracer concentration was quantified in cerebral cortex, hippocampus, cerebellum and basal nuclei.
Results. Intact females were resistant to SR-induced blood-brain barrier hyperpermeability. OVX did not change blood-brain barrier permeability to Na-fluorescein or Evans blue under basal and SR conditions in any of the studied brain regions. Neither tamoxifen nor selective antagonism of alpha estradiol receptors seemed to modify blood-brain barrier permeability in SR females. However, in sleep restricted females the selective antagonism of beta estradiol receptors increased the blood-brain barrier permeability to Na-Fluorescein in the cerebral cortex and basal nuclei and increased the permeability to Evans blue in basal nuclei.
Conclusion. Previous data suggested that female sex hormones play an important role in regulating blood-brain barrier permeability. Here we show that the loss of peripheral estradiol did not modify blood-brain barrier function during SR, but it seems that central estradiol is playing an important role in regulating blood-brain barrier function with a highly selective regional pattern. Our current data show that only beta estradiol receptors play an important role on the function of the blood-brain barrier during chronic sleep loss, suggesting that neurosteroids might be exerting a protective effect only in some brain regions.
Key words: blood-brain barrier, female rats, estrogen.
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Functional Electroencephalographic Connectivity and its Relationship with Hormones in Premenopause and Early Postmenopause.

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Post-menopause is the stage in a woman´s life in which her hormone levels decrease causing changes in her entire body, specifically her brain. Estrogens have shown to be one of the most significant hormones to influence these changes. Women were studied in postmenopause compared to women in premenopause in their ovulatory period specifically, because during this phase their estrogen levels are at their highest peak. A hormonal measurement was made for estrogen in this study. The electrical activity in their brains was recorded using electroencephalograms, each group measured held 13 women between the ages of 40 and 60 years old and every EEG was done with eyes closed condition. The frequency bands considered during this analisis were: Delta, Theta, Alpha1, Alpha2, Beta1 y Beta2. Graph theory was used to evaluate brain connectivity. Postmenopausic women showed an increased potencial of the Theta, Alpha2 and Beta 1 bands in frontal, central and temporal brain regions. In brain connectivity, postmenopausic groups showed a more global, local efficiency, and clustering coeficient for the bands Alpha 1, Alpha 2, Beta 1 and Beta 2. These analisis explain that postmenopause women compared to premenopause women have better functional connectivity in fast frequency bands, which is explained as a compensatory mecanism towards a posible brain disconnection.

Estrogens have been shown to be capable of producing structural and functional changes in the brain, by increasing the amount of dendritic spines and the amount of excitatory synapses. This could be verified by linking hormone levels with EEG activity. A significant difference was obtained between the level of estrogen and the power of the delta band in the frontal region ($r = -0.648$ $p = 0.023$) and in the temporal region ($r = -0.653$ $p = 0.021$) for the postmenopausal group. In contrast, a positive correlation of estrogens was obtained in the premenopausal group with the theta band in the frontal region ($r = 0.627$ $p = 0.029$) and in the central region ($r = 0.620$ $p = 0.032$). These results reflect the direct impact of estrogen in regions responsible for emotional and cognitive processing.

Keywords: Menopause, Electrophysiology, Estrogens.

Neuro-immuno-endocrine changes induced by high- fat diet are associated with increased anxiety- like behavior in Wistar rats

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Obesity is an entity present in around the world and it is related on developing several metabolic disorders such as diabetes type II, metabolic syndrome, among others. Furthermore, these illnesses aforementioned become a risk factor to cardiovascular diseases. Although exist a wide variety of risk factors that are involving obesity. Has been described that genetic susceptibility and socioeconomic factors may play an important role to elicit obesity or overweight. For another hand, endocrine and neural mechanisms which are involving on modulating food intake. Accordingly, it has known that high energy content meals impairs neural and endocrine mechanisms that underlie to energetic balance in some animal species, particularly in humans and rodents. Thus, an imbalance on the endocrine and neural mechanisms that give arise obesity state.

Meanwhile, leptin and insulin signaling into hypothalamus keeps on adequate energetic balance, an increment on adiposity is displayed when leptin and insulin signaling is deficient. Then, obesity is a chronic state of inflammation in which pro-inflammatory cytokines are released. Furthermore, there has been evidence that implicates these molecules evoking a dysregulation on the HPA axis. Therefore, states related to anxiety or stress are linked to pro-inflammatory chronic states such as obesity due to HPA imbalance. Accordingly, the main aim of this work is to indicate whether high-fat diet induces obesity in Wistar male rats and these animals displaying an increase in anxiety-like behaviors after underwent to animal models of unconditioned anxiety. Moreover, we will search for an increment on pro-inflammatory cytokines as well as an increment on metabolic parameters such as glucose levels, ghrelin, blood pressure, whereas, leptin and insulin levels will be decreased.

Preliminary results

To date, animals that underwent to a high-fat diet has been displayed an increase on body weight, glucose levels, blood pressure in contrast with group control, meanwhile in behavioral parameters the animals that underwent to a high-fat diet, exhibited more anxiety-like behaviors in shock probe burying test and elevated plus maze when compare with control group.

Key Words: Obesity, anxiety, neuroimmunoendocrinology.

Sexual motivation is diminished in diabetic female rat.

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Diabetes Mellitus (DM) has been associated with different diseases including sexual dysfunctions, including the decrease in sexual desire. The most popular animal model used to analyze the alterations present in DM is the streptozotocin (STZ)-induced diabetes that resembles some of the signs observed in type 1 diabetes mellitus (DM1) such as hypoinsulinemia and severe hyperglycemia. In preclinical studies it has been reported that females treated with STZ present alterations in the estrous cycle, a reduction in sexual receptivity (consummatory behavior), an increase in aggressiveness, and these effects are restored when insulin is exogenously administered. However, the motivational component of copula (considered as an equivalent to desire in humans) in hyperglycemic rats has not been fully studied. The aim of this work was to evaluate female sexual motivation (FSM) in a model of DM1 in two paradigms: the partner preference (PP) and the incentive sexual motivation (ISM). We injected STZ (i.p. 50 mg / kg in two consecutive days) to ovariectomized adult Wistar rats, 10 days after STZ injection, the females were administered with estradiol benzoate (10 µg, -24 h) and progesterone (3 mg, -4 h) and tested for sexual motivation in PP and ISM (in both a castrated male and a sexually experienced male were used as stimuli). For the insulin restitution experiment, STZ-treated animals were administered with a long-acting insulin analogue (glargine) every 12 hours for 10 days (2-4U). Body weight was recorded at the beginning and at the end of the study and glucose levels were also reported (only animals with blood glucose values ≥ 350 mg/dl were considered for the study). For PP we registered the time in each compartment and the time of interaction with each stimulus, in the ISM test, we calculated the time that the female stays in each incentive zone and the time the female invests sniffing the wall that isolates the stimuli. The hyperglycemic animals lost body weight and stayed the same amount of time with the castrated and the sexually experienced male (PP test) compared to the control group that stays longer with the sexually expert male. Similarly, in the ISM arena, the control females spent more time in sexual incentive zone, while those treated with STZ remained the same amount of time near to both stimuli; however, there was no difference between STZ and control females in the time spent sniffing the wall that isolated the stimuli. All these changes (in PP and ISM) were reversed with insulin to values comparable to those of the control group. Our data suggest that severe hyperglycemia decreases FSM and that insulin fully recovers such diminution.

Key Words: sexual motivation, diabetes, female rat, insulin

"Effects of progesterone on the expression profile of miRNAs in human glioblastoma cells"

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Area: Neuroendocrinology

Glioblastomas (GBM) are the most frequent and malignant cerebral neoplasms. We have identified progesterone (P4) as one of the factors associated with the development and evolution of GBM. P4 modifies the expression of genes that promote proliferation, growth, and tumor infiltration. This effect could be mediated through microRNAs (miRNAs), small molecules of non-coding RNA that regulates gene expression at post-transcriptional level.

We treated U251 cells derived from human GBM, for 6 h with P4 (10 nM), RU486 (10 μM), an antagonist of progesterone receptor, and a combined treatment (P4+RU486); then we conducted a microarray analysis, as well as a differential expression analysis to identify a set of miRNAs regulated by P4 and RU486.

Finally, we validated a pair of deregulated miRNAs in GBM: hsa-miR-1244 and hsa-miR-4485. We found that P4 regulates the expression of miRNAs in human GBM cells.

Palabras Clave: miRNA, progesterone, glioblastoma.

Evaluation of the proteomic profile of brain´s mouse by the effect of pharmacological regulatory compounds of cholecystokinin as a therapeutic alternative against overweight and obesity.

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Cholecystokinin (CCK) was discovered in 1928 in jejunal extracts as a factor for contraction of the gallbladder. It was later shown to be a member of a family of peptides, which are all ligands for the CCK_1 and CCK_2 receptors. It is known that CCK peptides are synthesized in the intestinal endocrine cells and in some cerebral neurons. But in addition, CCK is expressed in several endocrine glands (pituitary cells, thyroid cells, pancreatic islets, adrenal glands and testes), peripheral nerves, cells of the immune system, among others.

One of the functions of the CCK peptides is to stimulate the secretion of pancreatic enzymes, contraction of the gall bladder, intestinal motility, satiety and decrease of the secretion of acids in the stomach.

The CCK peptides also stimulate the secretion of calcitonin, insulin and glucagon, in addition, they can act as natriuretic peptides in the kidneys. The CCK peptides are derived from Pro-CCK with a sequence of YMGWMDF bioactive amide at the C-terminus, in which the Y (tyrosine) residue is sulfated. Plasma forms are CCK-58, -33, -22 and -8, while small CCK-8 and -5 are potent neurotransmitters.

In our laboratory we are developing a new drug that can regulate the functions of the CCK, in this work I present the analysis of the proteomic profile in the brain´s mouse and propose the change of expression of hormones or peptides that are generated when using this compound. When used as a therapeutic alternative against overweight and obesity in a murine model of obesity, in which results were obtained in the reduction of body weight and hypoglycemic.

Overweight and obesity drug, cholecystokinin

Transcriptional networks induced by prolactin in the hippocampus

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Prolactin (Prl) is a pleiotropic hormone with multiple functions in several tissues and organs, including the brain. In the hippocampus, Prl has been implicated in several functions including neuroprotection against excitotoxicity in vivo and in vitro studies. However, the molecular mechanisms involved in Prl actions in the hippocampus have not been completely elucidated. The aim of this study was to determine the hippocampal transcriptional network of female Prl treated ovariectomized rats. Transcriptomic analysis by RNASeq revealed 162 differentially expressed genes throughout 24 h of Prl treatment. Gene ontology analysis of those genes showed that 37.65% were involved in brain processes that are regulated by the hippocampus, such as learning, memory and behavior, and new processes that we did not foresee, such as glial differentiation, axogenesis, synaptic transmission, postsynaptic potential, neuronal and glial migration. Immunodetection analysis demonstrated that Prl significantly modified microglia morphology and diminution in the expression of Cd11b/c microglia activation protein, as well as the content and location of different neuronal proteins: Tau, Map2 and Syp, involved in axogenic and synaptic functions. This novel delineation of Prl activities in the hippocampus highlights its importance as a neuroactive hormone and opens a new avenue for the understanding of its actions, and supports its participation in neuronal plasticity of this brain area.

Area: Neuroendocrinology

Keywords: Prolactin, transcriptome, microglia.

Effects of clonidine and oxytocin in the modulation of anxiety in rat

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Anxiety, is an adaptative response that prepare an individual to contend a potential threat, when this response is disproportionate to the stimulus that is causing it or appears without apparent cause, then this response is consider to become pathological. The amygdala is a key structure for the modulation of anxiety and within it, both alpha-2 adrenoceptors and oxitocinergic receptors, play an important role in the modulation of anxiety. Given that, these receptors can be found close from each other in the central amygdala, it is possible that an interaction between both receptors exists and this interaction may cause an increase anxiolytic effects.
The main aim of this study is search to the existence of the interaction between oxitocinergic receptors and alpha 2 adrenoreceptors within the amygdala in rat. Then, through bilateral microinjections within the central amygdala of clonidine (adrenergic agonist α-2) and oxytocin (OT), we define effective dose and sub-threshold doses of both agonists, these doses was test in the elevated plus-maze (EPM), this test is employing to evaluate anxiety. Our results show that 1.2 µg clonidine increased the time spent in the open arms in elevated plus-maze. While,10 ng OT showed tendency to increase the time spent in the open arms in EPM. Alpha-2 adrenoreceptor activation had anxiolytic effects in elevated plus-maze, nevertheless, oxcitocinergic receptor activation seems elicit no anxiolytic effects. In accordance with our results, we will apply jointly sub-threshold doses of both agonists to examine the possible existence of an interaction between oxitocinergic receptors and α-2 adrenoreceptors, and this interaction is involving to increase the anxiolytic effects both receptors displayed.

To date, we studied the possible interaction with sub-optimal doses of both agonists (0.3 ng oxytocin + 0.5 µg clonidine, 10 ng oxytocin + 1.0 µg clonidine) Unfortunately, it was not observed anxiolytic effects when we employed these doses. However, in another sets of experiments there was a tendency to decrease anxiolytic effects of clonidine in presence of oxytocin antagonist, suggesting that anxiolytic effects evoked by clonidine maybe are related to facillitatory interaction with oxytocin receptors.

Key words: Clonidine, oxytocin, anxiety

The combination of fluoxetine-tramadol inhibits generalized seizures caused by pentylenetetrazole

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Area of work: Neuropharmacology

In several animal models of epilepsy an increase or decrease in serotonergic neurotransmission can generate or block seizures. The combination of Fluoxetine-Tramadol raises the levels of serotonin (5-HT). It has also been reported Fluoxetine and Tramadol have both pro-convulsant or anticonvulsant activity in several experimental models of epilepsy. In this study we assessed the effect of the combination of Fluoxetine plus Tramadol on the Generalized Tonic-Clonic Seizures (GTCSs) induced by Pentylenetetrazole (PTZ) in the rat. Male Wistar rats of 250-280g were treated with: Vehicle (0.9% NaCl solution), Fluoxetine (20 mg kg^{-1}), Tramadol (10 mg kg^{-1}) and Fluoxetine plus Tramadol (20-10 mg kg^{-1}) ip. One hour later, PTZ (70 mg kg^{-1} i.p.) was administered. We evaluated the latency to the first shake, GTCSs protection against GTCSs and the percentage of survival. In some animals, electrodes were implanted in the motor cortex to obtain electroencephalographic recordings. With vehicle administration, the latency at the first shake was 0.97 ± 0.03 minutes, 100% of the animals presented GTCSs and 0% survived. Fluoxetine significantly delayed latency to the first shake. The Fluoxetine-Tramadol combination also produced a significant delay at the first shake 38.57 ± 15.70 minutes ($p = 0.038$). This same combination inhibited 83.3% of GTCSs ($p = 0.02$) and increased survival to 100% ($p = 0.002$). These results indicate that the combination of Fluoxetine-Tramadol was able to reduce the seizures induced with PTZ. This effect was produced by a synergistic effect probably due to an increase in the cerebral concentrations of 5-HT to activate the receptors 5-HT1A and 5-HT2A located in GABAergic neurons.

Keywords: Fluoxetine; Tramadol; Pentylenetetrazol

"Exosomes of depression diagnosed-patients as a source of potential biomarkers"

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ABSTRAC

Major Depressive Disorder (MDD) is one of the most common and debilitating mental disorders around the world. This neuropsychiatric disorder has traditionally been considered to have a neurochemical basis or hypothalamic-pituitary-adrenal (HPA) axis abnormality involved in chronic stress, inflammation, reduced neuroplasticity, among other. However, its etiology remains unclear. Interestingly, recent hypothesis has pointed to the direction of a possible role of peripheral components on depression. In this regard, exosomes have gained attention due to the fact that they can act as mediators of intercellular communication especially because they contained proteins, peptides and miRNAs. In addition, it is also proposed that exosomes can contribute to neuropsychiatric disorders probably acting at the peripheral level but also at the central level. However, the protein content of exosomes of patients diagnosed with depression and how the pharmacological treatment impacts on their content is unknown. We thus here separated exosomes from serum of control subjects (n=5; women), depression diagnosed patients (n=5; women) and depression diagnosed patients after pharmacological treatment with fluoxetine (n=5; women). The expression of proteins related to exosomes was analyzed by western blot and the content of proteins in the exosomes was characterized with a proteomic microarray. Interestingly, exosomes expressed CD63 and neural cell adhesion molecule, the latter protein suggests the presence of exosomes generated from the central nervous system in human serum. Moreover, exosomes characterization indicates that the nanovesicles contains several types of proteins such as chemokines, cytokines and growth factors. Differences among healthy controls, depression diagnosed patients and depression diagnosed patients after pharmacological treatment with fluoxetine will be discussed.

Keywords: *Exosomes, depression, proteins.*

Area: Neurofarmacología

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SMB

Integration of the direct and indirect pathway in the substantia nigra reticulata and its modulation by cannabinoids

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The Basal Ganglia (BG) integrate information from the cortex and the thalamus through the direct and indirect pathways, which converge into the output nuclei of BG, the substantia nigra pars reticulata (SNr). The SNr is known to have the highest expression of the cannabinoid receptor type 1 (RCB1) and therefore its activity can be modulated by the endocannabnoid system. In spite of the anatomical and functional information, the exact contribution of the SNr during the integration of direct and indirect pathway information as well its modulation by the cannabinergic system remains unclear. Our objective was to characterize the activity of both pathways on the SNr and to evaluate the participation of the RCB1 in its modulation. To this aim, we recorded multiunit activity with high density multielectrode arrays in urethane anesthetized rats. Under these conditions somatosensory stimulation of the forelimbs produce robust and reliable responses in the neuronal activity of the SNr. Our data indicates that somatosensory stimulation produced complex responses characterized by transient inactivations and activations that reflect the recruitment of both direct and indirect pathways. Then, by using optogenetic manipulations, we characterized the specific participation of each pathway on the sensory representations on the SNr. On the same animals, we administered different doses of a RCB1 agonist (CP55940 i.p.) and observed that the inhibitory component of the sensory evoked representations was severely diminish. Optogenetic pathway-specific manipulations confirmed that RCB1 activation preferentially affected the direct pathway component of the nigral sensory-evoked representation. These results indicate that the activation of the RCB1 can modify the balanced activity in the SNr, suggesting a direct mechanism for the hypo locomotion effects associated to systemic cannabinergic administrations. We propose that, in future experiments, selective inhibition of both pathways in the terminals that reach the SNr will help us to understand basic integration mechanisms that could be fundamental in the context of motor control and pathology.

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Key words: Basal ganglia, nigra reticulata, CB1 receptor.

Neuronal plasticity evoked by somatosensensory stimulation in the cortico-thalamus-striatal circuits.

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Neurofisiología integrativa

It has been proposed that the dorsolateral striatum (DLS) integrates sensory-motor information from the corticostriatal and thalamo-striatal pathways to produce motor comands, however the specific role of the information provided by each pathway has not yet been clarified. I has been previously reported that that both pathways present multiple types of neuronal plasticity, but the implications of these results in the activity of the striatal microcircuit are to be determined. For these reasons, the objective of this work was to analyze the role of neuronal plasticity of the cortical and thalamic striatal projections in the activity of the striatal microcircuit, in an in vivo model in anesthetized animals. For this we have developed a model of somato-sensorial and optogenetic stimulation in rats, in conjunction with high density multiunit recordings. Our data indicates that, somatosensory information from the forelimbs arrives to the DLS through the primary somatosensory corte (S1) but also directly form the ventro-posterolateral nucleus of the thalamus (VPL), indicating that this model is suitable for studying both pathways. Different protocols of mechanic stimulation of the forelimbs, produced robust somatosensory representations and short-term neuronal plasticity visible at the single unit level but also at the population level of the DLS and S1. Moreover, population dynamics in the DLS reflected the sequential and temporal structure of the trains of stimulation. Finally, by expressing opsins for optogenetic control of the VPL/S1 and their terminals, we were able to isolate the cortical and thalamic components in the somatosensory representations in the DLS. Experiments and ongoing analysis will help us to understand the role of each path in striatal neuronal dynamics and later in behavior.

This study was funded by grants UNAM-DGAPA-PAPIIT: IA201916, IA201018 and CONACyT: FDC_1702. A.H-B is a master student from Programa de Mestría en Ciencias (Neurobiología), UNAM and supported by fellowship 478896 from CONACyT-Mexico

Dorsolateral striatum, neuronal plasticity and somatosensory information.

Investigating the role of the pallidal cannabinergic system in the control of speed

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The external segment of the globus pallidus (GPe) is the first relay of the indirect pathway of the basal ganglia. According to the classical model of the BG, the activation (inhibition) of the GPe would facilitate (inhibit) movements. Given its strategic localization in the BG circuitry, the GPe could be an ideal target for structural and pharmacological manipulations related to the control of movements. On the other hand, the GPe, is one of the nuclei with the highest levels of the cannabinoid receptor type I (CB1r), where it has been shown to modulate the release of GABA. The object of this project is to evaluate the effects of CB1r activation in the population activity of the GPe and its relationship with kinematic parameters of the execution of movement sequences. To this aim, we perform electrophysiological recordings in the GPe of anesthetized rats and evaluate the changes in neural activity induced by systemic administrations of CB1r synthetic agonist CP55940. To evaluate the behavioral impact of this manipulations, we use a behavioral protocol where rats running on a treadmill execute a motor sequence with tight spatio-temporal constraints. In the task, animals are required to adapt running speed on a trial by trial basis. Preliminary analysis on behavioral parameters indicate that systemic and local injections of cannabinoids decrease speed. Ongoing analysis on behavioral and neural data will help us to further clarify the effects of CB1 activation on the GPe.

Key words: external globus pallidus, cannabinergic system, speed.

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Exploring the role of dorsolateral striatum in bimanually coordinated movements in rats

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Many of our daily activities require bimanual movements with spatial and temporal coordination. This suggests that bilateral brain structures may work in synchrony to accurate execute such actions. In this context, the dorsolateral striatum (DLS) is anatomically privileged to integrate bilateral information to learn and perform skilled movements. DLS receives both bilateral and unilateral projections from sensorimotor cortices (MI/SI) and also from sensory thalamic regions such as the ventro-posterolateral nucleus (VPL). Therefore, we hypothesized that DLS uses bilateral sensorimotor inputs to coordinate bimanual outputs. To test this hypothesis, we designed a bimanual coordination task for rats where animals were trained to vertically and synchronously displace two levers (one with each forelimb) to get the reward. In this task, is possible to evaluate the onset/offset of bilaterally coordinated movements (a proxy of the beginning and end of the action) as well as the full movement trajectories of the forelimbs (a proxy of the execution of the action). Then we assessed the behavioral impact of unilateral lesions of the DLS or VLP. We found that with training, intact rats naturally developed coordinated forelimb movements, characterized by high correlation values between forelimb movements trajectories and by low interlimb onset/offset movement variability. In different groups of animals, unilateral DLS lesions performed before the beginning of the training significantly affected the correlation between forelimb movements but importantly, without affecting the interlimb onset/onset variability. Unilateral VPL lesions also decreased interlimb correlation but produced an increase in the interlimb onset/onset variability in many of the animals. Ongoing analysis in animals with similar lesions in the DLS performed after learning will complete the panorama. These results indicate that both DLS and VPL are indispensable for the development of bimanually coordinated movements. Ongoing experiments are focused on evaluating the role of bilateral sensorimotor cortical projections in this kind of movements.

Area: Integrative Neurophysiology

Key words: dorsolateral striatum, sensorimotor information, cortico-talamic projections

This study was funded by grants UNAM-DGAPA-PAPIIT: IA201916, IA201018 and CONACyT: FDC_1702 to P.R-O. A.P-F is a PhD student from Programa de Doctorado en Ciencias Biomédicas and supported by fellowship 463747 from CONACyT-Mexico.

Activation Of TLR9 With A Synthetic Ligand In A Murine Medulloblastoma Xenograft

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Area: Neuroimmunology

Introduction. Medulloblastoma is the most frequent malignant brain tumor in children. Long-term survival of patients increased in the last years due to therapy improvements. Yet, the heterogeneity of molecular and genetic markers among a single tumor creates major barriers for the development of targeted therapies that will be effective against the entire tumor. The immune response is a critical factor in the establishment of tumors. Toll-like receptors (TLRs) play dual responses in tumors, making them an important area of study for new treatment strategies. Different studies have proven that TLR9 stimulation with certain oligodeoxynucleotides (ODNs) elicits apoptosis of glioma cells, enhance survival of glioma bearing mice and prime long-term immunity. However, the effect of ODNs in medulloblastomas is not very studied. In this work we evaluate the effect of ODN in the PCNA levels, tumor size and TLR9 expression in a murine medulloblastoma xenograft.

Material and methods. HBT- 186 cells were cultured in EMEM FBS 10% and implanted subcutaneously in nu/nu mice. Body weight and tumor size of mice were monitored weekly. When tumors reached ≈70mm^3, two injections of ODN to the treated group and two injections of injectable water to the control group were administrated intratumorally, each injection with a 7 days difference. Tumors were dissected, the tissue was minced and cells lysed with protein extraction solution. Protein concentrations were measured with Bradford protein assay with bovine serum albumin as standard. Western blot assays were performed to identify PCNA protein and TLR9 expression.

Results. There is an increase in the PCNA protein levels in those tumors treated with ODN compared to the control tumors. On the other hand, tumor volume decreased in all the ODN treated mice. In addition, TLR9 expression seems to be slightly higher in the treated tumors.

Conclusions. ODN has an effect on tumoral cells proliferation modifying the PCNA protein levels, increased TLR9 expression in tumors and reduced the tumor size in meduloblastoma-bearing mice.

Keywords. Toll-like receptors, medulloblastoma, ODN

Increase of TNF alpha plasmatic concentrations is associated to depressive symptoms in residents from central zone in Veracruz

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Introduction: Depression is an affective disorder frequently found amongst populations in the world associated to factors such as age, sex, health status or changes in different biomarker's activity. The tumor necrosis factor alpha (TNFα) is a pleiotropic proinflammatory cytokine involved in the mechanism implicated in depression by a chronic overstimulation of the hypothalamo-pituitary-adrenal axis (HPA) that may affect emotional processing, cognition and learning. Several studies have researched the relationship between mood disorders and peripheral proinflammatory cytokines, but in Mexico especially Veracruz these studies are scarce. **Aim:** Evaluate TNFα plasmatic concentrations and its association with depressive symptoms in residents of central zone in Veracruz. **Materials and methods**: A cross sectional study was conducted in accordance to a prior approval by an ethical committee. Each participant signed the informed consent letter prior to answer the questionnaire. Depression symptoms were determined by Beck's Depression Inventory and blood samples were obtained by venipuncture in tubes with heparin. TNFα concentrations were analyzed by Enzyme Linked Immuno-Sorbent Assay (ELISA). Non-parametric tests and Spearman's correlation were performed for statistical analyses. **Results:** A total of 60 residents in central zone in Veracruz were included in the study. The average age was 43 years (20-69), 75% were women. 39% of population shown depressive symptoms (13% mild mood disturbance and 26% moderate depression) and 61% didn´t show symptoms (control group). TNFα and Beck's inventory score had negative correlation (Spearman's rho=0.355, $p<0.01$). The geometric mean of TNFα plasmatic was significantly higher in depressive symptoms group than in control group (*$p<0.01$). TNFα was not different by severity of symptoms even when age was higher than 40 years. **Conclusion**: Increase of TNFα concentrations is associated with depression symptoms in residents of central zone in Veracruz. Further studies should be performed to assess TNFα changes with evolution and severity of depressive symptoms.

Keywords: TNFα, depression, neuroinflammation.

Role of NADPH oxidase-2 in the progression of the inflammatory response secondary to striatum excitotoxic damage.

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Background: During excitotoxic damage, neuronal death results from the increase in intracellular calcium, the induction of oxidative stress, and a subsequent inflammatory response. NADPH oxidases (NOX) are relevant sources of reactive oxygen species (ROS) during excitotoxic damage. NADPH oxidase-2 (NOX-2) has been particularly related to neuronal damage and death, as well as to the resolution of the subsequent inflammatory response. As ROS are crucial components of the regulation of inflammatory response, in this work, we evaluated the role of NOX-2 in the progression of inflammation resulting from glutamate-induced excitotoxic damage of the striatum in an *in vivo* model.

Methods: The striata of wild-type C57BL/6 J and NOX-2 KO mice (gp91$^{Cybbtm1Din/J}$) were stereotactically injected with monosodium glutamate either alone or in combination with IL-4 or IL-10. The damage was evaluated in histological sections stained with cresyl violet and Fluoro-Jade B. The enzymatic activity of caspase-3 and NOX were also measured. Additionally, the cytokine profile was identified by ELISA and motor activity was verified by the tests of the cylinder, the adhesive tape removal, and the inverted grid.

Results: Our results show a neuroprotective effect in mice with a genetic inhibition of NOX-2, which is partially due to a differential response to excitotoxic damage, characterized by the production of anti-inflammatory cytokines. In NOX-2 KO animals, the excitotoxic condition increased the production of interleukin-4, which could contribute to the production of interleukin-10 that decreased neuronal apoptotic death and the magnitude of striatal injury. Treatment with interleukin-4 and interleukin-10 protected from excitotoxic damage in wild-type animals.

Conclusions: The release of proinflammatory cytokines during the excitotoxic event promotes an additional apoptotic death of neurons that survived the initial damage. During the subsequent inflammatory response to excitotoxic damage, ROS generated by NOX-2 play a decisive role in the extension of the lesion and consequently in the severity of the functional compromise, probably by regulating the anti-inflammatory cytokines production.

Keywords: NADPH oxidase, Excitotoxicity, Neuroinflammation.

