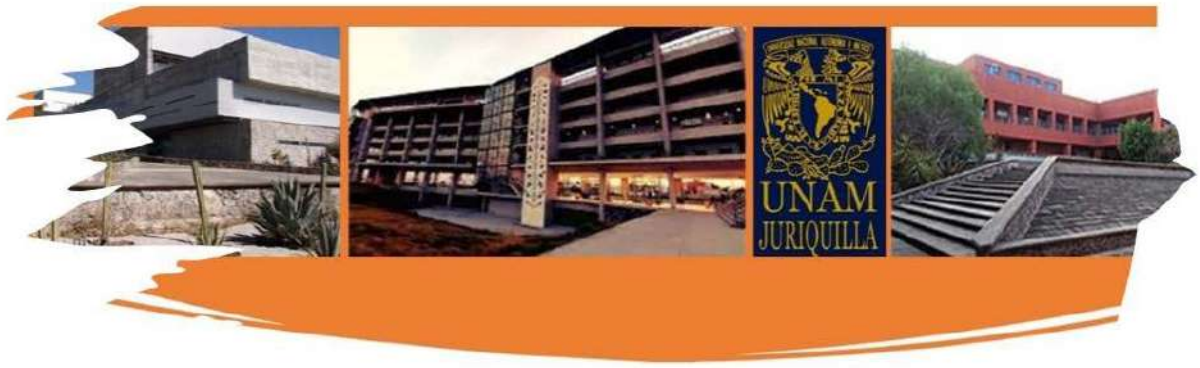
PROCEEDINGS



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WELCOME

Welcome to the 4th Symposium on Physiology and Pathology of Neuroglia (2022).

Thank you all for participating in our first hybrid modality. For those coming to Querétaro this will be a great chance to meet in person and show you our Campus that is growing as neuroglia research!

We are deeply grateful to all the Speakers for accepting our invitation and help us to build an outstanding program.

We acknowledge our sponsors for their support, thanks to them this event is free. The online modality will help us to reach those who will not be able to come. We are quite enthusiastic to see you too and interact with you in the virtual format.

We hope that this hybrid edition of the Symposium can help to meet new people in the field and generate new ideas and collaborations.

Sincerely,
"POR MI RAZA HABLARÁ EL ESPÍRITU"
UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO
Organizing Committee

Dra. Teresa Morales
Director

PREFACE

Neuroglia is the dominant population of brain cells and communication with neurons is fundamental for understanding the physiology and pathology of the Central Nervous System. The organization of the 4th Symposium on Physiology and Pathology of Neuroglia is an opportunity for our University to promote and disseminate recent findings made by leading researchers. The program is outstanding, and the Symposium is planned to reach a global audience in the hybrid format. The students and researchers will have a great scenario to present and discuss their results. We are grateful to our University for the support that made this event possible.

Our best wishes for the organizers and participants in delivering a successful meeting which is becoming a reference in the field.

Instituto de Neurobiología (INB)
Universidad Nacional Autónoma de México (UNAM)
Campus Juriquilla, Querétaro, Qro., México

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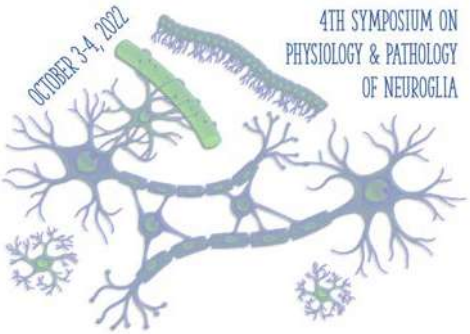

AKNOWLEDGMENTS

The previous edition of this event was online due to the pandemic. However, this was a great opportunity to reach worldwide through the virtual format, participants from all the continents were able to attend and participate in the Symposium completely free of charge. This was possible thanks to our sponsors but also to all the speakers that participated. Special thanks to Prof. Bruce Ransom who has been involved in all the editions of this Symposium, promoting our University and country internationally. We hope that our guests for this edition of the Symposium can enjoy this event as much as we do. Thank you to the Speakers, Students and Researchers for participating in the 4th edition of the Symposium.

The Organizing Committee is deeply grateful to Dr. Teresa Morales Guzmán (INB-UNAM) and Dr. Raúl Paredes (ENES-Juriquilla) for supporting the organization of the 4th Symposium on Physiology and Pathology of Neuroglia. We also appreciate Dr. Mauricio Díaz Muñoz (INB-UNAM) and Dr. Aurea Orozco Rivas (ENES-Juriquilla) for their assistance. Our acknowledgement to Dr. Maricela Luna Muñoz (Programa de Maestría en Ciencias -Neurobiología-, Coordinator) and Dr. Yolanda I. Chirino López (Programa de Doctorado en Ciencias Biomédicas, Coordinator) for supporting this event that reaches students and mentors from both academic programs. We appreciate the support of the Technical and Administrative Staff. Our recognition to Universidad Nacional Autónoma de México for providing the right environment to develop academic event like this Symposium (Posgrado-UNAM, PAEP-UNAM, INB-UNAM, ENES-Juriquilla).