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Effects of Anti-NMDA receptor antibodies on NMDA-induced intracellular Ca^{2+} rise: possible implications for anti-NMDAR encephalitis.

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A form of encephalitis (a-NMDARe) is caused by the presence of auto-antibodies (Abs) against NMDAR subunits GluN1 and GluN2B that provokes different neurologic and psychiatric symptoms. It has been established that long-term Ab treatment decreases surface NMDAR presumably by enhanced endocytosis. However, the short-term cellular effects have not been fully elucidated. Contradictory reports suggest that Abs from a-NMDARe patients alter NMDAR functionality prior to endocytosis. Here, we investigated short-term effects of different commercial anti-NMDAR Abs, previously shown to mimic behavioral effects of a-NMDARe in rat, on the i[Ca^{2+}] response of cultured cortical neurons to the application of NMDA-Gly. First, we tested the effect of 24 h incubation with an Ab raised against the extracellular (EC) domain of GluN2B or GluN1 subunits to 5 s applications of NMDA-Gly. The GluN2B Ab reduced i[Ca^{2+}] response, but unexpectedly, the GluN1 Ab slightly augmented it. After 60 min incubation with GluN2B Ab i[Ca^{2+}] the response to NMDA-Gly also decreased, whereas incubation with GluN1 Ab did not change. Interestingly, TCN, an inhibitor of GluN2A-containing NMDARs diminished the i[Ca^{2+}] response to NMDA/Gly but did not modify the effect of the GluN2B Ab. Strikingly, 60 min incubation with an Ab directed against the *intracellular* (IC) domain of GluN1, augmented the i[Ca^{2+}] response to NMDA-Gly and delayed the return to baseline. These data indicate that binding of Abs raised against NMDA subunits can modify NMDAR function in the short term. It remains to be examined how Ab binding to the receptor affects the response to the agonist. Supported by PAPIIT-UNAM AG200119.

KEYWORDS: NMDAR; encephalitis; antibodies

AREA: Neuroimmunology

Evaluation of the protein expression the Neurotrophic factors in rats with chronic spinal cord injury immunized with the A91 peptide

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Spinal cord injury (SCI) leads to permanent damage in motor, sensorial and autonomous nervous system functions. Research in this field has shown that immunization with neural-derived peptides (INDPs) like A91 could provide the necessary conditions to achieve the beneficial and avoid the detrimental effect of immune cells. Recent studies have suggested that modulation, rather than suppression, of immune response could be the best way to attain neuroprotection and neuroregeneration after SCI. The protective autoreactivity (PA) is supposed to modulate autoreactive mechanisms in order to promote neuroprotection activating microglia under a particular phenotype which low free radicals production. A91 is a modified neuropeptide that is able to diminish secondary neurons degeneration, promote motor recuperation in animals after SCI and increase the neurotrophic factors or Neurotrophins (NTs). Furthermore, NTs as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and Insulin-like growth factor 1 (IGF-1) have demonstrated positive effects on neuronal survival, axonal growth and synaptic plasticity. Therefore, A91 used in rats with SCI might enhance its protective and regenerative effect in acute phases but, there is lack information about the chronic phase. Hence, the aim of this work is to evaluate the effect of A91 during the chronic phase of SCI. In order to test this hypothesis, the protein expression of IGF1, BNDF, NT3, and NGF were explored in SCI rats using assay ELISA. Proteins levels was evaluated in 18 female Sprague Dawley rats after 60 days post-injury. Animals were divided in six groups Group 1: Rats with chronic spinal cord injury (SCI) treated with Complete Freund's Adjuvant (CFA) + PBS immunized 45 days after the injury (vehicle).; Group 2: Rats with chronic SCI immunized with A91 + CFA 45 days after the injury; Group 3: Rats with chronic SCI treated with CFA + PBS immunized 53 days after the injury; Group 4: Rats with chronic SCI immunized with A91 + CFA 53 days after the injury. Group 5: Rats with chronic SCI treated with CFA + PBS immunized 57 days after the injury; Group 6: Rats with chronic SCI immunized with A91 + CFA 57 days after the injury. The effect of A91 could be determined through the amount of NTs in chronic phase, as well as the right time for the administration of the therapy.

Keywords: SCI, A91, Neurotrophins.

Content and colocalization of progesterone receptor and protein kinase c alpha increased according to malignancy grade in biopsies of mexican patients

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Introduction: The astrocytic gliomas or astrocytomas are the most common primary brain tumors, these represent about 76% of all the gliomas and can be found in any part of the brain, especially in the brain cortex, thalamus, and basal ganglia. According to the 2016 World Health Organization (WHO) classification, astrocytomas are graded from I to IV according to their malignancy; astrocytoma grade IV or glioblastoma (GBM) exhibit more advanced features of malignancy with a poor prognosis, epidemiological data report that GBM occur in a greater proportion in men than in women (3:2). The National Institute of Neurology and Neurosurgery (INNN) reports that in Mexico, 9% of all brain tumors are GBM.

It has been seen that activated progesterone receptor (PR), promotes the growth and infiltration of high-grade astrocytomas cell lines. PR activation could be induced by phosphorylation, in this regard we know that PR can be phosphorylated by protein kinase C alpha (PKCα) at the Ser400 site. This phosphorylation induces PR transcriptional activity that leads to an increase in cell proliferation, migration and invasiveness of GBM cell lines, however, the presence and the localization of these proteins in human biopsies is unknown.

Methodology: 46 biopsies from patients diagnosed with astrocytoma (9 low-grade I-II, 12 grade III and 25 grade IV) were analyzed using an immunofluorescence assay for the identification of PR, PKCα and the pSer400 PR content and localization. After that, we analyze the correlation between the grade of malignancy and the expression of these proteins and the relation with the information founded on the Xenabrowser database.

Results: We found on Xenabrowser a cohort of 12839 patients that don´t present correlation between the levels of mRNA of PR with PKCα, however, at protein level, in biopsies and using immunofluorescence assay, we found a correlation between the content and colocalization of both proteins (PR and PKCα), the level of PR phosphorylation at Ser400 residue and the malignancy astrocytoma grade.

Conclusions: In this work, we found two proteins (PR and PKCα) and phosphorylation level of PR (pSer400) that can be used for prognosis biomarkers on biopsies of astrocytomas.

Keywords: Astrocytomas, Progesterone Receptor, Protein Kinase C alpha.

The proliferation of neural progenitor cells in the adult mouse hippocampus depends on the duration of the proinflammatory profile induced by LPS

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Área: Neuropatología

New neurons are continuously generated throughout life in the dentate gyrus of the mammalian hippocampus. Neurogenesis derives from the proliferation of stem/progenitor cells and their proliferative behavior is regulated by extrinsic factors such as neuroinflammation, a hallmark to several pathological conditions. Acute and chronic administration of LPS leads to neuroinflammation along with a reduction in the number of doublecortin positive (DCX+) young neurons. While this effect has been shown to occur during the early inflammatory response, the long-term effect of inflammation upon neurogenesis remains to be shown. Thus, the aim of this work was to establish if the reduction in DCX+ cells continues after the acute neuroinflammatory response and if a repeated intermittent administration of LPS along time induces a greater reduction compared to a single LPS injection. We administered one single intraperitoneal injection of LPS or saline or four repeated injections (one per week) of LPS or saline to young-adult mice. A cohort of new cells was labeled with three BrdU injections (one per day) four days after the last LPS injection. We evaluated systemic and neuroinflammation-associated parameters and compared the effects of the late neuroinflammatory response induced by each protocol on neurogenesis. Our results show that: 1) either single or repeated LPS administration promotes transitory sickness-related symptoms such as reduced locomotion and body weight-loss. These responses are resolved within one week after LPS challenge, 2) at 7 days after a single LPS injection there is a neuroinflammatory response characterized by an increase in IL-6 and TNF-α cytokine levels and activated microglia and reactive astrocytes. This response correlates in time with a decrease in BrdU+/DCX+ cell number and 3) a repeated intermittent administration of LPS does not elicit a late neuroinflammatory response although activated microglial cells persist. Noteworthy, this latter profile does not correlate with a further decrease in BrdU+/DCX+ cells beyond that associated to aging, as shown by age-paired controls treated with saline. Our results show that the neuroinflammatory response is a dynamic and complex process that involves the interplay of pro- and anti-neuroinflammatory molecules and does not necessarily lead to a sustained neurogenic reduction, thereby highlighting the complex interaction between the immune system and the neurogenic process.

inflammation; cytokines; neural progenitor cells

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"Tau hyperphosphorylation in mouse brain during diabetic ketoacidosis "

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Introduction: Diabetic ketoacidosis (DKA) and dementia are associated with deficient signaling by insulin and general brain acidosis that turns into neuronal loss and neurocognitive deficits. Previous reports indicated that hyperphosphorylation of Tau leads to neurodegenerative disorders such as Alzheimer´s disease under brain acidosis. There is a relationship between cognitive impairment and DKA in different animal models and patients. In this study, we showed hyperphosphorylation of Tau in a DKA mouse brain, suggesting an important role of Tau in dementia onset associated to DKA. **Materials and methods:** C57BL/6 male mice weighting 30-35 g were randomly assigned to 3 different groups: DKA, HFD (high fat diet) and WT (wild type). DKA group (n=4). Type I diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ, 150 mg/kg) in previously 6 h starved animals; water with 10% of dextrose was proportioned for 24 hours after STZ for preventing hypoglycemia. One day after the diabetes induction, mice received insulin treatment for 5 days (1 unit/24 h, s.c.). After the end of the treatment, the standard chow was replaced with a high fat diet, for promoting DKA. Urine pH, ketone bodies and glucose blood levels were measured every 5 days for 30 days. HFD group were handled as the DKA group except for STZ administration. The 3 groups of mice were sacrificed by cervical dislocation and the brain tissue was obtained by craniotomy. Hippocampus and cerebral cortex were homogenate. Different Tau hyperphosphorylated sites were analyzed by Western blot. **Results:** Mice from the KDA group presented diabetic ketoacidosis 5 days after the high fat diet started. Glucose and ketone bodies levels of the experimental groups were as follows: WT mice showed 170.5 ± 12.02 mg/dL of glucose and ketone bodies were not detected. Regarding to the HFD group, 162.25 ± 20.05 and 20 mg/dL of glucose and ketone bodies, respectively were detected. Glucose of the HFD group was initially affected, but during the last state of the treatment the levels return to their normal parameters. In contrast, DKA group showed an increase in both parameters: glucose levels (228 mg/dL) and ketone bodies (40 mg/dL). The pH was also affected since in the control group its pH is 7.5 on average and that of the group with DKA is 6. Phosphorylated Tau was higher than controls in most of the evaluated sites. **Conclusion:** The proposed animal model was successful, the decrease in the pH, and the increase of the glucose and ketone levels confirms the establishment of the diabetic ketoacid state. Additionally, the analysis of phosphorylated sites of Tau revealed that DKA can be associated with cognitive damage which could lead to dementia diseases' such as Alzheimer.

Keywords: Alzheimer Disease, Diabetic Ketoacidosis (DKA), Hyperphosphorylation.
Area: Neuropathology

LPS-induced neuroinflammation promotes distinct effects on the proliferation of defined subpopulations of neural progenitor cells in the adult dentate gyrus

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Área: Neuropatología

The generation of new neurons in the dentate gyrus of the hippocampus continues throughout the lifespan of several organisms, including rodents. Adult neural stem cells give rise to neural progenitors, which are highly proliferative and start to express neuronal lineage markers. Type-2a and -2b progenitors are commonly described as responsible for the expansion of the pool of cells available for further neuronal development and type-3 progenitors exit cell cycle and give rise to fully differentiated granular neurons. The neurogenic process is continuously regulated by extrinsic factors and it has been described that neural progenitors respond differently to the same stimuli. Neuroinflammation is a hallmark of several pathological conditions and induces neurogenic dysregulation. Systemic lipopolysaccharide (LPS) administration has been long-used as a model for inducing brain inflammation. The acute neuroinflammatory response caused by LPS administration leads to a consistent reduction of new-born neurons in the adult dentate gyrus. We have previously reported that one week after a single LPS intraperitoneal (i.p.) administration the brain proinflammatory profile continues, including astrocytic and microglial activation, as well as increased levels of proinflammatory cytokines, and a sustained reduction in the number $DCX^+/BrdU^+$ cells. This effect could be a consequence of increased cell death or of a diminished proliferation rate of neural progenitors. Therefore, in this work we evaluated the LPS-associated effects on different subpopulations of neural progenitors. To this end, we administered one i.p. injection of saline or LPS to young-adult male mice and sacrificed them seven days later. For the quantification of progenitor cells, we administered three BrdU pulses (1 i.p. injection/day) for three days before sacrifice. Using immunofluorescence, confocal microscopy and stereological-based analysis we estimated the number of $BrdU^+$ cells co-labeling with Tbr2 (type 2a), Tbr2 and DCX (type 2b) or DCX (type 3 and young neurons). Our preliminary results show that 1) on saline-treated animals the majority of $BrdU^+$ cells are $Tbr2^+/DCX^+$ and, 2) under LPS-induced neuroinflammatory conditions the proportion of $BrdU^+/Tbr2^+/DCX^+$ cells is reduced while the proportion of $BrdU^+/Tbr2^-/DCX^+$ is increased. We did not observed changes in the proportion of proliferating type 2a progenitors, but interestingly, contrasting changes are observed on type-2b and type-3 cells. Our results suggest that the different subpopulations of neural progenitor cells respond differently to the same neuroinflammatory challenge, highlighting the proliferative and survival dynamics of these cells. Since the expansion phase of the cell pool seems to depend on type-2b progenitors and a reduction in the proportion of these cells is observed, we conclude that the impaired proliferation of these progenitors highly contributes to the reduced number of adult-born neurons observed under neuroinflammatory conditions.

Key words: neuroinflammation, neural progenitor cells, proliferation

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A New Murine Model Of H-ABC Human Tubulinopathy

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Área del trabajo: Neuropatología

Tubulinopathies are a group of recently described diseases characterized by mutations in the tubulin gene. Tubulin is essential in all cell types; in the nervous system, it is of paramount importance in the process of brain development, contributing, among other things, to the formation and maintenance of myelin. In particular, mutations in the TUBB4A gene produce diseases such as dystonia 4 (DYT4) and hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC).
There is currently no animal model for the study of these pathologies. On the other hand, the spontaneous mutant taiep has a syndrome characterized by tremor, ataxia, immobility, epilepsy and paralysis, as the acronym suggests. The signs presented by these rats are similar to those of patients with mutations in the TUBB4A gene. We propose the taiep rat as a model for tubulinopathies. We performed TUBB4A exon analysis to corroborate the genetic defect that might generate the phenotype. A point mutation that cause an aminoacid change in position 302 was detected, and hypotheses about its effects on protein functionality were formulated. Optical microscopy of taiep rat cerebella and spinal cord confirmed the optical density loss in white matter associated with myelin loss, while neural fibers persist. The diffuse atrophy in cerebellum and spinal cord is related to the changes found in many human tubulinopathies and in particular in H-ABC patients, where myelin scarcity and degeneration at the level of putamen and cerebellum are a clinical trademark of the disease.

Palabras clave: tubulinopathy, TUBB4A, H-ABC

Friend or Foe? Participation of IRE1 in the unfolded protein response induced by glucose deprivation in cortical neurons

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Area: Neuropathology

Disturbances in cellular proteostasis can cause misfolded protein accumulation in the endoplasmic reticulum (ER) compromising cell viability. This leads to the activation of the unfolded protein response (UPR), which is orchestrated by three ER transmembrane proteins: IRE1 (enzyme 1 that requires inositol), PERK (PKR: endoplasmic reticulum kinase) and ATF6 (activator transcription factor 6). Together they induce a reprogramming of the cell characterized by the attenuation of global protein synthesis, the selective increase of proteins of the folding machinery and the degradation of accumulated misfolded proteins. IRE1 is the most conserved sensor of the UPR. This is a transmembrane glycoprotein with Ser/Thr kinase and endoribonuclease (RNAse) activities, capable of degrading RNAs and interacting with different proteins which activate different intracellular signaling pathways. In recent years, alterations in proteostasis have been associated with neurodegenerative diseases and ischemic injury. However, it has been found that the activation of UPR can either improve or worsen these neuropathologies depending on the intensity and duration of the stressing condition.

The aim of the present study was to evaluate the dynamics of IRE1 activation and its possible role in neuronal death induced by glucose deprivation (GD) and reintroduction (GR) in primary cortical cultures. IRE1 activation was evaluated by its phosphorylation as well as its interaction with different cofactors, as the pro-apoptotic proteins BAX and BAK, which increases its capability to break and degrade RNA by the mechanism known as Regulated IRE1-Dependent Decay (RIDD). The interaction with ASK1 and the subsequent activation of the ASK1-JNK pro-apoptotic pathway was also evaluated. Finally, the role of IRE1 downstream pathways in neuronal survival was evaluated after culture exposure to GD/GR.

Results show that IRE1 is early activated during GD and that its interaction with BAX and BAK promotes its RIDD activity. Increased IRE1 activity persists during GR and ASK1 is recruited to the IRE1 complex inducing JNK translocation to the nucleus. This promotes the up-regulation of the pro-apoptotic transcription factor, CHOP. Sustained activation of RIDD activity stimulates apoptotic death by positively regulating the ASK1-JNK pathway through mRNA degradation of ASK1 negative regulator (protein 14-3-3). Results also show that IRE1 is early activated as an adaptive response to GD, as its inhibition exacerbates neuronal death. However, IRE-1 hyper activation favoured by its interaction with pro-apoptotic proteins and persistent RIDD activity, contributes to neuronal death during GR.

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Estrogen receptor beta activation induces medulloblastoma cells proliferation whereas PKCs activation blocks it

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Medulloblastomas (MB) are the most common and aggressive pediatric brain tumors. Estrogen receptor beta (ERβ) is associated with development of these tumors due to its contribution to proliferation promotion of cells that originates them. Moreover, protein kinase C alfa and delta (PKCα and δ) are able to phosphorylate it; however, the effect of this posttranslational modification on ERβ is unknown.

The aim of this work was to study the role of ERβ, PKCα and PKCδ in MB development, as well as their interaction to regulate cellular proliferation using the MB-derived cell line Daoy and MB biopsies.

To establish the implication of ERβ in proliferation of Daoy cells trypan blue exclusion method and BrdU incorporation assay were carried out. We observed that the ERβ agonist, DPN, significantly increased proliferation after 72 hours of treatment, which was blocked by the ERβ antagonist, PHTPP. In classic and desmoplastic MB biopsies, using immunofluorescence, it was found that classic group had significantly higher ERβ content than cerebellar health tissue. These results suggest that ERβ is implicated in proliferation of DAOY cells and possibly in classic MB.

Through immunofluorescence assay it was observed that classic and novel PKCs activation with TPA, induced PKCα and δ translocation to nucleus, promoted their association and significantly increased phosphorylated ERβ content, which was blocked by PKCα and δ inhibitors. In addition, PKCs activation significantly diminished DAOY cells proliferation, effect that was enhanced by ERβ blocking.

Using immunofluorescence, we observed that there was no significant difference in PKCα and δ content in classic and desmoplastic biopsies compared to health cerebellar tissue. In addition, there was no significant Spearmen correlation between the proteins of interest; however, ERβ-regulation by PKCs phosphorylation cannot be discarded since it is determined by their activation state.

Overall, our results suggest that ERβ is important to promote proliferation in DAOY cells and possibly, in classic MB. Furthermore, ERβ phosphorylation by PKCα and δ could reduce proliferation of this cell line.
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Key words: Estrogen receptor beta, PKC, medulloblastoma

Estradiol induces epithelial-to-mesenchymal transition on human glioblastoma cells

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Area: Neuropathology

Epithelial-mesenchymal transition (EMT) is a mechanism reprogramming that drives cell plasticity. Some research has shown that EMT deregulation is determinant in the invasive phenotype of glioblastoma multiforme (GBM), the most common malignant brain tumor of the Central Nervous System (CNS). In this tumor, different intracellular signaling pathways activate the EMT program; however, the role of all the factors found within the tumor microenvironment is not yet clear. 17β-estradiol (E2) is a steroid hormone that acts through specific receptors (*Estrogen Receptors*, ER) that are widely distributed within the CNS and perform essential functions in the growth, differentiation, maturation, and migration of neurons and glial cells. The expression and activation of ERs are involved in the malignancy of GBM. Besides, E2-ER signaling is involved in the EMT induction in several tissues responsive to this hormone; however, this is still unknown in the GBM. In this study, we determined the effect of E2 on the EMT induction in U251 and U87 cells derived from human GBM through cell morphology analysis and expression of epithelial and mesenchymal markers. We analyzed ERα and ERβ receptors basal expression in U251, U87, T98G, and LN229, cells; and both receptors are expressed in the four cell lines. The cell morphology analysis by phase contrast microscopy showed that treatments with E2 (10 nM) and transforming factor β (TGF-β) (10 ng/ml) induced changes in shape, size and branching U251 and U87 cells. To evaluate the effect of E2 (10 nM) on the expression of EMT markers, we performed a temporal course by RT-qPCR and determined the gene expression of the markers ZO-1, vimentin, and N-cadherin at 0, 24, 48 and 72 h in U251 and U87 cells. We showed that E2 decreases the expression of ZO-1 and increases the expression of vimentin and N-cadherin in comparison with the vehicle. These data suggest that E2 induces the activation of EMT in cells derived from human GBM.

Keywords: EMT, GBM and ER

Olfactory alterations in a *Drosophila* Parkinson´s disease model expressing α-synuclein

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Area: Neuropatología

Chemoreception is essential for survival and environmental perception. Feeding, mating and avoidance of toxic substances and predators depend on detection of sensory cues, especially odors. On the other hand, olfactory alterations, such as anosmia and hyposmia, correlate with the etiology of some neurodegenerative diseases. Parkinson disease (PD), is the most common motor neurodegenerative disorder; in this disease olfactory disfunction often precedes motor symptoms by several years and it has been proposed that it may be used in PD diagnosis.

Motor ability and motor disfunctions of transgenic flies expressing PD related proteins (like α-synuclein) have been evaluated at Dr. Reynaud´s laboratory. Several groups have shown that *Drosophila melanogaster* it´s a good animal model to study PD. Nevertheless, no olfactory analysis had been made employing transgenic flies that express wildtype α-synuclein in their dopaminergic neurons, as it is use as a PD model. In general, there is little molecular and cellular information about the mechanisms that affect olfactory perception in this disease. Given the increasing incidence of neurodegenerative diseases and the need of early biomarkers for them, it is important to research the mechanisms of chemosensory alterations and to identify a simple model to study these olfactory changes.

We established ethological tests in order to measure olfactory deficits, evaluating the attraction index of flies of 1-5, 10-15 and 40-45 days old exposed to lactic acid at 2% and 4-methylcyclohexanol, substances that are respectively attractive and repellent. In this work we concluded that, as observed in PD patients, *D. melanogaster* transgenic line that expresses wildtype α-synuclein, exhibits hyposmia, that get worse through aging, during all their adult lifespan. This suggests that overexpression of wildtype α-synuclein in dopaminergic neurons, is enough to produce olfactory alterations. Also, we observed that olfaction in control flies go through a natural decay that is proportional to aging. We think that these results can be due to reduction and/or degeneration of antennal lobes through time. Currently, we are investigating the nature of this loss of olfaction in our model.

Key words: Parkinson´s disease, olfaction, α-synuclein

Calorie restriction modify stroke outcome in a mice model

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INTRODUCTION

Stroke is a disease produced by different causes that affects the arteries leading to and within the brain. Nearby 87 % of all strokes are ischemic stroke, which is triggered when a blood vessel supplying the brain is obstructed. In this pathology, there are two different damage areas: the core, in which cells quickly die; and the peri-infarct area (surrounding the core), in which cells are functionally weakened but can recover. Reactive astrogliosis that is not resolved in the peri-infarct area during the chronic stage of stroke contributes to establishing a non-permissive environment for functional recovery. Evidence from several studies suggests that the decrease in chronic reactive astrogliosis without disrupting the glial scar and increase brain derived growth factor (BDNF) are necessary for functional recovery. On the other hand, chronic calorie restriction has been showed to increase BDNF and decrease astrogliosis. In this work we tested the effect of calorie restriction in a mice model of stroke.

METHODS

Animals: Male C57BL/6 (n=40; 3-4 months old, 28-32 g). **Focal ischemia**: 24 animals undertook photothrombosis PT (2 mm diameter irradiation, positioned 1.5 mm lateral from bregma. **Calorie Restriction:** half of the animals with focal ischemia were randomly assigned to intermittent dietary energy restriction (IF; alternate day fasting) diets for 2 months. **Body weights**: were recorded weekly. **Behavioral testing:** Cylinder test and grid-walking test were performed 7 days before and 7, 14, 21, and 28 days after stroke (8 animals/group). Video analysis was performed by blinded raters. **Histology:** Forty-micro meter frozen sections were prepared as described previously and every third section was collected to quantify infarct volumes using Nissl stain (4 animals, ≥6 sections each per group).

RESULTS: There was no difference in body weights at the end of the experiments between groups. Moreover, there was no difference in infarct size between photothrombosis (PT) and photothrombosis plus intermittent fasting (PT +IF) animals. However, there was an improvement in behavioral of PT+IF compared with PT animals showed an increase in forelimb use asymmetry after stroke.

DISCUSION: Lack of any significant difference in infarct size or behavioral testing in the first 7 days after photothrombosis suggests that neuroprotection did not play a significant role in this improvement and support that recovery is due a cellular mechanisms of neuroplasticity.

CONCLUSIONS: We have shown that chronic IF treatment improves stroke outcomes in an apparently non-neuroprotective manner.

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SMB

Longitudinal evaluation of bundle-wise water diffusion changes following axonal degeneration in a region of fiber crossing

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Introduction. Axonal degeneration is a hallmark of many neuropathologies, with a defined time course presenting distinct histological features. In single fiber regions, the Diffusion-weighted magnetic resonance imaging (DW-MRI) tensor model provides reliable information in early and chronic phases of axonal damage. However, said model cannot accurately determine per-bundle characteristics in voxels occupied by axonal populations with different orientations. We evaluated two DW-MRI multi-fiber methods and performed histological quantifications of some parameters in an animal model of axonal degeneration (unilateral retinal ischemia) to provide information about the sensitivity of these models and their correlation with microstructural changes occurring in the acute and early chronic stages of pathology in a crossing fiber region.

Methods. Axonal degeneration of the optic pathway was induced through unilateral retinal ischemia[1] in 15 Wistar rats. Animals were divided into 3 groups (1, 7 and 30 days post-ischemia). Four rats served as controls. Tissue was fixed and brains were extracted and scanned in a 7 Tesla MRI scanner. Images had 80x80x80 μm^3 voxel resolution, acquired using 54, 52, 34 and 20 diffusion gradient directions (b = 7000, 5000, 3000 and 1000 s/mm^2), along with 20 non-diffusion weighted images. DWI-MRI were preprocessed and analyzed with multi-shell multi-tissue constrained spherical deconvolution (CSD[2]) computation and a multitensor model using multi-resolution discrete-search (MRDS[3]). Sections from optic nerves were obtained (400-500µm) and microphotographs of whole area were obtained. Automatic axon segmentation was performed (AxonSeg[4]) and axon morphology features derived were correlated with DW-MRI parameters.

Results and discussion. Multi-fiber methods discerned the damaged and intact fiber populations within the chiasm. Tensors derived from the MRDS model showed reduced fractional anisotropy (FA) and axial diffusivity, and increased radial diffusivity of bundles corresponding to the affected nerves at days 7 and 30 post-injury. Using CSD we found a reduction of apparent fiber density (AFD) at 7 and 30 days in damaged optic nerves, and the same temporal pattern was observed in the optic chiasm for the affected bundles. Related to histology, axon density decreased at 7 and 30 days post injury, this pattern was also observed for axon and myelin volume fraction (AVF/MVF). Multi-tensor (FA) and CSD (AFD) showed the highest correlations with axon density and AVF.

Conclusion. Multi-tensor and CSD analyses of dmri are sensitive to tissue abnormalities even in presence of crossing fibers, extending the ability to infer tissue microstructure non-invasively in clinical and research settings. **Keywords.** Magnetic resonance imaging, axonal degeneration, crossing fibers.

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Non-evoked electroretinogram reveals slow oscillatory activity that is altered in obese mice

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Neuropathology

Purpose

Spontaneous oscillations have been detected in adult mouse retinas but whether this activity can be detected by electroretinogram (ERG) remains to be determined. Furthermore, since electroencephalogram showed altered basal oscillations in diabetic brains, we explored if basal ERG oscillations are affected by the development of obesity-induced insulin resistance, a common complication of type 2 diabetes.

Methods

ERGs with no light flash were measured in both eyes of adult C57BL/6J female and male mice (1:1 ratio) that were either fed a high-fat diet (HFD, 60 % fat, N=4-5) or a standard diet (30 % fat, N=3-7) at week 4, 5, 6 and 12. Mice were dark-adapted before ketamine–xylazine anesthesia (7/3, i.p.). The pupils were dilated with tropicamide/phenylephrine (0.75 and 0.25 %); tetracaine hydrochloride was used as a cornea anesthetic; active electrodes were placed on each cornea and hydrated with 0.5 % hypromellose solution to maintain conductivity. Subdermal electrodes placed at the base of the nose (reference) and in the tail (ground). A 2-minute scotopic signal was amplified 1000-fold using a differential amplifier with a 0.1–1000 Hz bandwidth. Mice were then light-adapted for 15 minutes to record basal photopic ERGs as described for scotopic measures. ERG data were then analyzed by Fast Fourier Transform to calculate spectral density. Body weight, glycemia, insulinemia, glucose and insulin tolerance were weekly measured.

Results

Spectral analysis of basal ERG showed three main waves with a band frequency between 0.8-1.8, 1.8-2.5 and 2.5-3.5 Hz. The slow waves are present under both scotopic and photopic conditions and both in males and females. The peak frequency for the 0.8-1.5 Hz band is slower in photopic (1.27 ± 0.24 Hz) than in scotopic (1.42 ± 0.21 Hz) conditions. Under HFD conditions, we found a reduced peak frequency in the 0.8-1.5 Hz band after 6 and 12 weeks compared to control mice. In addition, after 4 weeks of HFD, mice are obese but they are still normoglycemic and tolerant to glucose and insulin. From week 5 of HFD, mice showed insulin resistance, glucose intolerance, and increased glycemia.

Conclusions

Our data revealed(identified) basal slow oscillatory activity in adult mouse retina using ERG and showed that it is slower under photopic conditions. No gender difference was observed. Obese, insulin-resistant mice showed alterations in basal slow oscillatory activity after 6 and 12 weeks of HFD. A longer follow-up is required to determine if slow oscillatory activity in basal ERG is affected by the development of obesity-related insulin resistance.

Keywords: spontaneous oscillations, ERG, obesity

Effect of a high-fiber diet on amyloid aggregation and memory performance of APP/PS1 transgenic mouse

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Introduction: Alzheimer's disease (AD) is a neurodegenerative disease characterized by hyper-phosphorylation of tau protein and aggregation of β-amyloid peptide in the brain. Of the total number of AD patients diagnosed, two thirds are women in postmenopausal state, an event related to hormonal disbalance. Several researches have associated the development of AD with modifiable no-genetics risk factors, such as insulin resistance, hyperglycemic state, cardiovascular diseases, and diet. It has been reported that the "Mediterranean diet" (rich in vegetables, fruits, seeds and fish) can modulate cognitive functions trough provision of essential nutrients for brain development, but also by the composition and diversity of gut microbiota (GM), which digest soluble fiber and releases short-chain-fatty acids and other bacterial products that can reach the brain. Those bacterial products have an important role in the neuroinflammatory brain state. Soluble-fiber intake can modulate risk factors associated to the development of the AD, like insulin resistance and obesity, and it has been postulated that by decreasing pro-inflammatory bacteria while increasing anti-inflammatory bacteria gut microbiota may exert a neuroprotective action. Here, we determined the impact of a diet rich in fiber on cognitive function and amyloid deposition in female APP/PS1 mice. **Methods:** Female wild type (Wt) and double transgenic (APP/PS1) mice were fed during 2 months with a control diet (AIN-93), a high-fiber diet (AIN93+5% fructans) (F5%) or a F5% diet plus an antibiotic cocktail (ampicillin [1 g/l], neomycin [1 g/l], metronidazole [1 g/l],and vancomycin [0.5g/l],diluted in drinking water, (F5%+Abx). T-maze, novel object-recognition (NOR), elevated plus maze and water maze test were performed when animals were at diestrus/metaestrus state before end of treatment. We used immunohistochemistry technique to evaluate beta-amyloid$^{1-42}$ peptide in selected brain regions. **Results:** We found that a high-fiber intake improves short and long-term memory, and decreased anxiety in APP/PS1 female mice. Notably, antibiotic treatment mitigates the cognitive enhancing effects of fructans intake. Amyloid aggregation in several brain regions was significantly higher in the F5% group compared to F5%+Abx group. **Conclusion:** A high-fiber diet can modulate the cognitive performance in transgenic AD mice despite the amyloid aggregation tend to increase. Even more, Abx treatment resulted in a reduction of amyloid plaques with no parallel improved cognition, suggesting that amyloid plaques may have a protective effect.

Area: Neuropathology **Keywords:** Female, Cognition, Microbiota

Inhibition of HDAC4 with sodium butyrate does not prevent AMPA-induced excitotoxic degeneration of spinal motoneurons in vivo

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Selective motoneuron (MN) loss is the pathological hallmark of amyotrophic lateral sclerosis, and one important mechanism that has been identified is excitotoxicity mediated by the overactivation of glutamate receptors (Amyothrophic Lateral Sclerosis 8:197, 2012). The consequent axonal degeneration leads to the structural and functional damage of the neuromuscular junctions (NMJ) (Brain 136:2359, 2013). Histone deacetylase 4 (HDAC4) has been established as a critical transcriptional regulator at NMJ since it regulates the transcription of muscle-derived growth factors and other proteins that participate in the formation and maintenance of NMJ. Thus, under neurodegenerative conditions HDAC4 is overexpressed and triggers NMJ damage (J. Biol. Chem. 282:33752, 2007; Science 326:1549, 2009), and therefore we hypothesized that HDAC4 inhibition might have protective effects against NMJ degeneration. To test this, we studied the effects of the systemic administration of sodium butyrate (NaBut), a pan-HDAC inhibitor, in our model of chronic spinal MN death and hindlimb paralysis induced by the continuous infusion of AMPA into the rat spinal cord using osmotic minipumps (J. Neuropathol. Exp. Neurol. 66:913, 2007). NaBut (500 mg/kg) was administered, beginning one day after minipump implantation, daily for 6 days in a group infused with AMPA 3 mM, and 9 days in another group, infused with AMPA 1.5 mM. We found that NaBut did not significantly ameliorate or prevented the motor deficits produced by AMPA, assessed by the rotarod test and grip strength test, and also failed to prevent MN loss, which was studied histologically at days 7 or 10. Western blots of muscle acetylated histone 3 showed a significant increase, indicating that NaBut inhibit deacetylation. We conclude that under these experimental conditions HDAC inhibition did not protect against degeneration or motor function deficits, indicating that HDAC pan-inhibition might not be an appropriate therapeutic intervention for motor neuron diseases. Indeed, recent reports have pointed out the relevant role of other HDACs, such as HDAC7, whose activity maintains NMJ function (Muscle & Nerve; 52:1098, 2015) and NaBut might be inhibiting these HDACs.

Keywords: motor neuron, excitotoxicity, histone deacetylase, neurodegeneration

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The Ketone body beta-hydroxybutyrate restores autophagic degradation in the brain of hypoglycemic rats

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During severe hypoglycemia alternative substrates to glucose such as the ketone bodies (KB), acetoacetate (AcAc) and β-hydroxybutyrate (BHB) can be metabolized by brain. Studies have shown that KB prevent neuronal death in different injury models, although the mechanisms involved are still not well understood. Previous studies from our group suggested that impaired autophagy, a lysosomal-dependent degradation process activated during energy failure, participates in neuronal death induced by glucose deprivation in cortical cultures. In these conditions, D-BHB stimulates the autophagic flux and prevents neuronal death. Now we aimed to investigate whether autophagy is activated in the brain during insulin-induced hypoglycemia and glucose reperfusion and whether the neuroprotective effect of D-BHB, is related to autophagy modulation. We analyzed the effect of D-BHB on cell death induced by the hypoglycemic coma, in cresyl violet and Fluoro-Jade B (FJB) stained brain sections. Data show that D-BHB decreases the number of degenerating neurons in the hippocampus but not in the cortex. We also analyzed by immunoblot the changes in the content of the autophagy proteins, LC3-II, used as an index of autophagosome formation and p62/SQSTM1, involved in autophagic degradation. Results show autophagosome accumulation after 2 h of severe hypoglycemia in the cortex and hippocampus, as evidenced by increased LC3-II levels. At 6 h after the hypoglycemic coma LC3-II content decreased to basal levels. However, at 24 h a second increase in LC3-II was observed. In rats receiving 250 mg/kg (i.p) of D-BHB during glucose reperfusion, a significant decrease in LC3-II was observed, suggesting less autophagosome accumulation. No changes in p62/SQSTM1 were observed in the cortex, while in the hippocampus, a significant decrease was evident in D-BHB treated animals suggesting the stimulation of the autophagic flux in this region. When the dose of D-BHB was doubled (500 mg/Kg) LC3-II and p62/SQSTM1 were reduced at 24 h in both regions. The role of the mTOR pathway on autophagy induction was also investigated. Results indicate that mTOR activity is lower in the cortex and the hippocampus of D-BHB-treated animals. Despite this, phosphorylation of the ULK1, an essential protein for autophagy initiation and an mTOR target, is not changed in the cortex while it increases in the hippocampus after the hypoglycemic coma. D-BHB treatment decreases ULK1 phosphorylation. Altogether, results suggest that treatment with D-BHB prevents autophagosome accumulation and stimulates the autophagic flux enhancing neuronal survival. In the hippocampus apparently, D-BHB also downregulates autophagy initiation.

Keywords: Hypoglycemia, ketone bodies, autophagy.

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The mRVG29 peptide as vehicle for delivery of the CDNF gene in an animal model of Parkinson's disease.

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Introduction: Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra pars compact and reduction of the levels of dopamine in the striatum. Gene therapy provides powerful tools for treating neurodegenerative diseases. Cell-penetrating peptides (CPP's) are a group of short peptides, which have the ability to delivery cargo molecules into the cells without causing a significant lethal membrane damage. Our research group has developed a CPP based delivery system that includes the Asn194Lys mutation in an amino acid sequence of the rabies virus glycoprotein (mRVG-9R). Promising candidates for neurodegenerative diseases gene therapy are the neurotrophic factors. The conserved dopamine neurotrophic factor (CDNF) has neuroprotective effect on dopaminergic neurons.

Objective: To evaluate the efficiency of the mRVG29 peptide to deliver CDNF gene as therapeutic molecule in an animal model of Parkinson's disease.

Materials and Methods: To increase the binding of the mRVG peptide with the DNA molecules, 9 arginines were added (mRVG-9R). The mRVG-9R peptide, a karyophilic peptide (KP) and a plasmid carrying the CDNF gene, were electrostatically bound to form the mRVG-KP-CDNF complex. The mRVGm-KP-CDNF complex was injected at day 0 and at 3 weeks in the striatum. For the induction of the PD model, mice were administered Paraquat (PQ) intraperitoneally twice a week for 6 weeks. Before sacrificing the mice for the histological analysis, the motor and cognitive function were evaluated.

Results: The CDNF has a protective effect on the mesencephalic dopaminergic neurons and oligodendrocytes against the damage caused by the treatment with PQ. In addition, the CDNF inhibits astrogliosis and the microglia activation induced by PQ.

Conclusions: The protective effect of prophylactic treatment with CDNF prevents motor and cognitive dysfunction in an animal model of PD. This strategy has great potential in the treatment of PD and other neurodegenerative diseases.

Key words: CDNF, mRVG-9R, Parkinson's disease.

Effect of nicotine abstinence on both the anxiolytic-like behavior and synaptic transmission of the ventral hippocampus in young rats

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Área: Synaptic Transmission

Tabaquism is becoming a more common practice among teenagers. Anxiety is one of the symptoms during withdrawal syndrome that occurs when smokers decrease or stop the consumption of tobacco, and it is more common in females. Adolescence is a stage characterized by plasticity and structural brain changes involved in regulation of behavior and mood. Hippocampus is one of these structures, in which ventral region has been related with anxiety. Thus, we decided to analyze the effects of nicotine withdrawal on the neurotransmission of ventral hippocampus and the behavior of anxiety in female young rats (postnatal day 51) exposed for 15 days to an intake of nicotine (25 mg/L; from postnatal day 35 to 50). For this purpose, we achieved both the open field test (OFT) and the elevated plus maze test (EPMT) to evaluate anxiety-like behavior during the early nicotine abstinence phase (24 h). To examine the probable changes in synaptic activity in the ventral hippocampus, we will use the patch clamp technic. Until now, we have found no significant difference between groups in the total distance travelled (control group: 3494.39 ± 424 cm and experimental group: 3516.53 ± 319.1 cm; $p = 0.8413$; $n = 5$ each group), and the time in the center of the OFT (control group: 78.06 ± 19.48 seconds and experimental group: 76.5 ± 12.04 seconds; $p = 0.5$; $n = 5$ each group). Furthermore, in the EPMT, we also found no difference between control and experimental group in the time spent in the open arms (106.7 ± 46.48 seconds and 85.78 ± 38.44 seconds, respectively; $p = 0.2778$; $n = 5$ each group) nor in the closed arms (control group: 143.8 ± 44.31 seconds and experimental group: 141.6 ± 44.12 seconds; $p = 0.4524$). In conclusion, we have seen that under our condition female rats show no anxiogenic-like behaviors by nicotine abstinence. This could be due to many factors as the time of abstinence o exposure to nicotine.

Keywords: Nicotine, adolescence and abstinence.

Acknowledgment: We thank MVZ José Martín García Servín for his assistance in the bioterium, and Dra. Deysi Gasca Martínez for her assistance with the behavioral tests. This work was supported by a PASPA grant from DGAPA, UNAM.

Dendritic complexity in prefrontal cortex and hippocampus of the autistic-like mice C58/J

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Introduction. Autism spectrum disorder (ASD) has been associated to atypical neuronal connectivity in the prefrontal cortex (PFC) and the hippocampus (HC), in part, due to an alteration in neuroplasticity processes such as dendritic remodeling. Moreover, it has been proposed that abnormal cytoskeletal dynamics might be underlying the disrupted formation and morphology of dendrites in the ASD brain.

Autistic-like mouse strain C58/J has previously demonstrated neuronal cytoskeleton abnormalities, suggesting atypical polymerization and depolymerization cycles of microtubule and actin filaments that may affect the cytoskeleton rearrangement during dendritic outgrowth.

Hence, in this work we focused on the characterization of the dendritic arbor of the pyramidal neurons localized in the layer II/III of the PFC and the CA1 region of the HC in C58/J mice brain.

Methodology. Neuron cell morphology was assessed by Golgi-Cox technique. We performed a Sholl Analysis optimized by Bonfire program in order to evaluate the complexity of the neuron dendritic arbor, which involves the rate of branching, length and number of dendrites.

Results. An abnormal length of primary dendrites and a lower number of tertiary dendrites were observed in PFC and HC of autistic-like mice C58/J, respectively, along with a different spatial disposition of the branching pattern. In line with this, both brain areas displayed a diminished extension of the entire dendritic arbor comparing to WT mice (C57 BL6/J).

Conclusions. In this work, we proposed that C58/J mice display changes in the complexity of dendritic arborization of the pyramidal neurons of the PFC and the HC that could be associated to an alteration of neuronal cytoskeleton dynamics. This finding might indicate a modified neuronal connectivity in both brain structures and could be involved in the autistic-like behaviors that C58/J strain exhibits.

Plasticidad Celular y Circuitos Neurales

Key words: Autism, dendritic outgrowth, cytoskeleton

Connectivity in the auditory and premotor cortex in the rat brain

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Abstract:
Sensorimotor synchronization (SMS) is the coordination of rhythmic movements with an external rhythm. This SMS ability is essential for a number of human behaviors such as language comprehension, dance and music performance, activities that depend on a dynamic interaction between the auditory and motor system. Neuroimaging and electrophysiological studies have shown that the motor cortico-basal ganglia-thalamocortical circuit (mCBGT), which includes SMA, pre-SMA and the putamen, is involved in the beat perception and entrainment. Although it has been demonstrated that neurons in premotor regions (SMA and preSMA) respond to the presentation of auditory stimuli it is still not clear how the auditory cortex reach this premotor area. Here, we describe an anatomical study whose purpose is to determine whether the auditory cortex is connected with the motor system of the rat. Using retrograde fluorescent tracers Fluoro-Gold, Alexa Fluor 488 and 594**,** and multiunit activity recordings in auditory cortex we found that neurons in superficial and deep layers of the auditory cortex (A1) project directly to the supplementary motor cortex (M2), and axons of other areas such as motor, visual and somatosensory cortex also target M2 with different magnitudes. Furthermore, preliminary data also propose that this pathway M2-A1 is reciprocal and the connectivity varied in accordance with the tonotopic organization of A1. These findings suggest a strong and direct audiopremotor loop in the rat.

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Área: 6. Plasticidad celular y circuitos neurales

Auditory, motor, sensorymotor synchronization

The improvement of living conditions increases the effects of Citalopram at the level of neuroplasticity and behaviors associated with depression

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Major depression (MD) is a mental disorder constituting an enormous individual, social and economic changes. Also, exist different types of pharmacological and alternative therapies, which have been effective in the MD treatment. However, the STAR*D project suggests that patients that have an acceptable quality of life, tend to respond better to pharmacological treatment than poor quality life patients. In this regard, some preclinical studies have indicated that antidepressant drugs administered during environmental enrichment exposure reverse depression like behavior in mice. Interestingly, in that study, exposure to stress was interrupted once the pharmacological treatment was initiated. However, in the course of the depression-treatment stress is not immediately eliminated in humans. Then, the modification of the environment during pharmacological treatment and in presence of stress may be a more realistic environment. We thus here investigated whether the improvement of living conditions after two weeks of pharmacological treatment could be beneficial to reverse depression-like behavior in adult female mice exposed to chronic mild stress. We used adult female Balb/C mice. Mice were assigned to one of the following groups: 1) Control (CTRL); 2) Stress (CMS); 3) Citalopram (CITAL); 4) Environmental Enrichment (ENR) and 5) CITAL followed by ENR (CITAL+ENR). Mice were exposed to 10 weeks of stress. Pharmacological intervention with CITAL was initiated in the week 5 and ENR in week 7, without the interruption of stress condition either pharmacological treatment. Then, animals were exposed to the following behavioral battery test: 1) Coat state; 2) Object Location Test (OLT); 3) Novel Object Recognition Test (NORT); 4) Pattern Separation Test (PST) and 5) Forced Swim Test (FST). Finally, animals were euthanized and the brains were removed. To evaluate the changes on hippocampal neurogenic niche we used specific antibodies to identify several cellular populations in the dentate gyrus (Ki67, BrdU, Dcx, Calretinin, Iba-1). Results indicate that the exposure at the combination between the Enrichment and Citalopram (CITAL+ENR), in depressive-like behaviors, there was an improvement in the coat state and having similar effects respect to indicator of despair from de FST in relation with the group that was exposed to CMS with negative effects. Also, we observed that CITAL+ENR group show better performance in the OLT and NORT. Moreover, we observed that CMS leads to reduce the different phases of neurogenesis and the opposite effects were obtained CITAL+ENR group. Thus, our results suggest that the exposure to an ENR after two weeks of initial treatment with CITAL is able to revert depressive-like behaviors.

Keywords: Adult hippocampal neurogenesis, Enriched environment, Citalopram.

Área: Plasticidad Celular y Circuitos Neurales, Cognición y Comportamiento.

Long-lasting effects of environmental enrichment on behavior: implications of neuroplasticity in male Balb/C mice

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Environmental enrichment (ENR) induces neuroplastic and behavioral effects at the level of learning and memory processes but also to cope against stressful situations. Interestingly, ENR acts as a regulator of hippocampal neurogenesis and its effects persistent in female mice. However, the long-lasting effects of ENR on behavior related to anxiety and on aversive memory in male Balb/C mice has not been explored yet. We thus analyzed the persistent effects of ENR in adult mice on behavior and on the regulation of several populations that are involved in the neurogenic process. We used 42 male Balb/C mice. Seven mice were assigned to one of the six groups: 1) control, 2) ENR, assesed after ENR cessation; 3) control, 4) ENR, assessed one month after ENR cessation; or ; 5) control, 6) ENR, assessed two months after ENR cessation. Then, mice were exposed to the next behavioral test: 1) rotarod, 2) open field, 3) elevated plus maze and, 4) passive avoidance test. Two hours after the last behavioral test mice were sacrificed to dissect out the brain. Brains were used for immunohistochemistry to identify some protein markers involved in the hippocampal neurogenic process (intermediate stages of neuronal development, doublecortin (DCX); mature neurons and mossy fiber tract, Calbindin (CB). Also, we analyzed the changes of glial cells (GFAP, CNPase). Finally, we analyze the hippocampal neuronal activation identifying FosB/Delta FosB and cFos expression. Results were analyzed with one- or two-way ANOVA followed by the appropriate post-hoc test. The data indicate that ENR effects on anxiety- and learning and memory processes persist one or two months after cessation. These effects were accompanied with changes at the level of doublecortin associated cells and on glial cells identified with specific markers (GFAP and CNPase). Finally, these results strongly suggest that ENR induces neuroplastic changes in the proneurogenic niche of the dentate gyrus in the hippocampus and prevents the development of anxiety-related behavior but improves the learning and memory process.

Key words: environmental enrichment, neurogenesis, astrocytes, oligodendrocytes.

Area: Plasticidad celular

Analysis of the multineuronal activity patterns in the respiratory rhythm generator and its reconfiguration during hypoxia

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The preBötzinger complex (preBötC), located in the brainstem, is the central pattern generator for the respiratory rhythms, which is able to adjust its activity to different oxygen availabilities. Under normal oxygen conditions (normoxia) the preBötC generates the normal respiratory rhythm (eupnea), while under decreased oxygen concentration (hypoxia) it generates gasping, through a reconfiguration process. Despite that the activity of a variety of neural networks has been described in terms of its neural ensembles' interactions, this characterization has not been performed in the preBötC. Moreover, the likely changes in the ensembles' interactions during the reconfiguration of the preBötC during hypoxia has not been described either. Thus, it is our interest to describe the multineuronal activity patterns generated by the neuronal ensembles of the preBötzinger complex, in order to understand the variety of neural circuit configurations that this network can acquire in normoxia and hypoxia. By recording extracellular multineuronal activity with multielectrode arrays in brainstem slices, containing the preBötzinger complex, and by using mathematic vector analysis, we described the multineuronal activity patterns of the preBötC and their sequences under both oxygenation conditions. We found that the preBötC exhibit a variety of multineuronal activity patterns that can recur and alternate in an orderly fashion. However, we found that a multineuronal activity patterns dominates preBötC activity during normoxia, whereas a different one dominates preBötC activity during hypoxia. Thus, we can conclude that the activity of the preBötC can be described in terms of its neural ensembles' interactions and that changes in its multineuronal activity patterns are involved in the reconfiguration of this circuit in the transition from eupnea to gasping generation.

Neuronal ensembles, Multineuronal activity patterns (MAPs), breathing.

Repetitive transcranial magnetic stimulation induces antidepressant like effects and modifies cellular populations involved in the generation of new neurons

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Abstract.

Depression is a neuropsychiatric disorder that courses with neurochemical, morphological and behavioral alterations. In order to treat depression, there are several alternatives including the administration of antidepressant drugs (ADDs). However, the low proportion of subjects responding to ADDs has pointed to the direction to search new interventions. In this regard, repetitive transcranial magnetic stimulation (rTMS) has gained attention due to the fact that it generates neuroplasticity related modifications. Interestingly, the neurogenic process in the dentate gyrus of the hippocampus is modulated by antidepressant drugs in animal models of depression and studies performed in post-mortem brain tissue of depression diagnosed patients have suggested that some events of the neurogenic process are modified by these drugs. Contrary to the well-known mechanisms of ADDs and in despite to the antidepressant effects of rTMS in humans, it is still unknown whether rTMS is able to promote antidepressant like effects concomitantly with the regulation of hippocampal neurogenesis. We thus here investigated the pro-neurogenic effect of rTMS (5Hz) in female Balb/C mice exposed to chronic unpredictable mild stress (CUMS). The results indicate that rodents treated with rTMS (5Hz) for 28 days exhibited a decrease depression-like behavior compared to the group of rodents exposed to CUMS. Moreover, rTMS reverted the alteration caused by CUMS in the events involved in the neurogenic process (proliferation, Ki67; intermediate stages, doublecortin). In addition, we explored the effects or rTMS on the modifications of glial cells (microglia, astrocytes, oligodendrocyte). Also, we found changes at the level of neuronal activity evaluated with the expression of Arc-protein in the prefrontal cortex, hippocampus and amygdala. The results indicate that rTMS (5Hz) acts pro-neurogenic and reverse behavioral alterations caused by CUMS exposure in adult female Balb/C mice. Finally, our data may suggest that neurogenesis is a substrate for the beneficial effects of rTMS in the treatment of depression.

Keywords: repetitive transcranial magnetic stimulation, depression, neurogenesis.

Area: Plasticidad celular o Neuropatología

Striatal Parvoalbumin expressing neurons activate the striatal microcircuit and switch between different network states.

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Área: Plasticidad Celular y Circuitos Neurales

The striatum is the main entrance nucleus of the basal ganglia. Composed by distinct types of neurons, whose activity makes up striatal microcircuit activity. However, how specific types shape microcircuit activity remains yet unknown and relevant to pathologies given by activity disorders. The present work centers on identifying the role of PV^+ neurons after cortico-striatal stimulation *in vitro* with calcium imaging and describing the effect on the microcircuit of optogenetically activating this population. We found a functional participation of 6-10% of these neurons even though the firing was underestimated due to the difference in firing frequency and the calcium probe. Optogenetic stimulation of PV^+ neurons activated the striatal microcircuit in control conditions for several minutes; hence SPN activity indirectly reported PV^+ activity. Additionally, when applying optogenetic stimulation in a pharmacologically activated microcircuit, PV^+ cause change in population activity and their grouping though some neurons activity remains unchanged. Despite technical limitations we conclude that PV^+ activation allows for neural population change as seen previously by cortico-striatal stimulation, being PV^+ a primary drive for such change and therefore a target for therapeutic strategies.

Keywords: PV neurons, striatal microcircuit, feed-forward inhibition

Alterations in dendritic spine density and morphology correlate with an abnormal BDNF content in the prefrontal cortex of the autistic-like mice C58/J

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Introduction. In postmortem brain samples from individuals with Autism spectrum disorder (ASD), differences in the morphology of neurites have been identified in the prefrontal cortex (PFC), such as an increase in the number of immature-shape dendritic spines in pyramidal neurons from II/III layer. Since the shape of dendritic spines can be related to their functionality and plasticity, it has been suggested that dendritic spine abnormalities might be related to the atypical connectivity in the PFC of subjects with autism and associated with the difficulties in executive functions that characterize the disorder.
Among different factors, neurotrophins, like the Brain-Derived Neurotrophic Factor (BDNF) modulate the development of dendritic spines and their architecture. Along with this, a misregulation of BDNF expression has been included in the gamma of brain atypia in ASD.

Hence, in this work we focused on the analysis of the relationship between dendritic spine morphology and BDNF level in the PFC of the autistic-like mouse strain C58/J.

Methodology. Dendritic spine density and morphology was assessed by Golgi-Cox technique. We performed a manual counting system for spine density determination, and a shape-classification analysis based on the neck length and head width of dendritic spines from apical and basal dendrites of pyramidal neurons from II/III layer of the PFC. BDNF content in whole PFC was evaluated by western blot technique.

Results. The total number of dendritic spines along apical and basal dendrites from pyramidal neurons was diminished in the PFC of C58/J mice, while shape-classification analysis showed a greater frequency of filopodia-like and branched dendritic spines in the proximal and the distal region of apical dendrites, respectively, compared to WT mice. Besides, a lower frequency of thin dendritic spines was observed along the apical dendrites from PFC of C58/J mice. Moreover, BDNF content was diminished in the PFC of autistic-like mice. This could suggest an increased rate of immature dendritic spines and a different distribution of mature spines, which might be involved with an atypical synapsis establishment.

Conclusions. In this work, we found evidence of an alteration of dendritic spine morphology in the PFC of C58/J mice which might be associated with the lower content of BDNF found. This finding could suggest that an impaired BDNF signaling might promote an abnormal maturation of dendritic spines in ASD.

Plasticidad Celular y Circuitos Neurales

Key words: Autism, dendritic spines, BDNF

Plasmid Transfection in mouse brain using cationic polymers

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Introduction. The gene transfection technique using non-viral vectors has been widely used to modulate the expression of a target gene in cell cultures. Through this technique it is possible to: 1) Induce the gain of a gene of interest by transfection of over-expression plasmids; 2) Induce the transient loss of the expression of a specific gene by transfection of shRNA plasmids and 3) Identify transfected cells by transfection of reporter plasmids such as green fluorescent protein (GFP).

Objective. To induce the transfection of genes in different areas of the adult mouse brain.

Materials and methods. Adult mice, males of the BCL6 strain were used and were transfected with the plasmid encoding the reporter protein GFP (CMV-GFP). The cationic polymer polyethyleneimine (PEI) was used to complex the plasmids at a N/P 6 ratio. The complexes were introduced into the lateral ventricle of the mouse brain and into the hippocampus by stereotaxic injection. To perform intracerebral stereotaxic injection, the mice were deeply anesthetized using isoflurane gas. The brains were recovered 48 hours post-transfection, were fixed and prepared to be observed under fluorescence microscope.

Results. GFP positive cells were observed along the lateral ventricle (ventral and caudal area) as well as in the hypothalamus. Under these conditions it was not possible to observe GFP-positive cells in the hippocampus.

Conclusions. The N/P 6 ratio is effective for transfecting the cells around the SVZ and the hypothalamus, however, it is necessary to test other proportions of PEI / plasmid to transfect the hippocampal cells.

Key words: Non-viral transfection, Plasmid brain delivery, adult neurogenesis.

Arsenic alters the expression but not the function of P2X7 and P2Y2 purinergic receptors in Neuro2a cells: implications for Alzheimer Disease

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Arsenic is a neurotoxic agent related with development of Alzheimer's disease (AD). Recent hypotheses suggest that an age-dependent ineffective activity of α-secretase is responsible of β-amyloid (Aβ) overproduction in AD. Previous reports of our group have suggested that arsenic decreases the activity of α-secretase as well as the increment of Aβ in diverse models exposed to arsenic and its metabolite DMA^V. Previous reports indicate that α-secretase activity is modulated by P2X7 and P2Y2 purinergic receptors, having opposite effects: P2X7 results in the inhibition while P2Y2 is an activator of α-secretase. Post-mortem studies in brains of AD patients show an increase in the immunoreactivity to ionotropic P2X7. In contrast, metabotropic P2Y2 is a neuroprotector factor that diminishes its expression as the disease progresses in animal models of AD. Our results indicate that arsenic exposure increases the expression of P2X7 and diminishes P2Y2 receptors in Neuro-2a cells. This alteration was found both at protein and RNA levels, suggesting a transcriptional modulation. The functionality of the receptors was evaluated through the patch clamp technique in HEK293 cells expressing P2Y2 and Kv7.2/7.3, followed by calcium capture in Neuro2a. BzATP-evoked P2X7 currents were increased in arsenic- and DMA^V-exposed cells. Results show that increased P2X7 are functional. On the other hand, P2Y2 was evaluated indirectly by means of Kv7.2/7.3 regulation. The activity of this channel is PIP2-dependent, thus P2Y2 stimulation induces convertion of DAG and IP3. We observed that ATP stimulation of P2Y2 receptor leads to an increased Kv7.2/7.3 current inhibition in arsenic- and DMA^V-exposed cells compared to control, suggesting a lower expression of this receptor. These data were corroborated by calcium capture assays in Neu2a exposure arsenic. We conclude that the activation of P2X7 and P2Y2 receptors affects the modulation of α-secretase in arsenic- and DMA^V-exposed neurons, promoting the AD pathogenesis.

Área: Transducción de señales

Keywords: arsenic, purinergic receptors, Neuro2a

GPR40 and GPR120 receptors activation with DHA and its implication in cytoskeleton rearrangement in hippocampal neurons of an autistic-like mouse

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Area: Signal transduction

Docosahexaenoic acid (DHA) is a ω3 polyunsaturated fatty acid. DHA supplementation in primary neuronal cultures has been implicated in changes in the complexity of the neuronal dendritic tree, promoting dendrite growth and increase branching. Structural changes in the dendritic tree are driven by the reorganization of the cytoskeleton; one of the components of the cytoskeleton is the microtubules (MTs) whose dynamics are regulated by associated proteins (MAPs). These MAPS are regulated by posttranslational modifications; Tau and MAP2 phosphorylation decrease their interaction with the MTs promoting depolymerization. Among the kinases able to phosphorylate Tau and MAP2 are Erk1/2 and AKT; these kinases can be activated by many transduction signals such as GPCRs (G protein coupled receptors) like GPR40 and GPR120 that are activated by DHA.

A neurodevelopmental disorder with changes in the complexity of the neuronal dendritic tree is the autism spectrum disorder (ASD). These changes have been reported in the hippocampus of humans and by our laboratory in a model of autistic-like mouse (C58/J). Interestingly these data correlate with changes in content of phosphorylated and total Tau, which is lower in the hippocampus of autistic-like mouse.

Taking all of these into account we wonder if DHA signaling through GPR40 and GPR120 could increase Tau and MAP2 phosphorylation via AKT and Erk1/2 kinases in wild type and autistic-like mouse strains; and if this signaling pathway leads to increase the complexity of the dendritic tree in both mice.

First we seek which Tau and MAP2 residues that could be implicated with microtubule interaction were phosphorylated by Erk1/2 and AKT. We used three software (GPS v3.0, KinasePhos, PPSP), to determine *in silico* the residues that might be phosphorylated by these kinases. We found 12 sites in Tau that could be phosphorylated by Erk1/2 (8), AKT (2) and by both kinases (3); and 18 sites in MAP2A, 16 phosphorylated by Erk1/2, 1 by AKT and 1 by both.

Next, we wanted to know if GPR40 and GPR120 activation by DHA could activate Erk1/2 and AKT. We stimulate primary cultures of embryonic hippocampal neurons with DHA (100 µM) for 5 minutes and analyze by western blot the phosphorylation of Erk1/2 and AKT. At 5 minutes DHA could increase Erk1/2 phosphorylation compare to control, but not AKT. AKT could, in turn, be activated at longer stimulation times.

These results suggest that Erk1/2 is activated by DHA stimulation at short times, which could phosphorylate Tau and MAP2 downstream the GPCR pathway.

Key words: Docosahexaenoic acid (DHA), GPR120/GPR40, microtubule associated proteins (MAPs)

Nucleus accumbens shell single-unit activity encoding of reward probability estimation

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The estimation of reward probability allows an organism to make predictions, adjust action selection and maximize the cost-benefit of the available response options. This flexible behavior is essential during foraging where, by estimating the reward probability that a food source is replenished or depleted, the animal could minimize energy expenditure and maximize the energy obtained. The capacity to assess reward probability relies on a complex network that includes the Nucleus Accumbens (NAc). Indeed, dopamine levels in the NAc core are sensitive to reward rate. However, it remains unexplored the role of the NAc Shell in the estimation of reward probability at the single neuronal activity level. To address this issue, we recorded single units of the NAc Shell, while rats performed an adaptative decision-making task. During a trial, the subject had to approach and place its nose into the central port for 0.7s; subsequently, an auditory stimulus was delivered (Go cue), signaling the subject to press the left or right lever, each one was associated with an independent reward probability: L10-90R, 10-50, 50-90, 50-50%, counterbalanced between subjects. Then the rat had to move to the opposite wall to emit two dry licks in the sipper, followed by three drops of sucrose (one per lick) If rewarded, or dry licks if unrewarded. The probabilities assigned to each lever were changed every 50 trials without any explicit signal. Thus, animals must continuously estimate reward probability across the session. We apply a scaling in time for each transition in the task (e.g. rat moving from the central port to the levers or the time between the lever press to the first lick), in order to observe more efficiently the onset of modulations in this transitions that were variant in time and scaling inter-lick interval, showing some neurons with a oscillatory response. We found neurons that were selectively modulated by the Go cue, the lever press, or the consummatory behavior; while other neurons encoded more than one variable of the task, displaying a more sensorimotor integrative profile. Interestingly, we found neurons encoding information about the chose lever just after the Go-cue and during the lever press. On the other hand, we found neurons encoding information about the reward (e.g. delivery or the omission of the reward). The firing rate of these neurons in a trial-by-trial basis covary as the reward probability function. The reward probability was meanly decoded at the time of reward delivery and it decay at the end of the trial. Our results uncovered NAc Shell neurons that estimate the reward probability in a flexible manner in every choice made.

Differential patterns of Evoked Related Events of the retrieval of spatial and temporal contexts

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Investigation area: Cognition and Behavior

Abstract

Episodic memory allows to remember events within a temporal and spatial context. It is known that the electrical brain, evaluated with Evoked Related Potentials (ERPs), is associated with the amount of information in source paradigms. However, there are few human episodic memory studies about temporal and spatial context, despite the definition of episodic memory. There is unknow how the brain electrical activity changes depending of what kind of information is remembered (i.e. spatial or temporal context) after learning an event presented with spatial and temporal contexts. The aim of the study was to evaluate the differences in the brain electrical activity pattern associated with the information recollected. Twenty-three (six men) subjects participated in this study, without psychiatric history. The participants performed a source memory task. The task involved six blocks of images. Every block had two phases: an encoding phase and a retrieval phase. The participants classified as natural or artificial the image during the encoding phase; during this phase, the images were separated on two series, and they could appear above or under a fixation point. During the retrieval phase, the participants pressed a button, in function of where (temporal context) and when (spatial context) the image was showed up in the encoding phase. The ERPs were obtained with the electroencephalography register of the retrieval phase. We found a differential effect by region in function of the information recollected in early latencies. On the one hand, the retrieval of temporal information was associated principally with frontal regions; on the other hand, the retrieval of spatial information was associated with occipital regions. The differences in the process of the retrieval of context information is given even from early temporal windows.

Clave words: Evoked Related Events; Episodic memory; Retrieval information;

Neuroprotective effects of Adiponectin in an Amyloid Beta1-42 model

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Área: Cognición y Comportamiento

Alzheimer's disease (AD) accounts for more than half of the world wide dementia cases. One of the first symptoms of AD is anosmia, this has been correlated with the burden of amyloid β. In recent studies it has been demonstrated that metabolic diseases such as diabetes mellitus type 2 (DM2), increase the risk of developing neurodegenerative diseases such as AD. It is also known that DM2 and aging, both show low adiponectina plasmatic levels, a hormone that increases insulin sensitivity and has anti-inflamatory and anti-oxidant effects. Adiponectin bounds to the receptors AdipoR1 and AdipoR2 widely expressed in the central nervous system, thus increasing insulin sensitivity in the hippocampus (Hipp) and olfactory bulb (OB).

Here we demonstrate that an intracerebroventricular (ICV) injection of adiponectin protects against the neurodegeneration induced by an intrahippocampal, determined by the decrease in GFAP and IBA1 glial markers in the Hipp and OB. We also determined a clear diminishment of lipoperoxidation markers in both nuclei.

Our present results indicate that the increase in Adiponectin levels in the brain can prevent the deleterious effects in memory induced by the Amyloid Beta1-42 model.

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Alzheimer's Disease, Olfaction, Adiponectin.

Evidence-Integration Mechanisms of Rhythmic Stimuli Discrimination

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12. Cognición y Comportamiento

The ability to detect fine differences in the temporal structure of repeating events lie behind the accurate execution of many important behaviors requiring anticipation or synchronization to dynamic signals (speech, movement, etc.). In order to optimally perceive these events, the mechanisms devoted to process sensory evidence through time are supposed to adopt an accumulative strategy: storing the incoming evidence and using it to activate a motor plan associated with the adequate response option. However, due to the temporal load caused by these stimuli, an alternative hypothesis could state a simpler detection strategy, based on noticing single above-threshold evidence units. We use psychophysics and computational modeling to test whether human subjects use accumulative or detection strategies to classify rhythmic stimuli. Stimuli in the behavioral task consist of a sequentially presented set of brief pulses, spaced at constant or randomly-varied intervals. We asked subjects to respond, as fast as they made a decision, if pulses were presented at regular or irregular pace, and we recorded responses and response times associated to every stimulus temporal structure. Our results show that human subjects can use randomly-distributed temporal evidence to discriminate rhythmic stimuli and optimize response times. Computational modeling of subjects' performance shows that an almost-perfect accumulative strategy is better than the simple accumulative or detection versions. We conclude that the mechanisms leading to stimuli discrimination based on their temporal structure are highly dependent on sensory modality and storage load, but also, that it is better explained by an accumulative with moderated leaking process.

Keywords: behavior; modelling; decision making.

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Perceptual decision making in the intraparietal sulcus: Implications in the modulation of local field potential.

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Perceptual decision making involves the conversion of noisy sensory signals to a discrete motor act. Spiking activity in the parietal cortices have been related to perceptual decisions. However, the relationship between local field potentials (LFPs) and decision-making in the parietal cortices is unknown. In the present work, we analyzed LFP recordings from the anterior intraparietal area (AIP) of two rhesus monkeys performing a tactile categorization task in which they had to communicate whether and object rotated clock- or counter-clockwise. The results show a power increase in the 20-40 Hz band that was informative of the subjects' decisions. These findings provide evidence that decisions can be decoded in the early sensory stages of the somatosensory hierarchical processing.

Keywords: Perceptual decision, local field potentials, somatosensory.

Area: Cognition and behavior.

Decision-making process in areas of sensory integration

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Perceptual decision-making engages a variety of cognitive processes. In order to understand them, we need to study changes in neuronal activity patterns, related to the sensory representation of a stimulus, and to the execution of a behavioral response. Our main goal was to determine how sensory representations and decision-making activity are encoded.

We trained two Rhesus monkeys in a tactile categorization task were they actively reach and grasp an object to determine its spatial orientation. We recorded the activity of single neurons in the anterior intraparietal sulcus (AIP) during the execution of the tactile task.

Neuronal activity was clustered using a hierarchical algorithm and the resultant patterns were related to the temporal dynamics of the task. We found that different groups of neurons in the AIP responded to specific task events; such as movement, stimulus representation, and decision-making.

Our findings revealed that combined activity of these different neuronal populations converge in the decoding of the events of the task, representing faithfully the physical characteristics of somatosensory stimuli and encoding the behavioral choices.

Keywords: behavior, decision-making, somatosensory system.

Optogenetic inhibition of the Dorsomedial versus Dorsolateral Striatum

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The basal ganglia is a system of subcortical nuclei involved in the selection of actions and the performance of voluntary movements. Within the basal ganglia, the striatum contains the cell bodies of the two communication pathways of this system; the direct pathway and the indirect pathway. According to the classical model of the operation of these pathways, the first promotes the movement, and the second decreases it. In recent years evidence testing these model presents some inconsistencies with this interpretation, which may be explained if the attributed function of these pathways is not generalized and we identified their specific contributions in sensorimotor *versus* association circuits within the striatum.

In this study, we performed optogenetic inhibition, using archaerhodopsine stimulation, of the direct and indirect pathways of the basal ganglia in the compartments that harbor the sensorimotor circuits (dorsolateral) *versus* associative compartments (dorsomedial) of the striatum during an action selection and on locomotion. Our results show different contributions of the striatal pathways cells in the dorsolateral striatum versus the dorsomedial striatum respectively.

We suggest that the functions of the striatal pathways can´t be generalized, the functions of these pathways depend on which striatal compartment is being implicated.

Keywords: Basal Ganglia, Striatum, optogenetics.

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High-Fat and High-Fructose Diet-Induced Obesity Impair Recognition Memory in C57BL/6 Adult Mice

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Abstract

Diet-induced obesity produces adverse effects on cognition. Several studies have reported that high-fat high-sugar diets produce deficits in recognition memory, a type of declarative memory that provides the ability to recognize objects, people and places previously experimented. However, these results are inconsistent, probably due to the different macronutrients of diets such as fat and fructose. It is unknown how the composition of diets with high amounts of fat and fructose impact on recognition memory in rodents. The aim of this study was to assess the effect of two hypercaloric diets administered in mice on recognition memory to determine whether the composition of these diets induce recognition memory impairment. Fourteen-weeks old C57BL/6 adult male were used in this study. A total of thirty two mice were housed in couples and divided into three groups: a control group (CD) fed with low-fat diet without fructose (n=10), a group (HFD) fed with high-fat diet without fructose (n=10), and a group (HF+FrD) fed with high-fat high-fructose diet (n=12) *ad libitum* and pellet form for ten weeks. Recognition memory was evaluated using the novel object recognition (NOR) and novel location (NOL) tasks at the end of diet administration. These tasks were performed in an open field box and using the software ANY-maze during four sessions with 24-h intervals. Compared to CD, mice fed with HFD and HF+FrD shown a significant reduction in times exploring in the novel or familiar objects during the execution tasks ($p<0.05$). Discrimination indexes were lower in HFD group ($p=0.02$) and HF+FrD ($p=0.02$) in the location task. In addition, HF+FrD mice showed a negative correlation between body weight and discrimination indexes for NOR ($r=-0.507$; $p=0.03$) and NOL ($r=-0.542$; $p=0.02$) tasks. These findings suggest that HFD and HF+FrD might be altering hippocampus-dependent declarative memory, particularly memories of familiar object locations.

Keywords: Obesity, diet, recognition memory

Association of Adiposity with Inhibitory Control and Prefrontal Symptoms in Women with Excess Body Weight

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Área: Cognición y comportamiento

Abstract

The inhibitory control, is the ability to stop or regulate automatic response to a stimulus and discard irrelevant aspects, both internal and external, by means of sustained and selective attention before, during and after performing an action. Recent studies have linked overweight and obesity with the lack of inhibitory control, which is mediated by the prefrontal cortex. The prefrontal symptoms can be an adequate measure of frontal lobe functioning by identifying those symptoms related to difficulties in planning, cognitive inflexibility, disorganization of behavior, impulsivity, deficits in working memory and motivation, that is, in executive functioning. However, little is known about the association of adiposity with the prefrontal symptoms. The aim of the current study was to correlate adiposity with inhibitory control and prefrontal symptoms in nonclinical population. Seventy young women between 18 and 25 years old, were grouped according to the Body Mass Index (BMI), 34 with excess body weight (BMI>25 Kg/m^2) and 36 with normal weight (BMI 18.5 to 24.9 Kg/m^2). Inhibitory control was assessed using the *Stroop* test and the prefrontal symptoms was measured with the Inventory of Prefrontal Symptoms (IPS). Anthropometric evaluation was measured based on the International Society for the Advancement of Kinanthropometry (ISAK); adiposity was measured by bioimpedance and skin folds by plicometry. Compared with the normal weight group, women with exess body weight showed a higer body fat ($p<0.001$), lower number of correct answers ($p<0.01$), higher number of errors ($p=0.02$), omissions ($p = 0.02$) and higher scores in IPS ($p<0.05$). Higher visceral adiposity was associated with higher prefrontal symtoms ($r=0.275$, $p=0.02$). Body mass index (BMI) was negatively associated with the number of correct answers in Stroop test ($r=-0.321$, $p<0.01$) as well as the percentage of body fat ($r=-0.321$, $p<0.01$); visceral fat ($r=-0.285$, $p=0.01$), waist circumference ($r=-0.271$, $p=0.02$), arm circumference ($r=-0.320$, <0.01), and suprailiac and tricipital folds respectively ($r=-0.275$, $p=0.02$; $r=-0.321$, $p=0.04$). These results suggest that adiposity plays an important role in executive, motivational and attentional control that could have an impact on eating behavior.

Keywords: Inhibitory control, adiposity, prefrontal symptoms.

Repetitive transcranial magnetic stimulacion (5 Hz) promotes learning and memory processes, increases the number of doublecortin associated cells and the axons of granule cells in Swiss-Webster female mice

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Abstract.

Repetitive transcranial stimulation (rTMS) is non-invasive intervention to treat neurological and neuropsychiatric disorders. Interestingly, rTMS has shown impresive effects in depression, Parkinson and Alzheimer diseases, respectively. However, the application of rTMS has suggested the cognitive improvement in patients of those disorders. One of the brain regions that may be affected by rTMS is the hippocampus. In this brain region exist a proneurogenic niche and the new neurons generated in the dentate gyrus of the hippocampus are involved in learning and memory processes but also in coping stressful experiences. Based on the above-mentioned antecedents, in this study we analyzed the benefits of rTMS (5 Hz) in the learning and memory processes and on the regulation of several populations that are involved in the neurogenic process. We used 16 female Swiss Webster mice. Eight mice were assigned to one of the two groups: 1) sham or 2) rTMS (5Hz). Mice received two sessions per day for 14 consecutive days. Two days after the last session of rTMS mice were exposed to the next behavioral test: 1) rotarod, 2) object location test, 3) novel object recognition test, 4) pattern separation test and, 5) passive avoidance test. Two hours after the last behavioral test mice were sacrificed to dissect out the brain. Brains were used for immunohistochemistry to identify some protein markers involved in the hippocampal neurogenic process (proliferation, Ki67; intermediate stages of neuronal development, doublecortin (DCX); mature neurons and mossy fiber tract, Calbindin (CB)). Also, we analyzed the changes of glial cells (GFAP, CNPase or CD-11b). Finally, we analyze the hippocampal neuronal activation identifying FosB/Delta FosB and cFos expression. Results were analyzed with one- or two- way ANOVA followed by the appropriate post-hoc test. The data indicate that rTMS (5 Hz) favors the learning and memory processes in female Balb/C mice. Also, rTMS /5Hz) increases the number of DCX-associated cells and increases the volume of the axons of granule cells identified with CB. In addition, hippocampal neuronal activation was higher in mice exposed to rTMS than in the sham group. These results strongly suggest that rTMS (5 Hz) induces neuroplastic changes in the proneurogenic niche of the dentate gyrus in the hippocampus and improves learning and memory.

Keywords: Repetitive transcranial stimulation (rTMS), Neurogenesis, Neuronal plasticity.

Area: Plasticidad celular, cognición y comportamiento

Repetitive transcranial magnetic stimulacion (5 Hz) promotes learning and memory processes, increases the number of doublecortin associated cells and the axons of granule cells in Swiss-Webster female mice

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Abstract.

Repetitive transcranial stimulation (rTMS) is non-invasive intervention to treat neurological and neuropsychiatric disorders. Interestingly, rTMS has shown impresive effects in depression, Parkinson and Alzheimer diseases, respectively. However, the application of rTMS has suggested the cognitive improvement in patients of those disorders. One of the brain regions that may be affected by rTMS is the hippocampus. In this brain region exist a proneurogenic niche and the new neurons generated in the dentate gyrus of the hippocampus are involved in learning and memory processes but also in coping stressful experiences. Based on the above-mentioned antecedents, in this study we analyzed the benefits of rTMS (5 Hz) in the learning and memory processes and on the regulation of several populations that are involved in the neurogenic process. We used 16 female Swiss Webster mice. Eight mice were assigned to one of the two groups: 1) sham or 2) rTMS (5Hz). Mice received two sessions per day for 14 consecutive days. Two days after the last session of rTMS mice were exposed to the next behavioral test: 1) rotarod, 2) object location test, 3) novel object recognition test, 4) pattern separation test and, 5) passive avoidance test. Two hours after the last behavioral test mice were sacrificed to dissect out the brain. Brains were used for immunohistochemistry to identify some protein markers involved in the hippocampal neurogenic process (proliferation, Ki67; intermediate stages of neuronal development, doublecortin (DCX); mature neurons and mossy fiber tract, Calbindin (CB)). Also, we analyzed the changes of glial cells (GFAP, CNPase or CD-11b). Finally, we analyze the hippocampal neuronal activation identifying FosB/Delta FosB and cFos expression. Results were analyzed with one- or two- way ANOVA followed by the appropriate post-hoc test. The data indicate that rTMS (5 Hz) favors the learning and memory processes in female Balb/C mice. Also, rTMS /5Hz) increases the number of DCX-associated cells and increases the volume of the axons of granule cells identified with CB. In addition, hippocampal neuronal activation was higher in mice exposed to rTMS than in the sham group. These results strongly suggest that rTMS (5 Hz) induces neuroplastic changes in the proneurogenic niche of the dentate gyrus in the hippocampus and improves learning and memory.

Keywords: Repetitive transcranial stimulation (rTMS), Neurogenesis, Neuronal plasticity.

Area: Plasticidad celular, cognición y comportamiento

Cortico-strital contribution to execution of a chain of sequences.

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It's has been suggested that the basal ganglia receives an internal signal from different cortices in order to perform an action sequence, e.g. from the supplementary motor area (in rodent M2) and from the prefrontal cortices (e.g. prelimbic; PL). To date, it's not understood how the cortices may guide the striatal activity to perform a chain of sequences.

In this work we ask whether the corticostriatal projections contribute to the learning or execution of a chain of sequences.

To address this question we designed a task in which animals do a chain of two sequences of lever press, in a stimulus-response or self paced manner. The data from the specific optogenetic inhibition of corticostriatal synapses and the electrophysiological recording of photo-identified corticostriatal cells will be presented.

Our preliminary results suggest that both M2 and PL contain corticostriatal cells that present spikes modulation during the performance of the chain of sequences; and that their synaptic contribution may be required for the initiation and proper performance of the chain of sequences.

Keywords. – execution; corticostriatal; sequences.

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An approach to the study of linguistic deficiencies in Alzheimer's patients through words association norms

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Alzheimer´s disease (AD) is a syndrome that can be caused by a number of progressive alterations, affecting cognition amongst other functions (Jurado, Mataró, & Pueyo, 2013). During the process of non-pathologic aging, language is one of the least affected cognitive functions. On the contrary, language impairment is considered as one of the most usual manifestations of AD and other dementias, causing serious linguistic deficiencies (Ober, Shenaut & Reed,1996). This research shows how Alzheimer's affects lexical access and semantic memory through word association norms (WAN), a corpus of free association of words in which the participant reads or hears a word and is requested to write or say the first word that comes to mind (Clark, 1970).

Eight older adults participated: four participants had Alzheimer's disease (AD) and the other half was of the control group (CG). The CG had no diagnosis of neurodegenerative disease and it was formed by participants as equivalent as possible in sex, age and years of education to the group with AD. The WAN task was carried out through the computer program *SS_Palabras 2.0*. which consists of the visualization of 118 stimulus words, presented one-by-one orally by a researcher who wrote in the computer program the participants' responses. For each stimulus, the participants had to respond verbally with the first word that came to their mind, based on Barrón-Martínez and Arias-Trejo (2014). The calculation of five WAN measures was performed: strength of association (SA), number of different associates (NA), idiosyncratic or unique responses (IR), blank responses (BRL) and response time (RT). Also, a classification of lexical relations was carried out according to Clark (1970) into syntagmatic and paradigmatic responses, as well as anomalous responses (answers with more than one word, onomatopoeias and blank answers).

Participants with AD showed less NA than the CG. Moreover, the AD group had a greater BRL, while in SA a small difference was observed between groups. In anomalous responses, significant differences were found between both groups, where the group with AD had a greater proportion than the CG. Additionally, the AD group had a higher response time than CG in the production of both paradigmatic and syntagmatic responses, which were only surpassed by the response time for anomalous responses in the AD group.

Keywords: Word association norms, lexical relations, Alzheimer's disease

Relation of animal protein intake and brain dynamics in indigenous infants of an Isolated Me'phaa community

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Area: Development and aging

Over the last 40 years, it has become more evident the critical role of nutrition for the development and functional maturation of the nervous system. Brain development is considered one of the most metabolically expensive events in life. For instance, there is an increment of 50% in glucose consumption at the ages between 5 and 10. Additionally, adequate protein consumption is vital throughout morphological, neurochemical and neuropsychological development, being the main source of amino acids required for optimal metabolism and structural maturation. Therefore, protein deficit during synaptic refinement could lead to dysfunctional connectivity and thus, cognitive impairment. It is estimated that food insecurity affects 23.3% of Mexican population; being more critical in isolated rural regions where only 4.5% present food security. Such populations are mainly conformed by indigenous people. Due to the low access of nutritional requirements, these communities might be the most affected in the development and functional maturation of the nervous system. Nevertheless, all studies have been done in urban societies in developed countries called "W.E.I.R.D" societies .
Here, we examined the relation between animal protein intake and brain dynamics using EEG record in 31 children (19 girls and 11 boys) between the ages of 5 and 10 from and indigenous community called Me-Phaa of the State of Guerrero in Mexico, during an eyes-closed/eyes opened resting condition. We used Fourier transformed in forty-five clean segments of one second for each EEG record to provide estimates for absolute power in delta, theta, alpha and beta classic bands of 5 regions of interest (ROIs): frontal left, frontal right, middle line, posterior left and posterior right. We applied a Food frequency Questionnaire and obtained anthropometric measure for these children. We found that in eyes opened condition, participants with lower animal protein intake displayed significant differences in absolute power values in the alfa and theta bands, between frontal and posterior regions in both hemispheres. These results have been previously described as indicator of brain maturation. There are only a few studies in these communities' type across the world and they open a window to know the effect of the animal protein intake in the development of the brain.

Keywords: QEEG, neurodevelopment, Indigenous Population

REGULATION OF ACTIN CYTOSKELETON BY p47 OVEREXPRESSION IN CEREBELLAR GRANULE NEURONS

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Reactive oxygen species (ROS) act as signaling molecules for the regulation of physiological processes such as cell migration, growth, differentiation and programmed cell death, among others [1,2]. It has been suggested that ROS control protein function through the oxidation of specific amino acids such as cysteine residues [3]. Particularly, H_2O_2 is the main ROS involved in these processes [4].

Recent evidence indicates that ROS participate in the regulation of neurites growth [5]. It is known that an increase or reduction of the physiological levels of ROS in cerebellar granular neurons induces growth cone collapse and short neurite phenotype, respectively [5,6]. On the other hand, intracellular ROS are produced by different sources, including the NADPH oxidase (NOX) enzymes [3]. Previous studies have shown that the knockout of NOX2 shows alterations in the development of neurites [7]. In spite of these evidences, the precise signaling mechanisms involving ROS and their sources in this event are still unknown.

Here, we propose that neurite growth is regulated by the action of ROS on actin polymerization. We evaluated this possibility in primary cultures of cerebellar granule neurons by the overexpression of the NOX subunit p47, by using Fluorescence Recovery After Photobleaching (FRAP) technique to evaluate actin polymerization. It has been shown that p47 overexpression leads to ROS production. Thus, we co-expressed LifeAct:mCHerry together with GFP or p47:GFP. LifeAct:mCherry is a fluorescent marker that allows the evaluation of actin polymerization in living cells by FRAP.

Our data analysis of FRAP indicated that secondary and tertiary axonal processes showed a similar polymerization rate, in contrast to dendrites that displayed a higher polymerization. In addition, our results showed that the complete recovery of fluorescence occurs after 500s under the pro-oxidant condition (p47:GFP). However, control neurons (GFP alone) showed a total recovery after 3500s.

Our results indicate that the dynamics of actin polymerization is different in axons and dendrites and that a pro-oxidant condition promotes actin polymerization. In addition, our data support the possibility that the NOX is a positive physiological regulator of the polymerization of actin in the elongation of the neurites in cerebellar granule neurons during development.

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CLUE WORDS

ROS, NOX, ACTIN

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Relation between the intake of lipids and the brain dynamics on indigenous children from a Me'phaa community

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Area: Development and aging

The environment where organisms inhabit sets ecological pressures that limit the available resources. Natural Selection benefits those individuals that efficiently allocate these limiting resources for their different life-history components, such as somatic growing, reproduction, immunity, and cognitive processes. Inside each organism, the amount of metabolic energy assigned to different functions will vary depending on the stage of life. In humans, during the first years of life, the brain has the major demand of metabolic energy in the whole body. At this age, the brain sets flexible routes of information management, even without specific cognitive demands. This cerebral process is called resting state cerebral activity and is fundamental for the cerebral communication at the moment of a cognitive task. The intake of lipids is crucial for the correct develop of these neural networks, since lipids are the main component of the neuron membranes, and play an important role in the cerebral maturation and communication. At the present investigation, the relation between the intake of vegetal and animal lipids, the nutritional state and the resting state electrical brain activity was studied by analyzing EEG recordings in resting state, open and closed eyes in a monopolar montage from 31 children, 19 girls and 12 boys from 6 to 11 years old from an Isolated Me'phaa community in the state of Guerrero. Additionally, in order to obtain the consumption of food with content of lipids, as well as their nutritional state, we also obtained different anthropometric measures (height and weight), and a food consumption questionnaires. The EEG recordings were submitted to power analysis of Delta (1-3 Hz), Theta (4-7 Hz), Alpha (8-14 Hz) and Beta (15-30 Hz) bands through Fast Fourier Transform, 42 segments of each condition were analyzed in five regions of interest left anterior (Fp1, F3, F7), right anterior (Fp2, F4, F8), left posterior (P3,T7, O1), right posterior (P4, T8, O2) and middle line (Fz, Cz, Pz). A negative association was found between the animal lipid consumption and the differences on the absolute power between posterior and anterior regions in the theta band in open eyes condition and in the two hemispheres. These results can be explained in the light of the cerebral maturation where with the increasing age, it's expected to decrease the absolute theta power, so we can say that the consumption of animal lipids is associated with the course of cerebral maturation. *Key words: Neurodevelopment, QEEG, Animal lipids, indigenous populations.*

The role of the autophagy during the early nervous system development

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Autophagy is considered as a critical stress response, this catabolic process allow to the cell obtain nutrients and eliminate protein aggregates or damaged organelles. However, autophagy also has other less known functions: it promotes type II programmed cell death, mediates protein traffic to the plasma membrane and secretes proteins by an unconventional pathway.

Usually, when we hear about *nervous system development* instantly we associate it with *neurogenesis* or *neural migration* but there are other events that occur earlier and are very important. In vertebrate, the primordium of central nervous system arises from a structure know as the neural tube. Briefly, the neuroectoderm receives signals from the notochord which provoke neuroectoderm thickening; it then flexes at a medial hinge point, forming two concave walls that extend along the embryo's anterior-posterior axis. Later, dorso-lateral portion of the walls bent causing their tips to meet at the midline and fuse forming a hollow cylinder known as the neural tube. When the neural tube does not form properly neural tube defects occur. Among these disorders, anencephaly and *spina bifida* have the highest incidence in newborns. Autophagy seems to contribute to proper neural tube closure, as the absence of activating autophagy protein (AMBRA1) causes neural tube defects in mouse embryos and lethality. Nevertheless, there are not direct studies to demonstrate whether autophagy, and no other unknown function of AMBRA1, indeed contributes to the fusion of the neural tube, and if so, nor what could be the mechanism.

In this work we searched in mice embryos for the presence of cells with higher autophagic activity along the fusion line of the neural tube and manipulated autophagy during ex-utero development to assess whether alterations in development occur. We will present our results and the possible mechanism by which autophagy contributes to the neural tube fusion will be discussed.

Acknowledgements: This work was funded by grants UNAM-PAPIIT IN206518; CONACyT Fronteras 2015-2 FC-921 and **Secretaria de Educación, Ciencia, Tecnología e Innovación de la Ciudad de México SECITI/042/2018 (INGER-DI-CRECITES-008-2018) "Red Colaborativa de Investigación Traslacional para el Envejecimiento Saludable de la Ciudad de México (RECITES)** to SCO; scholarship CONACyT 630665 was awarded to PSAR, a student of the "Programa de Doctorado en Ciencias Bioquímicas-UNAM". We are grateful to Dra. Beatriz Aguilar Maldonado for her technical assistance.

Development and validation of a biophysical mathematical model for studying aging in three types of hippocampal neuron

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Abstract

Aging is a complex physiological process still poorly understood, especially with respect to its effects on brain function. How biophysical properties and neuronal electrical activity change during aging, and how this translates into alterations of the network outputs are open questions. Electrophysiological recordings from non-human animals have helped us to understand how neuronal excitability and network output changes in normal and pathological aging conditions (e.g. Alzheimer's disease). However, the difficulty of simultaneously recording single cells and network activities, the existence of brain compensatory mechanisms, the intrinsic complexity of aging among other methodological challenges make it difficult to rely only on experimental approaches. Therefore, a multidisciplinary approach is needed to study brain function and aging. Mathematical modeling is a highly useful tool that allows us to dissect the specific contribution of different elements to neural and circuit activities; for example, it is possible to control which ionic currents are present in the model neurons and how their relative expression changes, without having to worry about compensatory effects. In this work, we developed a biophysical, minimal model that can be adapted to reproduce electrical activity in three types of hippocampal neurons, showing distinct changes in electrical activity during aging: (1) pyramidal cells in the CA1 region, (2) pyramidal cells in the CA3 region, and (3) granule cells in the dentate gyrus. We used these different model configurations and explain how parameters are varied to transition between the different cell types.

In addition, we show how these configurations reproduce both the variability in electrical activity seen in young cells, as well as age-related changes in excitability. We propose the use of this model as a valuable research tool in future studies of aging in the hippocampus.

Area: Desarrollo y Envejecimiento

Hippocampus, Aging, Mathematical modeling

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Effect of prolactin on the process of differentiation of mouse embryonic stem cells to cortical neurons

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The cerebral cortex is a structure of the central nervous system (CNS) generated by a constellation of interconnected neurons and glial cells to control and develop complex functions like language and memory. However, their development in mammals has remained uncertain due to the lack of experimental models. On the other hand, embryonic stem cells (ESC) are characterized by self-renewal and the capacity to differentiate into derivatives of the three embryonic layers. These properties offer an alternative in the establishment of new models in developmental biology, thus allowing the evaluation of molecules related to CNS development such as neurotransmitters, cytokines and hormones. Interestingly, prolactin (PRL) is a hormone related to over 300 physiological functions in vertebrates, i.e. maternal behavior and adult neurogenesis. Nonetheless, its possible role in cerebral cortex development is unknown. Here, we determined through a 2-step protocol in 2D and 3D the effect of PRL on the differentiation process of mouse ESC to cortical neurons. To this end, we administered several PRL concentrations during the proliferation or differentiation process. The highest PRL concentrations during proliferation generated an increasing trend of Sox2+ and Nestin+ cells. Similarly, we found an increasing trend in β-tubulin-III+ cells in all tested concentrations. Interestingly, we observed an increase in the marker Tbr1 with only the concentrations of 0.5 to 150 ng/ml of the hormone. We also found a decrease in Map2+ and NeuN+ cells at highest and lowest concentrations of the hormone, respectively. Besides, when the treatment was given during the late stage of the protocol, no changes were observed with respect to the control group. Finally, we established a protocol in 3D which can recapitulate the cytoarchitecture and the multilineage differentiation potential of the brain. These data suggest a regulatory of PRL during corticogenesis from mouse ESC.

Keywords: Prolactin, stem cells, cerebral cortex.

Development and aging.

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Early life stress, epigenetics and resilience, and their influence on the development of psychiatric illnesses.

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AREA: Docencia y Divulgación

Early life Stress (ELS) has been associated to an increased psychiatric illness incidence. ELS comprises childhood stress, emotional abuse, physical abuse, neglect, trauma, family conflicts, sexual abuse and mistreatment, these events can affect neurological development through mechanisms, such as interactions between genes, the environment and epigenetic regulation, which lead to the development of diseases, as well as the increase of comorbidity, pharmacotherapy response reduction and the increasing suicide risk during individual's lifespan.

Epigenetic mechanisms regulate the expression of genes without changing the DNA sequence that influences or affects the levels of protein expression and produces changes in the phenotype during life, which can influence the health and behavior of individuals. The epigenetic mechanisms that are associated with ELS are DNA methylation, posttranslational modification of histones, non-coding RNAs and chromatin interactions.

The aim of this paper is to understand how ELs influence the development of psychiatric diseases through epigenetic modifications and how these modifications can change the molecular response in stressful situations, these changes can be reversible and respond to environmental signals. Although ELS are an important risk factor of psychopathology development, it is not deterministic, since a resilient phenotype has been observed in individuals who have experienced moderate levels of anxiety and depressive behavior. These features make the epigenetics and resilience processes of interest for treatment of psychiatric illnesses.

Epigenetic modification patterns tend to be different based on different individual factors, such as genetic background, sex, age, and types of stressors.

More research is needed on how these factors interact and lead to altered gene expression and elucidate the functional and psychiatric consequences of these changes, since the ELS may be insufficient to increase vulnerability to stress, only a proportion of individuals need ELS experience the development of stress-related illnesses. Due to the presence of protective factors: external factors, social support and resilience internal psychological constructs.

It is important to investigate the factors influencing the differential susceptibility to ELS and how these factors interact with epigenetic machinery.

It would be a great advantage clearly understand the relationship between stress and resilience and how resistant individuals differ from non-resistant individuals.

Keywords: Early life Stress, epigenetic, resilience

Bachelor's program on Neuroscience: UNAM

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The bachelor's program in Neuroscience at UNAM emerged as a response to the necessity of professionals trained to unify the various visions of neuroscience for research and clinical multidisciplinary work.

The mission of the career consists in the formation of professional leaders in neuroscience, with a basic education as a solid platform for scientific research, development and technological innovation in Mexico, with the mission of becoming the country's leading program for the formation of future neuroscientists and professionals with teaching abilities and neuroscience communication for public awareness.

The academic program provides a multidisciplinary vision of current neuroscience; with a responsible, critical, purposeful attitude, and the capacity to serve the community with an ethical, legal, social, personal and collective commitment.

As a multidisciplinary program, the academic organization relies on the Schools of Medicine, Science and Psychology, as well as the Cellular Physiology Institute and the Neurobiology Institute.

The program is divided into eight semesters, with a basic, intermediate and advanced division within the subjects. The knowledge is divided in: Basic Science, Neurobiology, Behavioral Science, Instrumentation and Social-Humanistic.

Keywords: Neuroscience, bachelor's degree, education.

Evaluation of the protective effect of resveratrol on behavioral alterations and oxidative stress in prenatally stressed rats

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During the pregnancy process, by itself, a high level of stress and anxiety is generated to the future mother with negative effects for her and her baby. If the level of stress becomes excessive, this will generate prenatal stress that will produce an intrauterine environment unfavorable for fetal development that can negatively impact offspring, increasing the risk of developing physiological dysfunctions and behavioral impairment. The neonatal brain is particularly vulnerable to reactive oxygen/nitrogen species-mediated damage. Furthermore, oxidative stress levels are easily modifiable during pregnancy and early postnatal life. Because trans-resveratrol exhibits a potent anti-oxidative, immune regulatory, and antidepressant effects, in the present work it was proposed to evaluate, in specific brain regions, the impact of gestational stress in the offspring using animal models during puberty and early adulthood.
The anxious and depressive behaviors were evaluated by using the plus maze and forced swimming models, respectively. Preliminary results indicated that rats treated with trans-resveratrol showed better performance in the forced swimming test as compared to controls. Additionally, some markers of oxidative stress in the brain structures studied are increased in animals subjected to prenatal stress, particularly, total proteins and the activity of some metabolic enzymes. On the other hand, total sulfhydryls were significantly decreased in the prenatal stress group.

Prenatal stress, Trans-resveratrol, Depression.

EFFECTS OF CURCUMIN ON OXIDATIVE DAMAGE IN BRAIN OF MICE FED A HIGH FRUCTOSE DIET

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Area: Stress

Introduction: This study was to determinate the curcumin effect on oxidative damage in brain of mice fed high fructose content.

Material and methods: Male C57BL/6 mice of 6 weeks old were fed for a period of 15 weeks as follows: 6 mice received standard diet (SD; named group SD); 6 mice received 30% (w/v) of fructose in water (named group Fru); 6 mice received SD supplemented with 0.75% (w/w) of curcumin (named group Cur); finally, 6 mice received SD supplemented with 0.75% (w/w) of curcumin and 30% (w/v) of fructose in water (named group Fru+Cur). At the end of treatment, the mice were sacrificed and the hippocampus, frontal cortex (FC), cerebellum and striatum were isolated to determine the TBARS and carbonyls levels as markers of oxidative damage.

Results: In FC the carbonyl levels were significantly higher (416.2±73 ng of carbonyls/mg protein, $p<0.05$) in Fru group compared with the SD, Cur and Fru+Cur groups (252.5±52.3, 309±73 and 306.7±57.8 ng of carbonyls/mg protein, respectively). A similar effect was observed in cerebellum, being the carbonyl levels significantly higher (600±159 ng of carbonyls/mg protein, $p<0.01$) in Fru group compared with SD, Cur and Fru+Cur groups (424.8±58, 345.9±81 and 398.8±140 ng of carbonyls/mg protein, respectively); moreover, these levels were significantly lower ($p<0.01$) in Fru+Cur group than Fru group. With respect to striatum, fructose increased significantly the carbonyl levels (296±44 ng of carbonyls/mg protein, $p<0.01$) compared with SD and Fru+Cur groups (249.7±17 and 245±17 ng of carbonyls/mg protein, respectively); no differences were observed between Fruc and Cur (266±36 and 245±17 ng of carbonyls/mg protein) groups. In hippocampus, only significant differences were observed between SD and Fru groups (237±52 vs. 320±69 ng of carbonyls/mg protein, $p<0.05$); whereas these levels were similar with respect to Cur and Fru+Cur groups (284±29 and 280±61 ng of carbonyls/mg protein, respectively). With respect to TBARS levels, in the cerebellum, fructose significantly increased TBARS levels, and these were decreased for curcumin treatment; whereas TBARS levels were very similar in the hippocampus, FC and striatum.

Conclusion: The present findings suggest that fructose increases the oxidation to protein in the mice brain, whereas curcumin reduces these oxidation levels induced for the fructose treatment, suggesting that fructose may induce memory deficits, and curcumin may ameliorate this deficit.

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Keywords: Fructose, Curcumin, Oxidative damage

REACTIVE ASTROGLIOSIS IS EXACERBATED AFTER SPINAL CORD INJURY IN DIABETIC RATS

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Area: Glia

Spinal cord injury (SCI) could be caused by traumatic or non-traumatic injury, generating a cascade of pathologic events, causing permanent symptoms due to damage of the spinal tissue, which cannot currently be repaired with success. SCI can be aggravated by metabolic disorder, as Diabetes Mellitus (DM). Since a hallmark of SCI are neuronal death, the research has been mostly focused on axonal and neural regeneration, however SCI also involves active participation of numerous glial cells (such as astrocytes), which can be a two-edge sword because can facilitate repair or potentiate damage, a processes better known as reactive astrogliosis. In this work, special focus has been directed to explore and analyze the expression of the astrogliosis and how could contribute to exacerbate the spinal tissue damage in diabetic rats. In our model the type-1-like DM is induced to Wistar adult rats by streptozotocin (STZ), while the SCI is induced by compression with a vascular clip at the lumbar level (L1-L2, where the main components of the locomotor Central Pattern Generator are located). The experimental groups (sham, diabetes [D], lesion [L] and diabetes + lesion [D+L]), were perfused 4, 48 or 72 h post-injury. The samples were processed for immunohistochemistry to stained positive fibers against GFAP (specific intermediate filament of astrocytes) and pyknotic nuclei with DAPI staining in the WM (lateral and ventral regions). We found that in sham condition the reactive gliosis is present at low levels, while the immunoreactivity is increased after L condition at 48 or 72 h post-injury. However, after D and D+L conditions the astrogliosis is exacerbated since the first 4 h and prevails for the following 48 and 72 h post-injury. Although more studies need to be done, we could mention that diabetes is a pathological condition that *per se* amplifies the reactive astrogliosis in both areas of the WM, since the first hours after the SCI has occurred. There are still many open questions on glial subsets and functions, however glial cells are necessary for everything, thus understanding the multifaceted and context-specific functions of astrocytes, especial when two pathologies coincide, could contribute to the development of different neuroprotective strategies to limit the damage, when applied at the right time-point.

Key Words: Spinal Cord Injury (SCI), Diabetes Mellitus (DM), Reactive astrogliosis

Translational control by silica nanoparticles exposure in glial cells

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Area: Glia

Bergmann glia cells (BGC), a type of radial glia, is important in brain development and in the prevention of excitotoxic insults. Since neurons are highly vulnerable to oxidative stress, neuroglia represents a target of interest to the effects of xenobiotics in long and short term. Silica nanoparticles (SiNPs) considered to be non-toxic, cheap and easy to manufacture, have been quite attractive for different applications including electronics, food and medicine. Due to their small size, these particles can enter the central nervous system (CNS) causing an oxidizing microenvironment, an event associated with neurodegeneration pathologies. In current molecular neurotoxicology, the effects on translational control as an event prior to physiological deterioration and cell death are poorly studied. The aim of this work was to evaluate the effect of SiNPs in the regulation of elongation phase of the translation process using BGC as *in vitro* cell system. To this end, a treatment scheme was settled to evaluate the cell viability at different concentrations of SiNPs, once determined a harmlessness concentration we evaluated the phosphorylation levels of some factors of the translational machinery such as eEF2, eEF2K and eIF2α after treatment with 4.8 µg / mL of SiNPs at short times, in parallel we evaluated *de novo* protein synthesis by [^{35}S]-Methionine labeling. We were able to find that SiNPs do not affect significantly cell viability at low concentrations at the times analyzed (6 and 12 h). Tracing the *de novo* synthesized proteins with [^{35}S]-Methionine, we observed an increase at 15 min, restoring the baseline protein synthesis level after 30 min. This kinetic behavior is indicative of a biphasic and transient change, in agreement with the eEF2 phosphorylation level, which is downregulated at 15 min and with the phosphorylation pattern of its kinase eEF2K which increases at 10 and 15 min of treatment. These results suggest that nanoparticles, probably through a modification of the cellular redox status, modifies the protein repertoire in glia cells.

Keywords: Bergmann's glia, translational control, SiNPs.

Rotenone damages cytoskeleton and reduces glutamine synthetase and GSH in rat astrocyte primary cultures

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Area 1, Glia.

BACKGROUND. Among the central astrocytes' functions are the recycling of neurotransmitters, such as glutamate, and the supply of precursors of the antioxidant system. Neurodegenerative insults can lead to the astrocyte response known as reactive gliosis. In this condition, upregulation of glial fibrillary acidic protein (GFAP), intermediate filament protein of astrocytes, has been documented. As the inhibition of electron transport chain (ETC) is a way to trigger neurodegeneration, we hypothesize that rotenone, a well-known ETC inhibitor, would promote astrocytes activation, would impair the ability of astrocytes to recycle neurotransmitters and to supply glutathione, the main endogenous antioxidant.

OBJECTIVE. Evaluating the rotenone effect on proteins of cytoskeleton, glutamine synthetase, and antioxidant system on rat astrocyte primary cultures.

METHODOLOGY. Primary cultures of astrocytes were isolated from the cerebellum of Wistar rats and incubated with rotenone (0, 0.1, 1, 10, 50 and 100 μM) by 24 h. After, we evaluated a) cell viability, b) complex I activity, c) the intra and extracellular GSH, and d) GFAP, tubulin, glutamine synthetase, gamma glutamyl cysteine ligase, glutathione peroxidase, and glutathione reductase expression.

RESULTS. Rotenone diminished cell viability, intra, and extracellular GSH concentration and the expression of glutamine synthetase, tubulin, and GFAP. The activity of complex I and the expression of Gpx, GR, and GCL were not affected.

DISCUSSION AND CONCLUSIONS. As it has been reported for other cell types, the rotenone treatment triggered damage in cytoskeleton proteins. As expected, rotenone promoted a decrease in the main endogenous antioxidant. Despite the knowledge that rotenone is the main complex I inhibitor, we did not find a lower activity on this complex in astrocytes. We suggest that the main rotenone toxic effect in astrocytes is cytoskeleton disruption and not CTE alteration.

Key Words: astrocytes, glia, rotenone.

Role of Palmitic Acid in the hyperphosphorylated state of tau protein

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Area: Metabolism

The intake of diets with high content of saturated fatty acids, particularly palmitic acid (PA), has been associated with biochemical changes implicated in the physiopathology of some neurodegenerative diseases as Alzheimer's disease (AD). It has been suggested that the consumption of these diets contributes to tau hyperphosphorylation that may lead to the formation of intraneuronal neurofibrillary tangles (NFTs) -one of the histopathological markers in AD-. However, the mechanisms involved the deleterious effects of these diets have not been described at all. Tau protein is a very important regulator of microtubule dynamics and by this way of axonal cytoskeleton stability, signal transduction and axonal transport. GSK3β has been identified as one of the major candidate mediating tau hyperphosphorylation at the same residues as those found in brain tissues from AD´s patients. It has been shown that neuronal exposure to PA increases tau phosphorylation but it is not known which kinases are involved. Thus, the aim of the present work was analyze the role of GSK3β on the PA-induced tau hyperphosphorylation as well as the role of the acetylation state of tau. We have used differentiated neurons from human neuroblastoma cells which were exposed to different doses of PA (100, 200 or 300 μM) after short (1h) or long (24 h) period of time. Then we measured the protein content of total tau, p-tau (ser199/202), total GSK3β, p-GSK3β (ser9) and ac-tau (K280) by Western blot and analyzed the distribution of tau and p-tau by immunofluorescence and confocal microscopy. We have found an increment of p-tau after 200 μM of PA at 1 and 24 h concomitant with a reduction of GSK3β at the residue of inhibition that means an activation of GSK3β. Present results demonstrated that PA is able to activate GSK3β and induce tau phosphorylation in human neurons.

Key words: Palmitic Acid, p-tau, GSK3β.

High fat diet-induced obesity development modulates thyrotropin releasing hormone biosynthesis in the juxtaparaventricular perifornical lateral nucleus of the hypothalamus in male rats

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Thyrotropin releasing hormone (TRH) neurons are distributed throughout the lateral hypothalamic area (LHA); TRH is co-expressed with enkephalin and urocortin 3 in the juxta-paraventricular zone of LHA (jpLHA). Administration of exogenous TRH in the LHA modifies arousal and induces an anorexigenic effect. α-melanotropin (αMSH) neuronal endings from the arcuate nucleus (ARC) contact LHA TRH neurons. Furthermore, a high level of leptin receptor has been found in the LHA. We recently found that LHA-TRH mRNA levels decreased after a short period of food restriction in rats. Intake of high fat diet (HFD) modulates enkephalins, orexin and melanocortin mRNA levels in the LHA. In this work, we analyze the activity status of TRH neurons, using TRH mRNA levels as an activity proxy, during induction of obesity in rats fed with HFD. 60 days old Wistar male rats were fed with a regular diet (RD; 18% Kcal from fat) or a HFD (45% Kcal from lard fat) during 3 or 30 days. At day 3, HFD did not change animal body weight (BW); however, serum leptin and insulin concentrations were higher than in RD animals. At day 30 leptin and insulin serum concentrations, BW and weight of white fat depots were higher in HFD than in RD rats. HLA TRH mRNA levels decreased when rats fed HFD during 3 days but an opposite effect was detected if animals were maintained with HFD for 30 days. We used radioactive in situ hybridization to map and classify TRH neurons according to TRH mRNA levels (4 categories based on number of silver grains per cell profile) in different groups of LHA-TRH neurons. jpLHA TRH neurons showed a high level of TRH mRNA per cell compared to tuberal and peduncular LHA TRH neurons, which were mostly classified in the lower category. In response to HFD during 30 days, we found a significant increase in the number of TRH neurons in the jpLHA. The number of TRH positive neurons in the LHA-tuberal zone was non significantly increased in response to HFD. Finally, in the peduncular zone of LHA, the number of TRH positive neurons was not changed. In conclusion, we identified in the LHA a specific population of TRHérgic neurons that responds to changes in energy balance; it remains to be defined if they are responding to leptin, and/or inputs from the ARC.
Supported in part by grants from DGAPA-UNAM (PAPITT IN212411) and CONACYT (CB 128665 and CB254960).

Obesity, TRH and lateral hypothalamic area.

Thyrotropin-releasing hormone-degrading ectoenzyme null male mice are resistant to diet-induced obesity

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Neuroendocrinology

Thyrotropin-releasing hormone (TRH, pGlu-His-Pro-NH2) is expressed in the brain as well as in a few peripheral tissues. It is a short-lived intercellular signaling molecule that is hydrolyzed by the thyrotropin-releasing hormone-degrading ectoenzyme (TRH-DE), a narrow specificity peptidase whose only known biological substrate is TRH. TRH-DE is expressed in various brain regions, including at the base of the third ventricle, in β2 tanycytes whose cytoplasmic extensions contact TRH terminals in the external layer of the median eminence (Joseph-Bravo et al, 2016). Functional evidence suggests that median eminence TRH-DE controls the turnover of TRH before entry into the portal capillaries that connect the hypothalamus with the anterior pituitary and indicate that the peptidase controls the levels of thyrotropin in the circulation (Rodríguez Rodríguez et al, 2018). The activity of the enzyme in tanycytes is sensitive to energy balance cues and may contribute to adjust the thyroid axis to changing energy needs. To test whether the enzyme is indeed relevant for energy balance, we characterized a line of mice generated in the B6129S5 background in which exon was 2 deleted (Tang et al, 2010). TRH-DE activity was eliminated in the KO animals. The mutation was backcrossed for 11 generations on the C57BL/6NJ background. On a standard diet (SD), genotype-dependent effects were generally not significant. 70-75 days old male mice, either wild type (WT), heterozygous (HT) or homozygous (KO) for the mutation, were switched from a standard diet to a high fat (45% Kcal from lard fat) and high fructose (10% in water) diet (HFFD) for 9 weeks. Compared to WT animals, KO animals slightly reduced the amount of kcal of HFFD ingested. The body weight of HFFD WT and HFFD HT mice was much higher than that of HFFD KO mice. Bio-impedance data indicated a lower fat mass in HFFD KO mice, compared to HFFD WT or HFFD HT mice. The body mass index was also lower, and glucose tolerance higher in HFFD KO mice than in HFFD WT or HFFD HT mice. HFFD WT and HFFD HT serum leptin levels were higher than those of HFFD KO mice. HFFD WT serum T3 concentration was slightly higher than that of HFFD KO mice; there were no differences in serum corticosterone and T4 concentrations. TRH can induce the release of growth hormone and prolactin (Yamada et al, 2006). Genotype had no effect on growth hormone and prolactin concentrations in HFFD animals. The data suggest that constitutive ablation of TRH-DE reduces metabolic effects of high fat fructose diet-induced obesity. Further studies are required to clarify whether it is the central or the peripheral suppression of *Trhde* expression that is responsible for the phenotype. Obesity, TRH-DE, HPT TRH

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Expression and hormonal regulation of mPRδ and mPRε in human glioblastoma cells

Area: Neuroendocrinology

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Membrane progesterone receptors (mPRs) are a group of G-protein coupled receptors with a wide distribution and multiple functions. There are five mPRs subtypes described in humans: mPRα, mPRβ, mPRγ, mPRδ, and mPRε. The activation of these mPRs by progesterone triggers rapid intracellular signaling pathways that regulate specific molecular and cellular processes depending on the tissue context, both under normal and pathological conditions. It has been reported that human-derived glioblastoma cells express the mPRα, mPRβ, and mPRγ subtypes, and that progesterone promotes glioblastoma tumor progression by mPRα specific activation; however, it is still unknown if mPRδ and mPRε are also expressed in this type of tumor cells. In this study, we characterized the expression and hormonal regulation of mPRδ and mPRε in human-derived glioblastoma cells. Using RT-qPCR, Western Blot, and immunofluorescence analysis, we detected for the first time the expression of mPRδ and mPRε in human glioblastoma cells, further, the expression of mPRδ is higher than mPRε. and that the expression of these mPRs is down-regulated by progesterone. Our results suggest that mPRδ and mPRε should mediate progesterone actions in human glioblastoma cells.

Keywords: Glioblastoma, Membrane progesterone receptors, Progesterone

Stressed female rats during adolescence have a deficient response of HPT axis to energy demands

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Adolescence is an important critical period of development as puberty appears with hormonal changes and definition of sexual organs; in female rat it comprises the period between PN28 to PND 41; adolescence is extended to include formation of brain circuits between limbic areas and maturation of HPA axis (PND25-60). Isolation during juvenile and adolescent periods can have permanent behavioral and physiological effects as these periods are critical for development of social conducts. Acute or chronic stress inhibits HPT activity[1] and blunts cold response of male rats. Chronic stress during adulthood blunts also HPT response to exercise in male or female rats. As females are more susceptible to the deleterious effect of stress during adolescence[2], we studied the effect of isolation (ISO) in female Wistar rats during PND30-63, then regrouped and subjected to intermittent stressors during the following 2 weeks, and by 24 days of voluntary exercise. Control [C] rats were group caged.

After the isolation period, rats gained less body weigh in spite of equal food intake to C. Hedonic test (sweet drink) and open field test were performed at PND 64 and 66, behavior did not differ between groups. At PND 69 and 72 rats were stressed with White noise or elevated platform, at PND75 Iso were restrained 1h followed by hedonic test; Iso drank less sweet solution than C, anhedonia in Iso suggested the reported “depressed” state. After this period, body weight gain of Iso was similar to C. Corticosterone levels of Iso rats were higher than C.

Ten rats of C and of Iso groups were used at PND80 to evaluate the response of HPT to cold exposure. Five animals remained at room temperature (RT), in individual cages, other 5 of each group were introduced to the cold room for 1h. Cold exposure increased, as reported, corticosterone and thyrotropin levels in controls but in Iso group did not achieve significance.

At PND82, 12 C and 12 Iso rats were separated in 2 groups each, a sedentary (Sed) and an exercised (Ex) every night for 3 weeks; as Ex reduce their food intake, sedentary rats were pair fed to the amount consumed by exercised. C-Ex and Iso-Ex ran the same distance during the first 15 days but only C kept increasing, being significantly higher than to Iso during the remaining 12 days. C-Ex and Iso-Ex consumed equivalent amounts of food and thus their corresponding Sed groups; however, body weight gain (BWg) was higher in Iso-Sed than C-Sed, exercise diminished BWg by 40%. C-Ex decreased the amount of fat mass whereas Iso-ex lost was not significant but instead decreased muscle mass as well as Iso-sed. Serum levels of corticosterone were higher in Iso-Sed than C-Sed and exercised decreased them, significantly only in C-Ex. Decreased muscle mass relates with the increase in corticosterone and adrenal weight of a chronic stressed state of Iso group, as corticosterone has catabolic effects on muscle. TSH and T3 increased in C-Ex proportionally to distance ran.

Results support long-term effects of stress during adolescence that inhibit the adequate response to energy demands at adulthood. Determination of gene expression is in progress.

Key words: stress, adolescence, exercise, HPT, corticosterone, thyrotropin

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Is peripheral thyrotropin-releasing hormone-degrading ectoenzyme a therapeutic target for diet-induced obesity?

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Obesity is a major health problem, leading to diabetes type II and cardiovascular diseases, which are among the principal causes of mortality in Mexico, and world-wide. Among many other systems, energy related clues control the output of the hypophysiotropic neurons of the paraventricular nucleus (PVN) that project to the median eminence (ME) and secrete thyrotropin releasing hormone (TRH) into the portal capillaries. These neurons positively regulate the secretion of thyrotropin (TSH) by the anterior pituitary. In turn, TSH promotes the synthesis and secretion of thyroid hormones (TH), which control metabolism and thermogenesis. Once TRH is released into the ME extracellular space, it can be hydrolyzed by a narrow specificity peptidase, thyrotropin-releasing hormone-degrading ectoenzyme (TRH-DE), which is present in β2 tanycytes of the ME, other brain regions and has a secreted isoform released by the liver. Previous studies in the laboratory have shown that tanycyte TRH-DE controls TSH secretion in rats (Sanchez et al, 2009; Rodriguez et al, unpublished). Furthermore, the body weight (BW) of male TRH-DE KO mice on high fat carbohydrate diet (HFCD) is lower than that of WT mice (Cote et al, unpublished). We tested the hypothesis that chronic partial inhibition of TRH-DE peripheral activity produces a discrete enhancement of HPT axis activity sufficient to increase energy metabolism and decrease BW in a mouse (C57BL/6NJ young adult) model of obesity induced by HFCD. To inhibit peripheral TRH-DE activity, a phosphinic analogue of TRH (P-TRH) was administered to adult HFCD mice during 28 days through osmotic pumps connected to an intraperitoneal catheter. At the time when BW was significantly increased in HFFD mice (male: 60 days; female: 120 days consuming HFCD), we initiated the systemic treatment with P-TRH (120µg/day) or vehicle (saline 0.9%). P-TRH treatment induced a partial and marginal inhibition of TRH-DE activity in serum, and a trend to reduce it in EM of HFCD mice compared with HFCD mice treated with vehicle. Most of the data in male mice suggest that TRH-DE peripheral inhibition induces a small activation of the HPT axis, which slightly decreases the white adipose tissue weight but not the BW. Minor trends to reduce glucose blood levels and to increase brown adipose tissue were also detected. P-TRH did not induce any of these changes in female fed with HFCD. The status of peripheral metabolism is under study. Tentatively, these results suggest that the peripheral inhibition of TRH-DE activity may be insufficient to reverse BW changes induced by HFCD in adult mice.

Funding: CONACYT PN-562 and CB-254960

Key words: obesity, HPT axis and TRH.

Stress during rat adolescence modifies the thyroid axis response to voluntary exercise

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Adolescence is considered as a critical developmental stage because synaptic remodeling occurs and the Hypothalamus-Pituitary-adrenal (HPA) axis matures. Dysregulation of HPA axis responses modifies energy homeostasis, and alters the activity of HP-Thyroid (HPT) axis. Either acute or chronic stress inhibit HPT axis. We have demonstrated that stress history of the animal, as exposure to early-life stress, may program the activity of HPT axis in adulthood (Jaimes-Hoy et al., Endocrinology 2016), and that voluntary exercise activates the HPT axis proportionally to fat loss and exercise performed (Uribe et al., Endocrinology 2014). In this work, we evaluated the effect of two types of chronic stress on adolescent male and female rats in the response of HPT axis to voluntary exercise. Wistar male and female rats at postnatal day (PND) 30 were divided according to the experiment: In experiment 1, one control group of 16 rats was kept 2/cage and one isolated group of 16 rats was housed individually. In experiment 2, the control group (17 rats) was left undisturbed (2 or 3 rats/cage) and the experimental one (18 rats) was submitted to chronic variable stress (CVS); CVS consisted of applying different types of stress everyday during adolescence. Once rats reached adulthood (PND 60 to females; PND 70 to males) experimental groups were divided as follows: one exercised group (Ex) that was placed in a cage with running wheel on 10 alternated nights (Experiment 1) or 14 daily nights (Experiment 2), one sedentary group which was pair-fed to the same amount of food consumed by Ex group (PF), and another sedentary group with food *ad libitum* (Sed; only in Experiment 2). Hormones and mRNA levels were quantified by ELISA, RIA and RT-PCR in both experiments. In experiment 1: isolated males had higher *Crh* expression in hypothalamic paraventricular nucleus (PVN) than controls. Exercise did not change *Trh*-PVN expression, nor thyroid hormones serum levels, but increased *Dio2* and *Pomc* expression in mediobasal hypothalamus (MBH); effect attenuated by social isolation. In contrast, isolated females showed hypoactivity of HPA axis, an increase of TSH and T4 serum concentration, and a decrease of *Dio2*, *Trhde* and *Npy* expression in MBH. In experiment 2: CVS reduced the expression of *Trh* mRNA levels in PVN of both sexes but increased T3 and T4 concentration solely in females. *Crh* and *Avp* expression in PVN was not affected by CVS or exercise in males, but was reduced in females in CVS PF and Ex groups. Results suggest that intermittent exercise was not sufficient to observe reported changes in HPT activity in males, but did in females where isolation blunted HPT response. CVS inhibited basal HPT activity mainly in males, and exercise activated it but only in non-stressed of both sexes. We conclude that chronic stress blunted the response of HPT axis to voluntary exercise and attenuated the HPA axis in a sex dependent manner. *(Funded: CONACYT 284883, DGAPA IN204316; MAPM is recipient of CONACYT National Scholarship 273496)*.

Key words: Adolescent stress, Voluntary exercise, HPT axis

β2-tanycytes thyrotropin-releasing hormone-degrading ectoenzyme regulates thyrotropin secretion

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Área: Neuroendocrinología

The median eminence (ME) is a circumventricular organ enriched with hypophysiotropic terminal buttons that release hypothalamic releasing factors into the hypothalamus-pituitary portal vessels. Specialized glial cells, termed β2 tanycytes, line the base of the third ventricle and extend a process into the external zone of the ME. β2 tanycytes are critical for negative feedback regulation of the hypothalamus-pituitary-thyroid (HPT) axis; they express proteins involved in the transport and sensing of thyroid hormones (TH) and are a source of T3 that regulates thyrotropin-releasing hormone (TRH) neurons. Furthermore, β2-tanycytes establish synaptoid contacts with terminals of hypophysiotrophic TRH neurons and express a high activity of the TRH degrading ectoenzyme (TRH-DE), an activity regulated by TRH, TH levels and fasting. TRH-DE may control TRH availability in the portal blood and thus thyrotropin (TSH) secretion from the pituitary, since the short term systemic inhibition of TRH-DE activity enhances serum TSH concentration, although this effect could also be attributed to inhibition of extrahypothalamic TRH-DE activity, including a TH-dependent circulating form of TRH-DE expressed in the liver.

To determine whether TRH-DE from β2 tanycytes is critical to control TSH secretion we developed a method to modify gene expression in β2 tanycytes. For this purpose, we showed that the injection of serotype-1 adenoassociated virus (AAV1) expressing GFP in the third ventricle of rats transduces β2 tanycytes. In line with this, rats that were injected with AAV1 expressing TRH-DE showed an increased ME TRH-DE activity two or three weeks after virus administration. TRH-DE overexpression in ME was associated with a decrease of serum TSH concentration and enhanced food intake. In contrast, two weeks after the injection of an AAV1 expressing a truncated isoform of TRH-DE (TRH-DE*) with dominant negative activity we observed a tendency to decrease ME TRH-DE activity, associated with an increase of serum TSH concentration and lowered food intake. Injection of AAV1 expressing either isoform of TRH-DE didn't change body weight or fat content, serum TH, prolactin or growth hormone concentrations, nor the activity of the circulating form of TRH-DE. In conclusion, our experiments show that β2-tanycytes are the source of TRH-DE that controls TRH concentration in the portal vessels after release from hypophysiotropic neurons, regulating its capacity to promote TSH release from the anterior pituitary. Thus, β2 tanycytes TRH-DE activity adds another layer of complexity to the mechanisms orchestrating the HPT axis.

Keywords: tanycytes, HPT axis, thyrotropin, TRH

Progesterone metabolite, allopregnanolone, promotes migration and invasion of human glioblastoma cells

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ABSTRACT

Glioblastomas (GBMs) are the most common primary malignancies of the Central Nervous System (CNS). The poor prognosis of the patients with GBMs is due to the highly infiltrative potential of the tumoral cells to the brain parenchyma and the high rate of tumor recurrence. The steroid hormone progesterone (P4) promotes proliferation, migration, and invasion of GBM cells. Allopregnanolone (3α-THP) is a reduced metabolite of P4. In the CNS, 3α-THP is synthesized by neural and glial cells and, promotes its effects through different mechanisms of action than that of P4. 3α-THP induces proliferation and gene expression of cytoskeleton components in human GBM cells, however, neither the effect of 3α-THP on migration and invasion of GBM cells nor the mechanisms of 3α-THP on brain malignancies have been determined.

In the present study, we determined the effect of 3α-THP on the migration and invasion of U251, U87, and LN229 cell lines derived from human GBMs. After 24h (for U251, and U87 cell lines), or 48 h (for LN229), 3α-THP 10 nM induced cell migration similarly as P4 10 nM. Besides, 3α-THP 10 nM promotes cell invasion in the three evaluated cell lines. Such effects were verified after the silencing of Aldo-keto reductases enzymes involved in the active oxidation of 3α-THP into 5α-dihydroprogesterone, another active P4 metabolite. These findings suggest that 3α-THP promotes the malignity of glioblastomas in a very different way of that of P4 itself.

Keywords: allopregnanolone, neuroactive steroids, glioblastomas

Anticonvulsive and Neuroprotective effect of Scammonin 1 and Tyrianthin C on cortex and hippocampus in mouse brain

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Area 5: Neuropharmacology

Introduction. *Ipomoea tyrianthina* Lindley (Convolvulaceae) is an herb that belongs to the genus Ipomoea. These plants are widely distributed in Mexico [1] and have been used in traditional medicine for the treatment of diseases. Some glycosidic resins isolated from roots of *Ipomoeas* have been studied for their activity in CNS. Recent studies about characterization of these metabolites [1] have found that their effect on CNS (eg, sedative, antidepressant, anticonvulsant and / or neuroprotective), is probably on the GABA system [2,3].

Objective. Achieve the pharmacological evaluation of scammonin 1 and tyrianthin C, with respect to the neuroprotective and anticonvulsant properties of *Ipomoea tyrianthina*. **Methodology.** The glycolipids were purified and identified according to León *et al.* (2014), from a methanolic extract of the root of *Ipomoea tyrianthina*. The pharmacological evaluation was carried out under *in-vivo* models for anticonvulsive activity [4] and analyzing its histological effect on cortex and hippocampus in cerebral mouse.

Results. The acute administration of scammonin 1 and tyrianthin C decreased the number of seizures and increased the latency time to convulsion with respect to the doses administered, showing 16.7%, 66.7% and 100% protection against convulsions. The doses of 80 mg / kg of both glycolipids decreased neuronal alterations (neurodegeneration), astrocytic activation and interstitial edema generated by induction with PTZ in areas such as the cortex and hippocampus (dentate gyrus and CA3). The subchronic dose of scammonin 1 and tyrianthin C increased its anticonvulsant and protective effect respect to the acute dose of 40 mg / kg. **Conclusions.** Results suggest that the anticonvulsant and neuroprotective activities of scammonin 1 and tyrianthin C occurs through GABAergic mechanisms, where the increase in the release of endogenous GABA (previously reported) might counteracts the excitotoxic effect generated by PTZ-induced seizure. In addition, the effect of scammonin 1 and tyrianthin C on astrocytic reactivity and presence of edema, could suggest that they possess anti-inflammatory and / or antioxidant activity.

Keywords: *Ipomoea*, glycolipids, GABA, anticonvulsive, neuroprotection.

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Pioglitazone favors neurogenesis and increases dendritic spines in the hippocampus without affect learning and memory processes or depressive-like behaviour in female Balb/C mice

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ABSTRACT

Adult hippocampal neurogenesis (AHN) is a form of neural circuit plasticity which results in the generation of new neurons in the dentate gyrus (DG) throughout life. AHN is increased by antidepressants and is associated with positive effects on cognition and mood. On the other hand, peroxisome proliferator-activated receptors (PPARs) are ligand-modulated transcriptional factors which belong to the nuclear hormone receptor superfamily. In particular the gamma isoform (PPAR-γ) expressed in the hippocampal dentate gyrus, striatum, substantia nigra and cortex have been involved in neuroprotective and anti-inflammatory effects in many models of neurodegenerative disorders. Pioglitazone, a PPAR-γ agonist, acts on microglia and astrocytes to mitigate damage from inflammatory insults. Also, pioglitazone induces neuroprotection and it has been suggested that also exhibits an antidepressant-like effect. Thus, in the present study we tested the hypothesis that pioglitazone has a potencial role in neurogenesis and microglia to exerts antidepressant like effects. At the beginning of the treatment, female BALB/c mice (4 groups, n=7; 19-25g) were injected with the analogue of thymidine: BrdU (50 mg/kg;ip) to assess changes in neurogenesis. After this procedure, pioglitazone was administered (15 mg/kg; ip) for 14 days. At the end of the treatment, mice were evaluated in the following behavioral tests: rotarod, open-field, novel object recognition, food deprivation and Porsolt's test (forced swimming test). The animals were euthanized and the hippocampus was removed to analyze the expression of PPAR-γ by Western Blot. To immunohistochemical stains, each brain was frozen and sliced to detect BrdU-positive cells, doublecortin (DCX) and microglial cells (Iba-1) in the dentate gyrus. Moreover, a Golgi-Cox impregnation protocol was used to examine changes in dendritic spines. The results indicate that pioglitazone increases dendritic spines and neurogenesis. However, we did not find significant differences in the behavioral parameteres evaluated compared to the control group.

Categoría: M

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Influence of mental health and the use of antidepressant during pregnancy and its effect on the neurological development of Mexican children

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Background: Women with an adequate emotional health during pregnancy generate emotional processes that create a healthy mother-child link. The presence of depression traits in pregnancy transcendentally affect the generation of this link, hindering the mother for the adequate stimulation that favors an optimal neuropsychological development of the baby. The long-term effects of psychoactive exposure during pregnancy includes a delay in the psychomotor development and alterations in language, memory, attention, and behavior. However, in the Mexican population, the impact of antidepressants and the maternal emotional states on the neurological development of exposed children is unknown.

Method: A cross-sectional descriptive study was conducted in 15 children whose mother self-reported the consumption of antidepressants during pregnancy and 10 controls (non-consumers). For the evaluation of the presence of depression and anxiety traits, the Edinburgh perinatal depression scale and trait-state anxiety test was used. For the evaluation of cognitive deterioration, the Mini-Mental state examination was used. The Bayley 3 child development assessment scale was applied to all children in the first month of age.

Results: 40% of pregnant patients who consumed antidepressants showed features of depression, 66.7% anxiety state traits and 20% suspected cognitive impairment. Pearson's correlation test identified a negative correlation between pregnant patients with features of depression, anxiety-state, and suspected cognitive decline, and a delay in motor development of their children. Cognitive and motor delay was shown in 100% of children whose mothers used antidepressants and presented suspected cognitive impairment. The children of mothers who consumed antidepressants with depression traits presented delays in the motor (84%) and in the cognitive scales (67%). Mothers consuming antidepressants with state anxiety had children with delays in the motor scale (80%).

Conclusions: Emotionally disturbed mothers should be considered as potentially deficient in the processes of parenting and neurodevelopment of children.

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Key words: pregnancy, mental health, neurodevelopment

Changes in the functional coupling between mPFC and BLA associated with reversal learning of spatial memory task.

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Neurofisiología Integrativa

Development of flexible behaviours is essential for survival and adaptation of individuals to constantly changing environment. Behavioural flexibility has the prefrontal cortex (mPFC) as neurophysiological substrate and is susceptible to integration of emotional information to basolateral amygdala (BLA). The interaction of the PFC-BLA circuit is displayed through the generation of oscillatory electrical activity underlying the expression of flexible behaviour, whose characteristics provide information about the role played by the circuit, under both normal and pathological conditions. In the present study, male Sprague Dawley rats were implanted with electrodes for recording of electrical activity, into the medial PFC and BLA. Behavioural flexibility was tested trough performance of reversal learning spatial memory task, in Morris water maze. During the performance of tasks the theta activity (4-12 Hz) of PFC and BLA was recorded. The results of the analysis of swim length and escape latency indicated that the animals reduced these parameters when successfully learned the location of escape platform. Additionally, it was observed that the coherence between mPFC and BLA with respect to theta activity, increased with the learning of each task. On the other hand, a decrease in coherence was observed in relation to reversal learning; which increased again when the subjects learned the new location of the platform. According to these results, the functional coupling mPFC-BLA circuit increased during the acquisition of the spatial task. However, during reversal learning, in which the previously learned response must be inhibited to acquire new information, the coupling decreased as consequence, perhaps of the information update shared between mPFC and BLA. Once that new learning has been acquired, the coupling between structures increases again. In this way we can observe that although the tasks learned by the animals are dependent on hippocampal function, structures like mPFC and BLA seem to increase their functional connection during the acquisition and reversal processes of spatial learning.

Keywords: prefrontal cortex, behavioural flexibility, electrical activity.

Pharmacological manipulation of the cannabinoid receptor type I in the basal ganglia output nuclei in a model of Parkinson's disease in mice.

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Parkinson's Disease (PD) is a neurological disorder characterized by the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and resulting in motor symptoms that include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairments. It is believed that the lack of dopamine produce unbalanced activity of the direct and indirect pathway of the basal ganglia (BG) which output nuclei modulate directly the activity of thalamic motor centers such as ventrolateral (VL) and ventromedial (VM) nuclei.

Recently, it has been demonstrated that the systemic administration of cannabinoids improves motor symptoms in patients with PD, suggesting the manipulation of the cannabinergic system as a promising therapeutic alternative. The cannabinoid receptor type I (rCB1) is widely distributed in the central nervous system with their highest concentration in the BG, particularly in the output nuclei, the substantia nigra pars reticulata (SNpr) and the globus pallidus internus (GPi), where it regulates the release of GABA and glutamate from the direct and indirect pathways respectively. The aim of this work is to evaluate if pharmacological manipulations of the rCB1 specifically in the output nuclei of the BG could provide therapeutic effects for the motor symptomatology associated to PD. To this aim, we implemented a behavioral protocol in head-fixed mice where we evaluate the impact of cannabinergic treatments directly infused in the SNr/GPi in kinematic parameters of forelimb movements guided by visual cues and the associated dynamics of large populations of neurons in the thalamic VL/VM nuclei. Preliminary data indicates that mice are capable to associate visual cues with specific forelimb movements. This performance can be reliably followed in the course of several months making this task ideal to assess behavioral changes before and after the induction of PD. On the other hand, electrophysiological recordings in awake behaving animals indicate that VL/VM complex exhibit a robust spiking activity during movement execution. Ongoing experiments will help us to determinate the effects of local administrations of cannabinoids in our model of PD and in the associated neural activity.

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Key words: Basal ganglia, Parkinson Disease, Cannabinoids.

Evaluation of the participation of the central medial nucleus of the thalamus in a bimanual task and in the interhemispheric activity of the cortico-striatal circuitry

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The Central Medial nucleus of the thalamus (CMNT) is part of the Intralaminar nuclei of the thalamus. It has been proposed that this nucleus is involved in cognitive processes, attention, memory, sleep and awakness. Previous results have shown that the CMNT projects bilaterally to practically the entire striatum. The dorsolateral region of the striatum (DLS) has been involved in action selection, learning, motor habits execution and movement sequencing. In mammals, such behavior normally requires the coordinated participation of diverse effectors such as the upper limbs and because of their anatomic location, it has been suggested that the basal ganglia (BG) may be implicated in this function. The aim of this work is to study the specific role of the projections from CMNT to the DLS in the processes of interhemispheric coordination and related behaviors. To this aim, we perform interhemispheric electrophysiological recordings combined with pathway-specific optogenetic manipulations. Additionally, for behavioral evaluation we use an ad-hoc behavioral protocol where rats are required to coordinate their forelimbs to obtain reward. Preliminary results indicate that the activation of the CMNT produces synchronic interhemispheric responses in cortico-striatal regions including the DLS. Ongoing experiments in our behavioural model will help us to understand how this projection influences the execution of a coordinated bimanual movements.

Key words: electrophysiology, bimanual coordination, synchronically activity.

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Role of the direct and indirect pathway of the basal ganglia in the adjustment of speed during the execution of motor sequences

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The basal ganglia (GB) have been classically related to motor control and the adjustment of movement speed. According to the classic model, the indirect and direct pathways of the BG decrease and increase the speed of the movements respectively. But recent observations suggest that both pathways are capable of bidirectionaly control the speed of movements. The general objective of this project is to provide knowledge regarding the role of the direct and indirect pathway in the control and adjustment of the speed of movements. To achieve this goal, we modified a behavioral protocol in rodents, in which subjects must adjust their speed dynamically to obtain reinforcers. By using optogenetic techniques in rats, we evaluated the effects of the manipulation of the indirect pathway activity during the execution of the task. In contrast to previous literature, our results indicate that when we inhibit the direct pathway the animals are still very efficient in adjusting their speed to maintain high spatiotemporal precision during the execution of a pattern of stereotyped movements. Instead we found that during stimulated trials the animals delayed the change between actions.

Keywords: Basal ganglia, Speed, Motor sequences

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Pallidal GATs modulate cortical oscillations by inhibition of reticular neurons

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The nervous system is able to generate synchronous oscillations between circuits at multiple temporal and space scales, however tendency to oscillations in the circuits can lead to a massive synchronization of abnormal rhythms such as epilepsy and bradykinesia.

Spindle waves are an example of synchronized oscillation, its arise at 7 to14 Hz due to interaction between thalamocortical network and thalamic reticular nucleus (nRt). Burst firing in the nRt during generation of spindle waves result from modulation by afferent, recently it was shown that projection from the external globus pallidus (Gpe) modulates electrical activity of nRt.

The Gpe its GABAergic nucleus that synchronizes overall activity in the basal ganglia (BG) regulating the firing pattern of all nuclei and its alteration has been related to Parkinson's disease (PD) and epilepsy. Abnormal synchronized oscillatory activity in BG observed in PD occurs about 10 to 30 Hz, but currently associated circuits are unknown, in this framework one possibility for this inappropriately synchronized oscillation is activity in Gpe.

GABA modulates network by controlling firing that allows synchronization, however pharmacological inhibición of gaba transport (GAT´s), induced oscillation by increased gaba levels. This context, suggest that pallidal GAT´s could participate in genesis of cortical oscillation pattern by modulated nRt activity. Using pharmacological stimulation, extracellular unit recording and electrocorticogram we explore this hypothesis.

We observed that pharmacological inhibition of GAT I inhibit spiking of nRt in 46.86%, at the same time inhibition of GAT III decreased 64.84 %. This effect did not change the firing pattern, but decreased the power of the alpha and beta band oscillation. These results suggest modulation of cortical oscillations by the pallidal gabaergic transmission through the pallido-reticular pathway.

Keywords: Cortical oscillation, Gaba transport, Globus pallidus, Thalamic reticular nucleus

Topic: Integrative Neurophysiology/Neural Circuits.

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Sensory and Motor Cortical Input to Dorsal Striatum: Differences in Microcircuitry, Synaptic Physiology and Behavioral Effects

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The striatum is the main input nucleus of the basal ganglia and receives excitatory inputs from neocortex and thalamus. Areas including primary somatosensory (S1) and primary motor cortex (M1) send large convergent inputs to overlapping regions of the dorsal striatum (DStr). However, it has remained unknown whether S1- and M1- corticostriatal inputs have similar or distinct roles in behavior, and striatal innervation patterns. Here, we used optogenetic activation of S1- and M1-corticostriatal inputs *in vivo* in behaving mice to determine the effects on behavioral choice in a whisker-based texture discrimination task, and *ex vivo* acute brain slice recordings to determine S1 and M1 synaptic connectivity onto D1- and D2-expressing spiny projection neurons (SPNs) and parvalbumin-expressing striatal interneurons (PV-INs). Additional tracing experiments aimed to determine the subcellular innervation patterns of S1 and M1 inputs to single SPNs or PV-INs.

To investigate effects on behavior, Channelrhodopsin-2 (ChR2; AAV1.CaMKIIa.hChR2(H134R)-eYFP.WPRE.hGH) was expressed in either S1 or M1, and head-fixed mice trained to perform a Go/NoGo whisker-based texture discrimination task. Optogenetic activation of S1-Str synaptic terminals decreased behavioral responding, while activation of M1-Str synaptic terminals increased behavioral responding, increasing both Hit and False Alarm rates. Behavioral effects were not observed in open field and rotarod assays, suggesting that the observed differences in responding were task-specific rather than general motor effects of optogenetic stimulation. To determine the synaptic basis of S1- and M1-corticostriatal innervation patterns, *ex vivo* whole-cell recordings were performed in identified D1- and D2-SPNs and PV-INs. Optogenetic activation of S1-Str synaptic terminals revealed larger postsynaptic potential (PSP) in PV-INs compared to D1- or D2-SPNs, whereas optogenetic activation of M1-Str synaptic terminals revealed similar amplitude PSPs in D1- and D2-SPNs and PV-INs. We investigated whether anatomical differences in synaptic connectivity between S1- and M1-Str inputs account for the behavioral and synaptic results. Spaghetti monster GFP (pAAV.CAG.GFPsm-myc.WPRE.SV40) and Ruby2 (pAAV.CAG.Flex.Ruby2sm-Flag.WPRE.SV40) were expressed in either S1 or M1. Individual putative SPNs and PV-INs were filled with biocytin in *ex vivo* whole-cell recordings. Immunohistochemistry for GFP and Ruby2 Spaghetti monsters, biocytin, and the presynaptic marker basson was performed post hoc. Confocal imaging revealed colocalization of S1 and M1 afferent synapses onto putative SPN and PV-IN dendrites. Preliminary counts indicate that M1 synapses onto putative striatal neurons at double the level of S1. Ongoing work is investigating potential differences in subcellular distribution of S1 and M1 synapses.

Overall, our results indicate that activation of S1- and M1-corticostriatal projections produce opposing effects on behavior, which is mediated through differential functional and anatomical innervation of striatal microcircuitry by these two cortical regions.

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The role of KChIP3 in the development of Alzheimer's disease

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The classic concept of neurodegenerative diseases excluded the inflammation as a particular feature of these conditions. Today it is well accepted that a chronic inflammation caused by different factors, induces neuronal death in specific regions of the brain, which leads to the development of different pathologies, such as Alzheimer's disease (AD). However, the molecular mechanisms involved in the neurodegeneration process are little known. A protein that has been observed to increase in both, AD patients and murine models is KChIP3. The protein KChIP3/Calsenilin/DREAM is a neuronal protein that participates in various functions in the cell. In the membrane, interacts with potassium channels, in the cytosol it works as a calcium binding protein and in the nucleus is a transcriptional repressor of genes involved in neuronal activities like c-fos, bdnf and creb. In previous studies, it has been described the interaction between KChIP3 and presenilins 1 and 2. The presenilins are part of the enzymatic complex γ-secretase. That complex is responsible of generated the peptides β-amyloid (βA). Therefore, KChIP3 it could be involved in the development of AD, regulating the activity of γ-secretase, increasing production of βA, promoting inflammation and decreasing the cognitive ability.

In this work we had analyzed the role of KChIP3 in the context of AD. For these purpose, we have used the KChIP3 knockout mouse (KChIP3-/-) and a murine model of AD (5XFAD). We crossed these two genotypes to generate a transgenic model in which KChIP3 is silenced in the context of the AD (5XFAD/KChIP3-/-). The phenotype of this mouse was characterized, measuring the levels of inflammatory markers such as IL-1β, IFN-γ, IL-6, IL-10 and TNF-α. Likewise, the concentration of βA plaques was analyzed and the cognitive capacity evaluated by the Morris water maze behavioral test. To characterize the molecular mechanism mediated by KChIP3 in the development of AD we performed a quantitative proteomic analysis (iTRAQ) from the 5XFAD/KChIP3-/- mice brain.

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Keywords: KChIP3, Neuroinflammation, Alzheimer´s disease.

Evaluation of the expression of genes associated with inflammation and regeneration in rats immunized with the A91 peptide before a chronic spinal cord injury

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Area Neuroinmunology

The spinal cord injury (SCI) results in a permanent impairment of motor, sensory and autonomic functions of the autonomous nervous system. Several therapeutics has been proposed to protect the neural tissue, including immunization with modified neural peptides, which has shown significant effects on the self-reactive response. The protective autoreactivity mechanism proposes the modulation of the autoreactive phenomenon to promote neuroprotection by activating microglial cells under a phenotype characterized by low production of free radicals. Active immunization with modified neural peptides as "A91" could reduce the secondary degeneration of neurons and improves functional motor recovery after SCI animals. There are not studies in the literature of the effect of the protective autoreactivity mechanism if it is immunized before the SCI. The aim of this study was to evaluate the gene expression of IL-10, IL-4, IL-1β, IFN-γ, TNF-α, NT-3, IGF-1,BDNF, NGF, Arg, CSF and GAP43 using quantitative RT-PCR after 60 days post-injury (n = 3). The experimental groups were distributed as follows: Group 1: Rats with chronic spinal cord injury (SCI) treated with Complete Freund's Adjuvant (CFA) + PBS immunized 45 days after the injury (vehicle).; Group 2: Rats with chronic SCI immunized with A91 + CFA 45 days after the injury; Group 3: Rats with chronic SCI treated with CFA + PBS immunized 53 days after the injury; Group 4: Rats with chronic SCI immunized with A91 + CFA 53 days after the injury. Group 5: Rats with chronic SCI treated with CFA + PBS immunized 57 days after the injury; Group 6: Rats with chronic SCI immunized with A91 + CFA 57 days after the injury. The statistical analysis showed significance in the IGF1, TGFβ, IL-4 e IL-10 expression in the injury site. The results suggest that immunization with A91 53 days after the SCI promotes a better microenvironment for chronic phase regeneration.

Keywords: SCI, A91, Inflammation, Regeneration

Pericyte detachment during sleep loss disrupts blood-brain barrier

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Introduction: Sleep loss produces blood-brain barrier hyperpermeability by increasing endocytosis and promoting tight junction disassemble. Similar effects have been reported in PDGFRβ KO mice. As our previous reports show that pericytes seem to detach from the capillary wall in sleep restricted animals, we aimed to evaluate the changes in brain endothelial cell-pericyte interactions and its consequences on barrier function during sleep restriction.
Methods: Male Wistar rats were subjected to chronic sleep restriction using the multiple platform technique during 20h with 4h daily sleep opportunity. After 10 days of chronic sleep restriction animals were euthanized and the brain was removed to isolate brain microvessels from the cerebral cortex and hippocampus. Those samples were used to evaluate the expression of claudin-5, occludin, connexin 43, PDGFRβ, MMP-9, NFkB, P-NFkB, A2A adenosine receptor and CD73 by western blot. Immunofluorescent assay was made for connexin 43 and PDGFRβ in isolated blood vessels from the cerebral cortex and hippocampus. Another group of rats was used to perform permeability assays to Na-fluorescein (10mg/mL) and rhodamine 123 (1mg/mL).
Results: In isolated blood-vessels of cerebral cortex, sleep restriction reduced the expression of connexin 43; meanwhile, in the hippocampus there was a trend to reduce connexin 43 expression with respect to the control group. Likely, sleep restriction reduced PDGFRβ expression in the isolated blood vessels of the cerebral cortex and hippocampus as compared to the controls sleeping *ad libitum*. Sleep loss decreased the expression of claudin-5 in the isolated blood vessels of the cerebral cortex but not of the hippocampus; while it decreased occludin expression in the isolated blood vessels of the hippocampus but not in the cerebral cortex as compared to the control group**.** Sleep restriction increased MMP-9 expression in isolated blood-vessels of cerebral cortex and hippocampus, meanwhile NFkB expression did not change between the groups, nevertheless P-NFkB was increased only in cerebral cortex *versus* intact group. Sleep loss increased the expression of A2A receptor in isolated microvessels of hippocampus but not in cerebral cortex while that the expression of CD73 was not modified in any region. Both regions presented an increase in blood-brain barrier permeability to Na-fluorescein and rhodamine 123.
Conclusion
Chronic sleep restriction induces a detachment of the pericytes from capillary wall, it is related with a decrease in the expression of tight junction proteins and an increase in the blood-brain barrier permeability. The mechanism that may module the interactions between brain endothelial cells and pericytes after sleep restrictions seems to be a low-grade inflammatory status.

Key words: Blood-brain Barrier, pericytes, brain endothelial cells.

Caspase-1-dependent inflammation alters the protein levels of the TNF/TNFRII neuroprotector and the proBDNF/p75 neurodegenerative modules in a familial Alzheimer´s disease mouse model.

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Alzheimer's disease (AD) is the most common type of dementia, characterized by the accumulation of β-amyloid (βA) peptides and neurofibrillary tangles. Worldwide, there are about 46 million people affected with the disease[1].

Different research groups, including ours, using mouse models for AD have shown that the neuroinflammatory process controlled by the inflammasome plays an essential role in the development of AD[2]. Although, TNF and its receptors (TNFRI and TNFRII) have been also implicated in this process[3], the specific roles of each TNFR in AD development is not clear, since it has been suggested that TNF signaling via TNRI leads to neurodegeneration while signaling through TNFRII is neuroprotective[3]. Therefore, we propose that the alteration in the TNFRI/TNFRII ratio promoted by the presence of βA peptides could also play a role in the outcome of an inflammatory environment on neural function. In addition, it has been observed that the levels of the neuroprotective BDNF factor and its receptor (TrkB) decrease in patients with late stages of AD[4]. In contrast, the neurodegenerative modules such as the truncated TrkB (TrkBt), the immature form of BDNF (pro-BDNF), and $p75^{NTR}$ receptor, increase as AD progress[4,5]. Here, we investigated which of these changes is triggered by caspase-1-dependent inflammation in response to βA accumulation in the 5xFAD murine model for familial AD.

We used five and eight months old male mice from the following genotypes: wild type (Wt), transgenic 5xFAD, 5xFAD/Caspase-1 KO (CaspKO) and CaspKO, in a C57/SJL background.

Together, our data show that the negative effect of inflammation on cognitive impairment at early stages (five months) of the AD does not involve: i) Alterations in either levels or ratio BDNF/pro-BDNF; nor ii) alterations in TrkB isoforms protein levels. However, we observed that caspase-1-mediated inflammation triggered by βA peptides increased TNFRII protein levels in the hippocampus of 5 months old mice. Accordingly, intraventricular administration of TNF to 10 weeks old mice impaired memory and learning, as determined by the novel objects test. Therefore, at early stages of AD, the onset memory and learning decline is driven by TNF/TNFRII signaling, since TNF directly affects the cognitive abilities of young mice despite the presence of BDNF and its receptor. In contrast, at late stages (eight months), although BDNF/TrkB or TrkBt protein levels were not altered, we observed increased proBDNF and p75 protein levels in the hippocampus of 5xFAD mice. This was dependent of caspase-1 activation and a significant decrease in TNFRII protein levels, which was independent of the inflammatory process triggered by caspase-1. Therefore, at late stages, the negative effects of caspase-1-dependent inflammation on memory and learning alterations could be mediated by proBDNF-p75 neurodegenerative signals.

Keywords: Alzheimer´s disease, Inflammation, Caspase-1, BDNF, TNFR.

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4-Aminopyridine protects against motor alterations in a chronic excitotoxic model of spinal motor neuron degeneration

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Several data suggest that excitotoxicity due to excessive glutamatergic neurotransmission may be an important factor in the mechanisms of motor neuron (MN) death in several pathologies. We have shown that overactivation of the Ca^{2+} permeable α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamate receptor, through the continuous infusion of AMPA with an osmotic minipump in the lumbar spinal cord of adult rats, results in progressive rear limb paralysis and bilateral MN degeneration (J. Neuropathol. Exp. Neurol. 66:913, 2007). Using this model, in this work we have tested the possible protective effects of 4-aminopyridine (4-AP), based on its known therapeutic effects in some neurological disorders such as multiple sclerosis or Lambert-Eaton myasthenic syndrome (Neuro Cli pract 7:65, 2017), which are probably due to the stimulatory action of 4-AP on nerve conduction velocity and on remyelination (EMBO Mol Med 8:1409, 2016). In addition, 4-AP exerts a strong stimulatory effect on neurotransmitters, including acetylcholine release in neuromuscular junctions, (Proc R Soc Lond (Biol) 183:421, 1973.). Rats infused with AMPA 1.5 mM were treated daily with a single intraperitoneal injection of 4-AP (0.3 mg/kg, a previously established non-convulsive dose) for 10 days after minipump implantation and motor function was assessed with two behavioral tests, rotarod and grip strength, each day 10 minutes and 24 h post- 4/AP administration. Since day 4 on the rotarod test and since day 6 on the grip strength test, animals infused with AMPA and administered with 4-AP showed significant constant progressive recovery when compared to AMPA-vehicle controls. Importantly, 4-AP did not prevent at all the MN loss induced by AMPA at day 10 after pump implantation. We conclude that 4-AP did not have any significant immediate effect, since the protection was progressive and sustained from day 4. Because of the chronicity of the effect, our data suggest that the effect of the drug might be explained by its regenerative effect and facilitation of axon conductance, rather than by a stimulation of acetylcholine release. In order to better identify the specific mechanism by which 4-AP is acting, it is necessary to evaluate the interaction between axons and muscle.

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Key words: Motoneuron, 4-AP, Excitotoxicity

Evaluation of 25-OH Vitamin D levels in multiple sclerosis: association with clinical and hematological parameters in Mexican patients

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Área: Neuropatología

INTRODUCTION: Multiple sclerosis (MS) is a chronic neuroinmunoendocrine disease that is characterized by demyelinating lesions affecting the central nervous system and spinal cord which leads to progressive neurological deterioration. Previous studies have associated low serum levels of 25-OH Vitamin D with the clinical course of MS and other autoimmune diseases, which contribute the development of the disease. OBJECTIVE: The aim of this study was to evaluate the possible association of serum levels of 25-OH Vitamin D with clinical and laboratory parameters in multiple sclerosis. METHODS: 50 Mexican patients with diagnosis MS were included and classified according to McDonald criteria 2010, and 50 Mexican control subjects (CS) adjusted by age and sex. The hematologic evaluation of peripheral blood was measured using an automated hematology analyzer, ESR was determined by Wintrobe method and serum levels of 25-OH Vitamin D were determined by ELISA method. The data was analyzed with STATA v12 software and $p<0.05$ was reported as statistically significant. RESULTS: MS patients had elevated levels of several laboratory parameters than CS group: hemoglobin (15.6 g/dL vs 14.8 g/dL, $p=0.004$), ESR (13 mm/h vs 8 mm/h, $p=0.001$), lymphocytes (43% vs 35%, $p=0.013$), banded neutrophils (4% vs 1%, $p<0.001$), eosinophils (1% vs 0%, $p<0.001$); moreover, MS patients had decreased than CS group levels of: erythrocytes ($5.2x10^6$/µl vs $5.4x10^6$/µl, $p=0.036$), segmented neutrophils (43% vs 57%, $p<0.001$) and platelets ($198x10^3$/µl vs $260x10^3$/µl, $p<0.001$). In addition, serum 25-OH Vitamin levels were also reduced in patients with MS patients compared to CS group (19.1ng/mL vs 23.8ng/mL, p=0.004) and 94% of patients with MS had insufficient levels of vitamin D (<30 ng/ml) compared to 78% of CS group (p=0.038). Also, we found that 25-OH Vitamin D is positively correlated with erythrocytes (r=0.3132, p=0.004), hematocrit (r=0.2606, p=0.018); however, 25-OH Vitamin D is negatively correlated with years of disease progression (r=-0.2702, p=0.014), EDSS (r=-0.3075, p=0.005), Ashworth scale (r=-0.2255, p=0.042), RDRS-2 (r=-0.2859, p=0.009) banded neutrophils (r=-0.3525, p=0.001). CONCLUSION: This study revealed that MS patients have low levels of 25-OH Vitamin D regarding CS group and these levels correlated with hematological and clinical parameters. These suggest that 25-OH Vitamin D could be used as a serological marker of diagnostic and progression in Mexican MS patients.

Keywords: Multiple sclerosis, 25-OH Vitamin D, hematological and clinical parameters

Progesterone induces the activation of cSrc protein through its intracellular receptor in human glioblastoma cells

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Abstract: Glioblastomas are the most common and aggressive primary brain tumors in adults. To date, there is no an effective therapy for the treatment of this malignancy. In the last ten years it has been proven that sexual hormones such as progesterone (P4), can induce grow, migration and invasion of glioblastoma cells, through its intracellular progesterone receptors (PRs) which are members of the superfamily of nuclear receptors. However, it has also been reported that these proteins induce nongenomic effects. These effects are consequence of the interaction between a polyproline motif in the amino terminal domain of PR with the SH3 domains, very common sequences in several signaling proteins such as the members of the Src family kinases (SFKs). cSrc, one of proteins of this group, plays a major role in the development and progression of glioblastomas. Nevertheless, there is no evidence about the relation between PR and cSrc and its effects in glioblastoma cells. Our results showed that P4 and R5020 (specific PR agonist) activates cSrc protein since both progestins induce an increase in the p-cSrc(Y416)/cSrc ratio in U251 and U87 cell lines. When siRNA against PR was used and cells were treated with P4, the activation of cSrc was abolished in human glioblastoma cells.

Key words: glioblastoma, progesterone intracellular receptor and cSrc.

Chronic administration of glutamate decarboxylase inhibitors in the rat spinal cord induces motor alterations and motor neuron death

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Neuronal death is the main characteristic of neurodegenerative diseases. In the case of amyotrophic lateral sclerosis (ALS) such death is predominantly of cortical and spinal motor neurons (MNs), and alterations in the spinal synaptic inhibitory circuits seem to be an important factor in MN degeneration (Acta Neurol. Scand. 106:34, 2002; Neuroscience 362:33, 2017; Neuropharmacology 82:101, 2014). GABA is the main inhibitory neurotransmitter in the spinal cord and its synthesis depends strictly on glutamate decarboxylase (GAD) activity. This enzyme can be inhibited by 3-mercaptopropionic acid (MPA, competitive inhibitor), thiosemicarbazide (TSC, blocker of the coenzymatic action of pyridoxal-5'-phosphate, PLP) and PLP-γ-glutamyl hidrazone (PLPGH, inhibitor of pyridoxal kinase), compounds that induce epilepsy and neurodegeneration when injected in the hippocampus (Epilepsy Res. 116:27, 2015). These inhibitors were administered in the rat spinal cord by acute (through microdialysis, J. Neurochem. 89:988, 2004) or chronic (using miniosmotic pumps, J. Neuropathol. Exp. Neurol. 66:913, 2007) procedures. The acute administration of 20 mM MPA, 15 mM TSC or 25 mM PLPGH, separately, did not induce any motor alteration or MN damage at 24 h after the administration. In contrast, chronic infusion during 10 days of 3, 10 and 20 mM MPA, 15 mM TSC or 25 mM PLPGH, separately, caused myoclonus at days 2-3 and persistent flaccidity of the ipsilateral phalanges (quantified by a new test designed by us), as well as ~60% motor deficit, assessed by the rotarod test. Histological and immunohistological analysis at day 10 showed a reduction of ~50% in the number of MNs and notable reactive gliosis, detected by GFAP, mainly in the ipsilateral ventral horn. In other group of rats, GAD activity was measured at day 3 by a radioactive method in homogenates of the two ventral horns of the infused region; it was found that the three inhibitors tested decreased the activity by 50-70% in both horns, as compared with the control group. These results suggest that the chronic inhibition of GABA synthesis results in a decreased GABA inhibitory action, indicating that the inhibitory GABAergic circuits in the ventral spinal cord play an important role in the regulation of MN excitability and therefore their blockade results in excitotoxicity.

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Neurodegeneration, GABA, spinal cord.

Topic: Neuropathology

Effect of inhibition LPA_1 in an *in vivo* glioblastoma model

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Glioblastoma (GBM) is the most frequent and aggressive brain tumor, within different factors that collaborate with the growth of this kind of tumors, lysophosphatidic acid (LPA) has been described to promote cell proliferation and migration through its receptor LPA_1. The aim of this work is to use a competitive inhibitor of LPA_1 receptor: Ki16425, to study the effect of this antagonist in the tumoral growth in a heterotopic glioblastoma model.

To establish the implication of inhibition of LPA_1 in glioblastoma tumor growth, $2.5x10^6$ U251cells/80µL in PBS were injected into NSG™ mice flanks. Once tumors reached $30mm^3$ (day 17) tumors were allowed to grow for 8 more days (day 25) to start treatment with Ki16425 (30mg/Kg), every third day, until day 38.

Results showed that no changes were detectable in the tumor volume between Ki16425 treated animals compared with control. Interesting eosin and hematoxylin staining exhibited that tumor treated with Ki16425 presented larger pseudopalisades areas compared with the non-treated tumor, as well as, fibrous zones. These results suggest that inhibition of LPA_1 with Ki16425 has an effect on the tumor histology in a heterotopic glioblastoma model and apparently no effect in tumor volume.

Keywords: Glioblastoma, LPA_1, Ki16425.

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Allosteric modulation of nicotinic receptors reduces L-DOPA induced dyskinesias in parkinsonian mice

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Dopamine (DA) precursor L-3,4-Dihydroxyphenylalanine (L-DOPA) remains the most effective symptomatic treatment of Parkinson's disease (PD), which is primarily due to dysfunction of the nigrostriatal dopaminergic pathway. However, long-term administration of L-DOPA induces the development of abnormal involuntary movements known as L-DOPA induced dyskinesia (LID), which can be quite incapacitating and are a major challenge in PD management. Mechanisms underlying LID are not fully understood and its medical treatment is generally unsatisfactory. Neuroprotective effects of nicotine and its amelioration of LID in different parkinsonian animal models have been reported. Nicotine exerts its effect primarily through nicotinic receptors (nAChRs), of which those that contain the α7 or the β2 receptor subunit are the most abundant in the brain. In this study we sought to determine whether nicotine may also reduce LID in a mouse model of PD and whether this response can be potentiated by the positive allosteric modulation of the $\alpha7$ and the $\alpha4\beta2$ nAChRs. Adult male CD1 mice were stereotaxically injected with 6-OHDA in the forebrain bundle (unilaterally) to induce PD-like symptoms. These mice were then exposed to nicotine via drinking water (30 mg/l) for 3 weeks after which they were treated daily for 4 weeks with L-DOPA (12 mg/kg i.p). Nicotine concentration in the water was maintained for the entire period in these animals. Controls were treated identically, except no nicotine was present in the water. Once the animals were dyskinetic, two groups were formed, the first one was administered with PNU-120596 (allosteric modulator of the $\alpha7$ nAChRs) and the second one was administered with NS9283 (allosteric modulator of $\alpha4\beta2$ nAChRs). Afterwards the dyskinesias were evaluated. Our findings indicate that animals exposed to nicotine plus the allosteric modulators had significant abatement of dyskinesia, even better than the nicotine treatment by itself. Together, our results provide further support for therapeutic potential of nicotine in LID and suggest that the allosteric modulators PNU-120596 and NS9283 may also be useful to reduce it.

Key words: Parkinson's disease, nicotinic receptors, dyskinesias

Autophagy inducers trehalose and metformin prevent dopaminergic cell death

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Area: Neuropathology

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the selective loss of dopaminergic neurons, mitochondrial damage, oxidative stress, and disruption of the protein degradation pathways mediated by the proteasome and autophagy. Autophagy plays an essential role in neuronal maintenance since an impairment of autophagy leads to neurodegeneration and its stimulation has a protective effect. Therefore, it is crucial to study the potential neuroprotective effect of different autophagy-inducing molecules such as trehalose and metformin. Trehalose induces autophagy through a mTOR-dependent and independent pathways, and metformin only through a mTOR-dependent pathway. Therefore, we evaluated the effect of autophagy inducers trehalose and metformin in a cellular model of PD. First, we confirmed the induction of autophagy in response to trehalose and metformin in the SH-SY5Y dopaminergic cells through detection of an increase of the LC3-II marker by western blot, and a higher number of autophagosomes by transmission electron microscopy. Then, we analyzed whether autophagy stimulated by trehalose and metformin had an antioxidant effect in the experimental model of PD induced by the herbicide paraquat (PQ). Autophagy was stimulated 1 h before PQ treatment and oxidative stress was evaluated at 24 h by flow cytometry using dihydroethidium. Unexpectedly, trehalose did not show an antioxidant effect, while metformin increased the levels of oxidative stress induced by PQ. Since mitochondria are the main target of PQ, we evaluated the effect of autophagy induction with trehalose and metformin on the mitochondrial activity at 48 h. PQ decreased the mitochondrial activity, and when autophagy was stimulated with trehalose and metformin before PQ treatment, the mitochondrial activity was increased. Importantly, trehalose and metformin showed a protective effect on PQ-induced cell death. Interestingly, our results suggest that even the induction of autophagy with trehalose and metformin has no antioxidant effect on the oxidative stress induced by PQ, it exerts a protective effect on cells by improving the mitochondrial activity and protecting cells from PQ toxicity. Therefore, trehalose and metformin represent autophagy inducers with a promising potential for the treatment of neurodegenerative diseases such as PD.

Keywords: *Parkinson's disease, autophagy, oxidative stress*

Effect of the environmental enrichment on klotho levels in transgenic mice.

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Area: Neuropatología

Keywords: Environmental enrichment. Klotho, Alzheimer's disease

Introduction: Cumulative evidence shows that modifications in lifestyle factors constitute an effective strategy to modulate molecular events related to cognitive decline confirming the relevant role of the homeostatic reserve. Environmental Enrichment (EE) represents an approach to ameliorate cognitive decline and neuroprotection related to aging and neurodegenerative diseases like Alzheimer's disease (AD). An increased of klotho levels have been related to improvement in cognitive decline and it increase after cognitive stimulation. Here we evaluated EE neuroprotective influence on 3xTg-AD mice.

Methods

Mice: Male 3xTg-AD (n=30; 6 months old, 35-38 g). **Cognitive stimulation programs**: *group 1*; just housed in normal cage at vivarium, *group 2*; were stimulated with Morris water maze (MWM) training for 5 days every month for 3 months and housed in normal cage at the vivarium, and *group 3*; got the same stimulation with MWM and housed in EE that changed every 7 days. **Memory test**: All three groups were tested in the Barnes Maze paradigm after 3 months of stimulation programs. **Immunohistochemistry**: after memory test, we obtained the brain and sixty-micro meter frozen sections were prepared as described previously and used klotho antibody to measure the levels of this protein in different areas.

Results

The results suggest that neuroprotection depends on the type of stimulation received. Both protocols improved learning and memory. However EE is significative better than just MWM. Equally both programs modified klotho levels according to the type of stimulations.

Discussion

EE represents social, cognitive sensory and motor stimulation and its effect on learning and memory is greater than memory stimulation alone. Is possible that klotho is related to this neuroprotector effect.

Investigation of the therapeutic potential of autophagy induction in a mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is a progressive, age-associated neurodegenerative disorder representing the leading cause of dementia worldwide. An abnormal accumulation of beta-amyloid and intraneuronal neurofibrillary tangles lead to an extensive loss of synapses in the cerebral cortex and hippocampus along with neuronal death.

The precise molecular mechanisms leading to AD are not known yet, however, mounting evidence emphasizes the role of autophagy in the pathogenesis of AD. Dysfunctions in numerous steps of the autophagic pathway have been observed in both human AD patients and rodent AD models, making it a suitable target for therapy. As experiments with autophagy-inducing chemicals have been repeatedly shown to cause undesired side-effects, studying physiological autophagy inducers as well as natural chemicals that activate the degradation pathway might pave the way towards novel and better targeted treatment options for AD. One way to physiologically induce autophagy is by food restriction. Another dietary intervention that has been shown to act neuroprotective and to induce autophagy is Ketogenic Diet. A third way to induce autophagy naturally is by Trehalose, a disaccharide present in non-mammalian species. Here, we investigate the therapeutic potential of autophagy induction by these treatments in a triple-transgenic AD mouse model (3xTg). 3xTg mice develop an age-related AD neuropathology characterized by both extracellular plaque deposition and tangle formation. By treating the model with the novel approach of mild physiological autophagy inducers, our aim is to investigate whether this method has a mitigating effect on the Alzheimer pathology while, at the same time, representing a potential chronic treatment option translatable to humans, due to the lack of drug-caused toxic side effects.

Key words: Neurodegeneration, Alzheimer's Disease, Autophagy

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Sensory changes due to dopamine lack in a mouse model of Parkinson's Disease.

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This work belongs to the Neuropathology Area of the meeting, having the keywords: Visual disfunction, Parkinson's Disease, mouse model.

Parkinson's Disease (PD) is a motor disorder mostly characterized by its motor symptoms, such as tremor, bradykinesia, muscle rigidity and postural instability which has been linked to loss of dopaminergic cells across the midbrain in the nigrostriatal pathway (Chaudhuri & Ondo, 2009).

However, nonmotor symptoms also have a great relevance, examples of these are lower visual acuity and contrast sensitivity, which can derive in dementia and hallucinations (Matsui et al., 2006), reducing in the quality of life of PD patients (Lin et al., 2015).

The relationship between contrast and spatial frecuency, and it has been described as a "U-inverted" curve, being observed that PD patients have lower acuity in mid-high spatial frequencies (Weil et al. 2016), requiring more contrast in these zone to perceive correctly.

This curve has also been proposed in mice (Histed, Carvalho, & Maunsell, 2011) but to our knowledge has not been linked a relation between contrast or spatial frequency sensitivity in a model of hemiparkinsonism by infusing 6-OHDA in the SNc (Ungerstedt, 1968) and evaluating the performance of mice in a visuomotor task (Carrillo-reid, Han, Yang, & Akrouh, 2018).

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Role of ROS produced by mitochondria and NADPH-oxidase (NOX) in the apoptotic death of cerebellar granule neurons.

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It has been described that reactive oxygen species (ROS) play a role in multiple processes during physiological and pathological conditions. The main cellular sources of ROS are the mitochondria and NADPH-oxidases (NOX). It is known that both sources are implicated in neuronal death, the detailed mechanism of ROS in this event is still unknown. Particularly, there is no sufficient information about the possible interplaying between mitochondria and NOX during neuronal death. On the other hand, it has been shown changes in the mitochondrial morphology under apoptotic conditions. These changes, known as mitochondrial dynamics, is mediated by the participation of several proteins. DRP1 is one of the proteins involved in the fission of mitochondrial membranes. It is not totally understood whether the ROS produced by mitochondria or by NOX are related to the mitochondrial dynamics and if this association could be involved in the apoptotic neuronal death process.

The aim of this study is to determine whether the mitochondria and/or NOX is the main source of ROS production involved in neuronal apoptotic death and if this process involves the mitochondrial dynamics, particularly DRP1-mediated fission.

We used cultured neurons that were treated with ST (0.5μM) or potassium deprivation to induce apoptotic death. We measured cytoplasmic ROS with dihydroethidium (DHE) or Mitotracker red CM-H_2XRos for mitochondrial ROS levels. Mitochondrial activity was estimated by MTT reduction and the mitochondrial membrane potential was determined with JC-1. The mitochondrial morphology was asses by staining mitochondria with Mitotracker Green. DRP1 and p-DRP1 levels were analyzed by Western blot.

Our results showed that ST or K5 treatment induced both an early cytoplasmic ROS production (0-30 min) and a higher significant increase of cytoplasmic ROS levels after five hours. Interestingly, we also found an early increase of mitochondrial ROS levels under apoptotic conditions. Cell death induced by ST and K5 was only partially reduced with a mitochondrial antioxidant treatment. We also observed a significant decrease in the mitochondrial membrane potential elicited by ST and K5. On the other hand, we observed an early mitochondrial fission process in cells treated with ST or K5. In addition, these two conditions induced a DRP1 activation measured as p-DRP1.

These results suggest that early produced mitochondrial ROS could participate in the neuronal death induced by ST or K5. It is suggested that ROS produced by NOX are the final mediator in this process. Additionally, the increase of ROS levels are accompanied by mitochondrial morphological changes and the DRP1 activation. Thus, we speculate that early ROS production by apoptotic conditions lead to mitochondrial morphological changes related to neuronal death.

Keywords: Reactive oxygen species, NDPH-Oxidase, Mitochondrial dynamics

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SMB

Anxiogenic effect of the methanolic extract of *Habranthus concolor*

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Area: Neuropatología
Keywords: *Habranthus concolor,* galantamine, anxiety

Introduction

The genus *Habranthus* is composed of approximately 30 species that are originally from the American continent. *Habranthus concolor* (Amaryllidaceae) is a herbaceous plant species endemic of Mexico, distributed in xerophyte vegetation from Guanajuato and San Luis Potosi to Mexico City. The methanolic extract of the bulbs has two main alkaloids: galantamine and chlidanthine. These have shown activity as selective and reversible inhibitor of acetylcholinesterase. Galantamine hydrobromide currently used as a treatment of diseases like Alzheimer's disease in early stages, because delays the degradation of acetylcholine in the brain and therefore improves the neurotransmission. Galantamine has an additional mechanism of action, it is an allosteric modulator of nicotinic acetylcholine receptors (nAChRs). It is known that galantamine improves cognition but little is known about the effect of Amaryllidaceae alkaloids on anxiety. In this work, we tested the effect of the methanolic extract of the bulb of *Habranthus concolor* containing galantamine and chlidanthine on anxiety behavior of mice.

Methods

Animals: Male C57BL/6 (n=20; 6 months old, 35-38 g). **Treatment**: 100mg/kg body weight of methanolic extract of the bulbs of *Habranthus concolor* with 10% of alkaloids orally. Analysis of the extract was performed by gas chromatography coupled to mass spectrometry (GC-MS). Treatment was daily for 3 months. **Behavioral test**: *Elevated T-maze;* with 1 trial as baseline, 4 trials for avoidance and 2 escape trials with 24 hr. in between. *Open field*; registering number of feces and time in the inner or outer zone.

Results

We found that *Habranthus concolor* has a significant effect on open field test increasing time of the mice in the inner zone and decreasing time in the outer zone. In the elevated T-maze we observed that the extract increased the voidance time and escape time.

Discussion

The results mean that the *Habranthus concolor* extract treatment produces an increase in anxiety behavior and no memory improvement.

Acknowledgments. To Dr. Javier Pérez Flores for performing GC-MS analysis.

Human olfactory neural progenitor cells derived from the olfactory epithelium (hNS/PCs-OE) show differences in the soluble factors content in depression-diagnosed and in borderline personality disorder- patients

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Abstract

Neuropsychiatric disorders courses with neurochemical, morphological and behavioral alterations. Clinical studies have indicated that in the neuropsychiatric disorders exist alterations in the periphery but also at the central level. Then, several biological samples such as blood or serum have been used to search for biomarkers of neuropsychiatric disorders. Also, inducible pluripotent stem cells have been used to study some aspects of neuropsychiatric disorders. However, the olfactory epithelium, a region in which the generation of new neurons constitutively occurs, has gained attraction to search for biomarkers of several diseases. In this regard, we recently reported the capability of hNS-PCs-OE to release soluble factors. Also, we identified some of those soluble factors in a healthy subject. We thus here analyzed whether hNS/PCs-OE derived from depression (DD) diagnosed or borderline personality disorder (BPD) patients show differences in the soluble factors. Human NS/PCs-OE were obtained from 10 control healthy subjects, 10 DD and 10 BPD participants. Cells were growth under specific culture conditions to obtain sufficient amount of protein in the conditioned medium. Once conditioned medium was collected, hNS/PCs-OE were lysed and processed for the identification of proteins by western blot. Also, soluble factors were assessed in a proteomic antibody microarray approach. In addition, we determined the concentration of some of the soluble factors identified in the proteomic approach by ELISA. Human NS/PCs-OE expressed nestin, Sox2, Mash-1, NeuroD, beta III tubulin, however, differences in the expression of these proteins were found among control, DD and BPD derived hNS/PCs-OE. Also, the analysis of soluble factors revealed significant differences among the groups. Differences among controls, DD and BPD will be discussed.

Keywords: Olfactory epithelium, depression, borderline personality disorder, neurogenesis,

Area: Neuropatologia

LPS-induced neuroinflammation impairs the cell cycle progression of DCX+ neural progenitors in the dentate gyrus

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Adult hippocampal neurogenesis is a finely tuned process modulated by extrinsic factors. Neuroinflammation sets a non-permissive microenvironment underlying neurogenic dysregulation. Systemic lipopolysaccharide (LPS) injection has been long-used as an experimental strategy for inducing brain inflammation leading to a reduction of adult-born neurons. We have recently reported that a proinflammatory profile along with an impaired neurogenic rate, continues seven days after a single LPS challenge. To analyze the nature of such impairment, we evaluated the proliferative behavior of neural progenitor cells under a neuroinflammatory context. We administered a single i.p injection of LPS or saline to young-adult mice and sacrificed them 7 days afterwards. We analyzed the proliferative capacity of neural progenitors by labeling a cohort of new cells with 3 BrdU pulses (1 i.p. injection each 2h) and 24h later we estimated BrdU+ cells co-labeling with Ki67+ using immunofluorescence, confocal microscopy, and stereological-based analyses. Under control conditions, BrdU+Ki67+ cycling cells were mostly DCX+ indicating these progenitors undergo the highest proliferative rate. LPS-induced neuroinflammation elicited a decrease in the number of proliferating DCX+ cells indicating a deficit in their ability to re-enter the cell cycle. To evaluate if the impaired cell cycle progression of DCX+ progenitors was a consequence of a lengthening in their cell cycle, we performed a double S-phase labeling strategy using IdU and CldU and quantitatively analyzed the S-phase (Ts) and the total cell cycle (Tc) lengths. LPS-induced neuroinflammation promoted a decrease in Ts and an increase Tc of DCX+ progenitors suggesting a lengthening of G1 phase of the cell cycle. Our data indicate that the expansion of the progenitor cell pool highly depends on DCX+ cell proliferation and suggest that a premature exit of DCX+ progenitors from the cell cycle contributes to the reduced number of adult-born neurons observed during neuroinflammation.

Key words: neuroinflammation, neural progenitor cells, proliferation, cell cycle

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Changes in synaptic vesicle recycling associated to aging in Alzheimer´s disease model

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Background/Aims: Aging has been linked to cognitive impairment that may be due to altered synaptic function. The synaptic vesicle exo/endocytosis is probably one of the main control mechanisms to maintain the efficiency of neurotransmitter release and neuronal communication. In this regards, recent evidence has linked alterations in synaptic vesicle recycling process with age-associated brain disorders, such as Alzheimer's disease (AD). Thus, we aimed to analyze changes in the kinetics of synaptic vesicle recycling and in the levels of related proteins during aging in isolated nerve ending (synaptosomes) obtained from the 3xTg mouse model of AD.
Methods: We have obtained cortical and hippocampal synaptosomes from WT and 3xTg-AD mice at different ages. The vesicular recycling analysis was assessed by the incorporation of the fluorescent dye FM4-64, measured in real time by confocal microscopy. Protein content was assessed by Western blot.
Results: The incorporation of FM4-64 to the synaptosomal membrane increased after depolarization at all ages studied. The increase in the fluorescence was totally dependent on external calcium indicating that vesicle exocytosis was a depolarization-dependent mechanism. We found changes in the kinetics of FM4-64 fluorescence at different ages and in the AD model. Young synaptosomes incorporated more FM4-64 and the kinetics of this incorporation was faster than the one obtained at synaptosomes from old mice. On the other hand, when comparing young synaptosomes from 3xTg-AD and WT mice, we observed that 3xTg-AD incorporated more dye than WT with significant changes in the kinetics. Conversely old synaptosomes from 3xTg-AD exhibited slower vesicle exocytosis than old WT synaptosomes.
Conclusion: These results suggest functional changes of the exo/endocytosis mechanism in pre-synapses associated to age and to the disease progress. We are now exploring if these changes are due to mitochondrial-dependent reduction of ATP and/or to changes in synaptic calcium levels which would affect either fusion or docking of synaptic vesicles to active zones.
Key words: Alzheimer, neurotransmission, exo/endocytosis.

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THEPARTICIPATION OF ARYL HYDROCARBON RECEPTOR IN THE AGING PROCESS AND ALZHEIMER'S DISEASE

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AREA: Neuropatología

BACKGROUND: Aging in the central nervous system (CNS) is distinguished by chronic inflammation. The aryl hydrocarbons receptor (AhR) participates in the inflammatory response. Currently, evidence in animal models shows that the appearance of aging characteristics is associated with changes in AhR levels. However, there is no information on the behavior and participation of AhR in the CNS of humans during aging and neurodegenerative diseases such as Alzheimer's Disease (AD).
OBJECTIVE: To evaluate the expression of AhR in human hippocampal postmortem tissue and in serum from participants of different ages with and without AD.
METHODS: We included postmortem hippocampus tissue from autopsies performed at the General Hospital of Mexico and serum samples obtained from healthy university students (J, 20-30 years), older adults (AM, ≥60 years) and patients with AD (AD, ≥60 years) from INNN. In postmortem tissue AhR, GFAP and Iba-1 were quantified in immunohistochemistry, whereas AhR serum levels were measured by ELISA.
RESULTS: The elderly people tissue presents reactive gliosis, microgliosis and astrogliosis (** $p < 0.01$) characteristic in aging processes. The AhR expression is greater in the AM tissue compared with J (* $p < 0.05$). AhR colocalized with the reactive glia in both astrocytes and microglia and AhR is mainly cytosolic. We have evidence pointing to a greater expression of AhR in AD compared to AM. We found higher serum levels of AhR in AD (* $p < 0.05$) with respect to J and AM. The AhR increase in AD patients seems to depend on disease severity.
DISCUSSION AND CONCLUSIONS: The results suggest that AhR participates in the aging process and probably in the development of AD through the response of glial cells to the proinflammatory environment in the CNS. AhR could travel in vesicles from the brain or other tissues of patients with AD into the bloodstream. With this study, we can propose to the AhR like a protein that characterizes aging, and a possible molecular target for the treatment of neuroinflammation.
This work was supported by CONACYT [grant 262295 to MATR].

Key words: neuroinflammation, glia, human hippocampal.

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Optical control of pathological neuronal ensembles in a model of Parkinson's disease

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Área: Neuropatología

The neuronal ensembles are groups of neurons defined by the presence of coordinated activity (Carrillo-Reid et al., 2008). *In vitro* experiments have demonstrated that the characteristic absence of dopamine in the model of Parkinson's disease causes an abnormal synchronization of the striatal neuronal ensembles (Jaidar et al., 2010; Pérez-Ortega et al., 2016). In addition, using optogenetics it has been reported that continuous unilateral stimulation in striatal neurons of mice causes ipsilateral turns to the lesion, this behavior is similar to hemiparkinsonian animals, contrarily, when stimulated in pulses the rotation was contralateral (Jaidar et al., 2019). However, it is still unclear how the activity of the striatal neuronal ensembles is related to pathological motor behaviors in in vivo models. The aim of this work is to characterize motor behavioral changes in the context of different light stimulation protocols by the administration of RuBi-Glutamate (a caged compound that releases glutamate upon contact with light) to control animals and hemiparkinsonian animals. We designed a head fixed trackball setup to quantified the movement of hemiparkinsonian animals. Subsequently, RuBi-Glutamate was administered and stimulated with different frequencies (1 Hz, 5 Hz, 10 Hz, 20 Hz and 50 Hz). The preliminary results show a difference in distance, speed and direction of movement between a hemiparkinsonian animal and control. We have also seen that photostimulation with different frequencies shows a tendency to increase movement. The result of this investigation will allow to known if it is possible to correct the pathological behavior in the model of Parkinson's disease by using caged compounds and optical stimulation.

Hemiparkinson, Trackball, RuBi-Glutamate.

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Striatal Sub-Circuits and Cholinergic Interneurons Activity in Behavioral Flexibility

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Field: Neural Circuits

Behavioral flexibility is the ability to update actions in response to changes in the environmental contingencies. The striatum is a subcortical nucleus involved in the adaptation of behavioral strategies, reinforcement learning, and movement. This nucleus is mainly constituted by GABAergic projections neurons (~95%) and a small fraction of striatal interneurons (~5%). From this small fraction, Cholinergic interneurons represent only ~3% of striatal neurons. Despite their low proportion, the cholinergic striatal interneurons are implicated in the update of actions in response to changes in contingencies.

In this study, we aim to evaluate the contribution of the striatal cholinergic and projection neurons on the update of a contingency. To this end, we standardized a head-fixed response licking task and performed optogenetic inhibition or calcium imaging (GCaMP6f) of these cells *in vivo*.

Our preliminary results show that the striatal neurons' activity correlates with the learning of specific auditory stimuli. And that optogenetic manipulation of the dorsomedial striatum or its cholinergic interneurons alters the update of licking responses.

Key words: Behavioral Flexibility, Striatal Circuits.

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Cerebellum – Basal ganglia interactions circuits

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Cerebellum (CB) and basal ganglia are structures directly linked to motor control. Classically, they communicate with each other through brain cortex by parallel pathways, however, the recent evidence suggests the activity in the striatum is modulated by the CB activity, through the thalamus. The CB sends axons to the ventral and the intralaminar regions of the thalamus; opening the question about the role of each pathway in the control of movements.

In this study, we aim to evaluate the contribution from the CB projections to the ventral (VL) versus the intralaminar region of the thalamus on movements to achieve a goal-directed trajectory of a joystick.

1) From whole-cell recording, our preliminary results indicate that cells in the different regions of the thalamus, that project to the basal ganglia, receive functional connections from the CB.

2) From manipulations in vivo, we have observed that the optogenetic manipulations of the CB projections to the thalamus suggest that these projections may be necessary for the update of trajectories. This is consistent with the idea of the thalamic projections to the thalamus contributing to the refinement of movements.

Key words: 1) Cerebellum; 2) Basal ganglia; 3) Motor learning.

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Synaptic long-term depression mediated by mGlu and NMDA receptors in individual dendritic spines from SHANK3 mice

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Area: Cellular Plasticity and Neural Circuits.

Changes in synaptic weight are thought to be the physiological basis for learning and memory. These changes can result in either potentiated or depressed synaptic transmission at individual synapses this phenomenon is called G synaptic plasticity, and may physically alter neuronal connectivity through structural changes at synapses, this is called structural plasticity, specifically refers to changes in number, size or shape of dendritic spines.

It has been reported a correlation between neurological disorders and morphological alterations of dendritic spines. Reports indicate that autism spectrum disorders (ASD) are associated with mutations in a host of genes that are critical regulators of synaptic structure and function. For instance, the Phelan-McDermid syndrome (PMS) is considered as ASD. This syndrome is cause by loss of one copy of Shank3 gene in the telomeric portion of chromosome 22. This deletion is likely responsible for some of the neurological features of the Phelan McDermid syndrome. SHANK3 is a scaffold protein of the postsynaptic density of glutamatergic neurons, it interacts indirectly with glutamatergic receptors. It is unknown how the haploinsufficiency of Shank3 can lead the clinical features of PMS. We hypothesized that misregulation of synaptic plasticity and its structural correlates may lead to cognitive impairments of PMS.

In order to address this, we used two-photon glutamate uncaging to induce LTD mediated by mGluR or NMDA at individual dendritic spines from organotypic hippocampal slice cultures from SHANK3 mice. Our results show a spine density reduction of dendritic spines in SHANK3 mice in comparison with wild type mice. In addition, we found that the expression of mGluR1 and mGluR5 was not altered. Besides, the expression of GluN2B subunit of NMDA receptors was increased in SHANK3 mice.

In addition, regarding to synaptic activity we found that the haploinsufficiency of Shank3 inhibit the LTD mediated by mGluR by contrast seems to promote a potentiation. On the other hand, the LTD mediated by NMDA was long-lasting while in wild type was short-term. These data show for the first time that the haploinsufficiency of Shank3 disrupt the synaptic plasticity response, specifically synaptic depression and its structural correlates.

Palabras clave: SHANK3, Synaptic plasticity, dendritic spines

Visual stimuli representation in striatal neuronal ensemble activity

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Area: Cellular plasticity and neuronal circuits

Basal ganglia are a group of interconnected subcortical nuclei, which have been traditionally implicated in functions such as motor learning, habit formation and action selection. Among them, the striatum is considered the main recipient of external input and an integrative hub of information arriving from the talamus, cortex and some other brain regions. Until recently it was believed that most cortical areas provided inputs to the striatum but evidence of a direct cortical projection from primary visual cortex was elusive. In the last decade a few works using retrograde and anterograde tracers found that this direct monosinaptic projection from V1 left its axon terminals in a thin columnar array along the dorsomedial striatum, adjacent to the lateral ventricle.(Hintiryan et al., 2016) Moreover, unicellular electrophisiology provided evidence that this anatomic projection was able to elicit a response in both direct and indirect pathways medium spiny neurons.(Khibnik, Tritsch, & Sabatini, 2014) Although this conection proved being not only anatomic but also funcional, the response in the striatum has only been studied at the unicellular and field level. Using two photon calcium optogenetic methods, it has been found that there are intrinsic neuronal ensembles in V1, that these ensembles respond to visual stimuli and can be artificially activated(Carrillo-reid, Yang, Miller, Peterka, & Yuste, 2017). Given this direct cortical projection, we seek to understand how visual stimuli activate neuronal ensembles in dorsomedial striatum.

Keywords: neuronal ensembles, striatum, primary visual cortex.

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Electrophysiological evaluation of the adult dentate gyrus plasticity after excitotoxic damage

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Area: cellular plasticity and network circuitry

The hippocampus integrates and temporally stores information from a variety of subcortical and cortical areas. The dentate gyrus (DG) is the main gate through which this information enters to the hippocampus. Dentate granule cells receive excitatory input from the entorhinal cortex (EC) thorough the perforant pathway (PP) and send excitatory output to the CA3 hippocampal region via the mossy fibers. In this way, the DG exerts control over the flow information and excitability in the hippocampal formation. The DG is vulnerable to suffer anatomic and functional impairment after an excitotoxic brain insult, as observed, for example, after status epilepticus. It is unknown how these perturbations impact on the morphology as well as on the function and plasticity of the DG, over time. How can the DG process the incoming information in time after it has been injured? In attempt to solve this question, we induced a DG excitotoxic lesion in young adult mice injecting 150 nl (0.75mM) of kainic acid (KA) and evaluated at two different time-points (10 and 30 days post-lesion, dpl) the: 1) anatomical organization of the DG by Nissl staining, 2) DG behavioral-associated function through the analysis of the contextual Fear (CF) task and, 3) The ability to induce LTP in the PP. Our preliminary results show that both, the anatomy of the DG and its electrophysiological plastic properties are highly impaired at 10 dpl. The damaged region displays mainly two morphological features: 1) lack of cells in suprapyramidal layer and hilus, and 2) dispersion of all dentate granular cell layers without layer interruption. At this time point, compared to sham and intact controls, injured animals also show an impairment to generate LTP in the PP, and deficits in learning and memory performance in the CF task, reflected by a low freezing percentage during acquisition and retrieval phases. We are now evaluating the plasticity response after 30 dpl, however our first results show that the integrity of the adult mice DG is essential to CF learning and memory, and to the correct integration of information arriving from the entorhinal cortex.
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Keywords: Dentate gyrus, plasticity, injury

Neural activity in the primary visual cortex of SHANK3$^{+/-}$ in response to an over specificity visual task

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Area: Cellular Plasticity and Neural Circuits

The Autistic Spectrum Disorder (ASD) is considered as a neurodevelopmental disease. The core symptoms include impairments in verbal and nonverbal communication, impairments in social interaction and repetitive or stereotypic behaviors. The causes of ASD are currently under research, nowadays it's known that a strong genetic component is associated to 20% of the cases, this genetic component include chromosomal re arrangements, variations in the numbers of copies of a gen or variations in the sequence codification of genes. Some of these affected genes code for structural or functional proteins that compose the synapse, so this type of diseases are called synaptopathies. A clear example is the Phelan-McDermid Syndrome (PMS) that is also a part of the ASD.

The deletion of the Shank3 gen in only one of the alleles causes the PMS. Shank3 codes for a protein with the same name (SHANK3), this protein is located inside the post synaptic density of the glutamatergic synapses. It is a scaffolding protein with structural domains with the ability to interact with ionotropic and metabotropic glutamate receptors.

It has been reported that human patients diagnosed with ASD have alterations in the neural activity related to visual processing. Recent publications show the prevalence of over specificity of learning, this is defined by an inefficient task acquisition that reveals behavioral inflexibility and an impairment in the cognitive mechanisms that stablish the generalization of a learning rule. In addition, data obtained by our lab show alterations in the activity of the primary visual cortex in a PMS mouse model.

In this work we hypothesized that the molecular alterations in PMS create alterations on the neural activity and as a major consequence a failure in the system synaptic plasticity thus the PMS mouse model will have a major probability to develop over specificity of learning and be unable to learn a new visual task.

We observed that the Shank3$^{+/-}$ mice develop over specificity of learning in a visual discrimination task, also we observed differences in the proportion of selective neurons to the different task components and how this population modified certain properties of their response in different stages of the task.

Phelan-McDermid, Visual Cortex, Learning

Behavioral correlates of atypical V1 neurons activity in a genetic mouse model of autism (Shank3)

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Area: Cellular Plasticity and Neural Circuits.

Autism spectrum disorder or ASD is a neurodevelopment disorder. Have been reported that patients with ASD shown differential activity in cortical regions, for instance increased in neuronal activity in visual processing brain areas and atypical visual perception compared with no autistic people.

The causes of these alterations remain unclear, but many studies demonstrate strong genetics basis correlated to ASD. Some identified mutated genes in ASD are related to synaptic function and structure, because of this some ASDs are called “synaptopathies”. An example of this is the Phean-McDermid syndrome (PMS), which is caused by a deletion of *shank3* gene in one allele in the chromosome 22. *Shank3* encodes for the SHANK3 protein, a postsynaptic scaffolding protein that is present in glutamatergic synapses. However, underlying neural mechanisms of this activity disturbance remain unknown.

Previously, in our lab we assessed the neural activity in layers 2/3 of V1 from SHANK3 mice, in order to investigate the consequences of Shank3 haploinsufficiency in cortical processing of sensory information. We recorded the neural activity *in vivo* from head-fixed awake mice in response to a visual stimuli (gratings in eight orientations) using genetically encoded calcium indicator (GCaMP6f) and two-photon imaging through a cranial window in V1. We found a bigger proportion of responsive neurons in SHANK3 mice. Furthermore, we found that neurons from SHANK3 mice are more selective to orientation but no to direction of the visual stimuli. Based on the results outlined above, we are studying how the haploinsufficiency of SHANK3 may be influencing the brain function that is important for learning. In order to assess this, we are training mice in a visual discrimination task using a Go – No go paradigm. Our hypothesis is that SHANK3 mice may have a low performance, related to the alterations in the neural activity. Surprisingly, our first dataset shows a faster learning in SAHNK3 mice in comparison to wild type. Our next step is to analyze the changes in the V1 neuronal activity driven by learning.

Autism, visual cortex, two-photon

Thalamo-striatal contribution to switch between actions sequences

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Field: Neural Circuits

Action sequences are necessary for animals' life. These sequences can contain more than one kind of action or can be developed in different contexts depending on its needs. Such as playing the piano, it can follow the music sheet or just follow the sensorial feedback from the ear. The action will be the same but the subject is capable to change the modality based on the context. Nowadays, it has known the cerebral circuits responsible for action sequences are the neural sub-circuits connecting Cortico-Basal Ganglia-Thalamic loop. The striatum (principal input core from the Basal Ganglia) has been related to action initiation and switch between sequences of actions. However, we do not know which structure provides that the information to initiate or chain an action sequence. The striatum receives two principal inputs, the cortex, and the thalamus. The hypothesis proposes that the thalamus provides rapid sensorial information without processing while the cortex provides processed information.

Here, we study the contribution of the thalamo-striatal circuit to switch between sequences of lever presses with or without a stimulus (the retraction of the lever) and in other study Sanchez-Fuentes develops Cortico-striatal contribution. First, Sanchez-Fuentes developed a task to train the animal to perform a chain of two sequences of lever press (four each lever). Next, we recorded the Parafasicular of the thalamus while the mice were performing the task. Finally, we inhibited the thalamo-striatal projections with optogenetics tools, during the initiation and the switch between action sequences

Our preliminary results show that the Parafasiculars' neurons increase their activity during the initiation and the execution of the chain sequences of lever presses. We recorded neurons that show a negative correlation between the number of lever presses and their activity, also we found neurons positively correlated with the transition time. Finally, the inhibition of thalamo-striatal shows decreasing the number disruption the chain. These results suggest that the thalamus provides information about the future actions contrasting the results of corticostriatal inhibitions where show that increasing the number of interruptions of chain.

Key words: Action selection, Optogenetics, Striatal Circuits.

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Ophthalmic administration of a DNA plasmid harboring the murine Tph2 gene: evidence for exogenous recombinant Tph2-FLAG in brain structures.

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Institución en dónde se realizó el trabajo: Unidad de Investigación Biomédica en Inmunología e Infectología, Hospital de Infectología, Centro Médico Nacional "La Raza", IMSS. Paseo de las Jacarandas s/n esquina Calzada Vallejo, Col. La Raza. C.P. 02990, CDMX., México. Tel: (+525) 57821088 ext. 24322. / 0445518592240
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Área que pertenece el trabajo: 14: Tecnología e Innovación

Tryptophan hydroxylase-type 2 (Tph2) is the first, rate-limiting step in the biosynthesis of serotonin (5-HT) in the brain. The ophthalmic administration (Op-Ad) is a non-invasive method that allows delivering genetic vehicles through the eye to reach the brain.
Hence, *TPH2* gene, it is an ideal candidate gene to understand the role of dysregulation of cerebral serotonergic homeostasis. There are studies both in animals and humans that suggest an important relationship between altered Tph2 activity and depression.
Thus, Beaulieu et al. (2008) have reported that mice harboring a single point mutation producing a R439H substitution in Tph2 in addition to have reduced 5-HT synthesis and tissue levels exhibit increased depression-, anxiety- and aggression-like behaviors. It is noteworthy, for our purposes, that an analogous human mutation, R441H has been identified in a late life depression cohort. In addition genetic analysis have associated several noncoding polymorphisms in the human TPH2 gene with depression, bipolar disorder, and suicidality.
Here, the murine *Tph-2* gene was cloned in a non-viral vector (pIRES-hrGFP-1a) generating pIRES-hrGFP-1a-Tph2, plus the Tag-FLAG. The detection of the recombinant Tph2-FLAG was tested *in vitro* and *in vivo.* For this, 25µg of pIRES-hrGFP-1a-Tph2-FLAG were Op-Ad to mice. The construct was capable of expressing and producing the recombinant Tph2-FLAG *in vitro* and *in vivo.* Thus, *in vivo*, the construct efficiently crossed the Hemato-Ocular-Barrier and the Blood-Brain-Barrier, reached brain cells, passed the optical nerves, and transcribed mRNA-GFP in different brain areas. The recombinant Tph2-FLAG was observed clearly in amygdala, and brainstem, mainly in raphe dorsal and medial. These results demonstrated that the pIRES-hrGFP-Tph2-FLAG, administrated through the eyes, was capable to reach the brain, transcribe and translate the Tph2. Finally, our study showed the feasibility of delivering therapeutic genes, such as the *Tph2,* the first enzyme, rate-limiting step in the 5-HT biosynthesis. Further studies will be needed to test the production of serotonin in the brain and its effects on animal behavior.

Key Words: **ophthalmic administration, non-viral vector-plasmid, tryptophan hydroxylase-type 2 - serotonin.**

Early focal cerebral ischemia induces expression and phosphorylation of PEBP1 in rat hippocampus

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Ischemic stroke constitutes for around 85% of all stroke cases causing high social and economic burden. Ischemic stroke occurs when the blood supply to brain becomes blocked and ischemic brain injury often leads to neuronal dysfunction, cell death and, unfortunately, there is only a narrow time therapeutic window. Without proper treatment, neurons located in and around the injury site can die quickly. The phosphatidylethanolamine-binding protein 1 (PEBP1), also called Raf kinase inhibitor protein (RKIP), is a protein highly-expressed in the brain, that participate in cellular response to aggressive stimuli leading to survival or death. PEBP1 is the precursor of the hippocampal cholinergic neurostimulating peptide (HCNP), which induces acetylcholine synthesis. Previous reports have demonstrated that PEBP1 varies in several neurological disorders, including Alzheimer's disease, Parkinson's disease, dementia and depression, probably through its role in cell signaling pathways. In this work, to know the role of PEBP1 during early focal cerebral ischemia (ECI), its expression and phosphorylation were analyzed in the rat hippocampus by proteomic strategies. ECI was induced in adult male Wistar rats, as experimental model, occluding temporarily the middle cerebral artery (MCAO) (30, 60 and 90 minutes), followed by 24 h of reperfusion (R; I/R). Animals with surgery only were used as controls (sham). Hippocampus proteins were analyzed by two-dimensional electrophoresis (2-DE) and a spot of 23 kDa and pI 5.7, that increased its abundance at 60 min after ECI, was identified as PEBP1 by Mass Spectrometry (MS) and its identity confirmed by 2-DE Western Blot using anti-PEBP1. Expression of this protein was validated by WB and immunohistochemistry (IHC) using anti-PEBP1 and anti-pPEBP1-S153 antibodies. In one-dimension electrophoresis (1-DE) WB, two bands were recognized by PEBP1 and pPEBP1-S153 antibodies. Following 1-DE/WB, PEBP1 species reached a peak after 60 min of ischemia, decreasing at 90 min with I/R. Similar results were found by IHC analysis of total and phosphorylated forms of PEBP1 on the rat hippocampus under early focal cerebral ischemia. These results, in addition to the known roles of PEBP1, allow postulate that this protein could regulate signaling pathways, probably related to protection mechanisms, during periods where the cerebral blood flow is reduced. These results agree with those reported recently, where during late global ischemia PEBP1 is overexpressed and a role on cellular survival was proposed.

Keywords: Ischemia, Hippocampus, PEBP1

LPA$_1$ receptor activation induces PKCα nuclear translocation in glioblastoma cells

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Abstract

Lysophosphatidic acid (LPA) is a ubiquitous lysophospholipid that induces a wide range of cellular processes such as wound healing, differentiation, proliferation, migration, and survival. LPA signaling is increased in a number of cancers. In Glioblastoma (GBM), the most aggressive brain tumor, autotaxin the enzyme that produces LPA and its receptor LPA$_1$ are overexpressed. LPA$_1$ is preferentially couple to Gα$_q$ proteins in these tumors that in turn activates PKCs. PKCs are involved in many cellular processes including proliferation and metastasis. In this study, we aimed to determine if a classical PKC (α isozyme), could be activated through LPA$_1$ in GBM cell lines and if this activation impacts on cell number. We found that LPA$_1$ induces PKCα translocation to the nucleus, but not to the cell membrane after LPA treatment and the cell number diminished when LPA$_1$/PKCα signaling was blocked, suggesting a relevant role of LPA$_1$ and PKCα in GBM growth.

Keywords: Glioblastoma, LPA$_1$ receptor, PKCα


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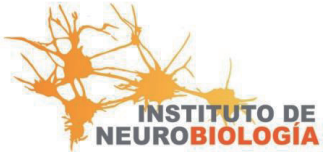
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