PROGRAM

MONDAY		
Mexico city time	October 3rd, 2022	
7:45 – 8:00	**Welcome Ceremony, Teresa Morales**, Director, INB-UNAM	CAC
8:00 – 8:45	**Bruce Ransom**, City University of Hong Kong	CAC
8:50 – 9:35	**Xiaoping Tong**, University of Shanghai *NG2 glia, GABA synapses, and beyond*	
9:40 – 10:00	**Edith Arnold**, INB-UNAM *Hormonal regulation of the antioxidant response of astrocytes*	CAC
10:05 – 10:25	**Alberto Javier Ramos**, Universidad de Buenos Aires *Unveiling the spatio-temporal profile and activation pathways that control reactive astrocyte pathological remodeling after brain injury*	
10:30– 11:15	**Nathalie Rouach**, College de France *Astrocytes, guardians of critical period plasticity in the visual cortex*	
11:15 – 11:30	**Coffee Break**	
11:30 – 12:00	**Oral Poster Session** *Chairs: Adrián Rodríguez-Contreras & Abraham Cisneros-Mejorado*	CAC
12:00 - 12:35	**Virtual Poster Session**	Online
12:35 – 12:55	**Gabriela Caraveo Piso**, Northwestern University *Octopamine orchestrates a lactate shuttle between astrocytes and neurons to protect against α-synuclein proteotoxicity*	CAC
13:00 – 13:20	**Friederike Klempin**, Charité-Universitätsmedizin Berlin *Serotonin directs microglia function in the adult brain*	
13:25 – 14:10	**Amanda Sierra**, Achucarro Basque Center of Neuroscience *Not just corpse removal: How microglial phagocytosis maintains tissue homeostasis*	CAC
14:15 – 16:00	**Lunch**	
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TUESDAY		
Mexico city time	October 4th, 2022	
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8:50 – 9:35	**María Cecillia Angulo,** Institute of Psychiatry and Neurocience *Early interneuron-oligodendroglia interactions shape cortical inhibition and behavior*	
9:40 – 10:00	**Abraham Cisneros-Mejorado,** INB-UNAM *β-carbolines in focal and systemic demyelination-remyelination models*	CAC
10:05 – 10:25	**Raúl Russo,** Instituto de Investigaciones Biomédicas Clemente Estable *Connexin signaling in the awakening of endogenous progenitors after spinal cord injury*	
10:30– 11:15	**Cristina García Cáceres,** University of Munich *Beyond neurons in the hypothalamic control of systemic metabolism*	
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11:30 – 12:00	**Oral Poster Session** *Chairs: Adrián Rodríguez-Contreras & Mónica López-Hidalgo*	CAC
12:00 - 12:35	**Virtual Poster Session**	Online
12:35 – 12:55	**Gerardo Ramírez-Rodríguez,** Instituto Nacional de Psiquiatría *Repetitive transcranial magnetic stimulation reverses microglia modifications in the hippocampal neurogenic niche in chronically stressed mice*	CAC
13:00 – 13:20	**Ana María Estrada Sánchez,** IPICYT *Contributions of astrocytes to the neuronal alterations observed in Huntington's Disease*	
13:25 – 14:10	**Blanca Díaz-Castro,** University of Edinburgh *Architecture of astrocyte-vasculature interactions*	CAC
14:15 – 16:00	**Lunch**	
16:00 - 16:45	**Alfonso Araque,** University of Minnesota *Tripartite synapses: Astrocyte regulation of synaptic function, network activity and animal behavior*	CAC
17:00 – 17:15	**Closure**	CAC

Monday

October 3rd, 2022

Lectures

Bruce Ransom
City University of Hong Kong, CN

Xiaoping Tong
Shangai University, CN

NG2 glia, GABA synapses, and beyond

Edith Arnold
Universidad Nacional Autónoma de México, MX

Hormonal regulation of the antioxidant response of astrocytes

Alberto Javier Ramos
Universidad de Buenos Aires, AR

Unveiling the spatio-temporal profile and activation pathways that control reactive astrocyte pathological remodeling after brain injury

Nathalie Rouach
College de France, FR

Astrocytes, guardians of critical period plasticity in the visual cortex

Gabriela Caraveo Piso
Northwestern University, US

Octopamine orchestrates a lactate shuttle between astrocytes and neurons to protect against α-synuclein proteotoxicity

Friederike Klempin
Charité, DE

Serotonin directs microglia function in the adult brain

Amanda Sierra
Achucarro Institute, ES

Not just corpse removal: How microglial phagocytosis maintains tissue homeostasis?

Axel Nimmerjahn
Salk Institute
La Jolla, CA, US

Neuron-astrocyte communication in sesorimotor processing and behavior

NG2 glia, GABA synapses, and beyond

Xiaoping Tong

Shanghai Jiao Tong University School of Medicine, Shanghai, China, 200025.

NG2 glia, also known as oligodendrocyte precursor cells (OPCs), play an important role in proliferation and give rise to myelinating oligodendrocytes during early brain development. In contrast to other glial cell types, the most intriguing aspect of NG2 glia is their ability to directly sense synaptic inputs from neurons. However, whether this synaptic interaction is bidirectional or unidirectional, or its physiological relevance has not yet been clarified. Here, we report that NG2 glia form synaptic complexes with hippocampal interneurons and that selective photostimulation of NG2 glia (expressing channelrhodopsin-2) functionally drives GABA release and enhances inhibitory synaptic transmission onto proximal interneurons in a microcircuit. The mechanism involves GAD67 biosynthesis and VAMP-2 containing vesicular exocytosis. Further, behavioral assays demonstrate that NG2 glia photoactivation triggers an anxiety-like behavior *in vivo* and contributes to chronic social defeat stress.

Hormonal regulation of the antioxidant response of astrocytes

Edith Arnold [1,2].

[1]Departamento de Neurobiología Celular y Molecular, Instituto de Neurobiología de la UNAM

[2]CONACYT-Instituto de Neurobiología de la UNAM.

Astrocytes exert a wide variety of functions in health and disease, including regulating defense against oxidative stress in the brain. Several types of stress, injuries and brain diseases induce mitochondrial dysfunction and oxidative stress that led to astrocyte death. Agents that can improve astrocytes antioxidant defenses could be potential therapies for brain pathologies associated with oxidative stress and neurodegeneration. Our group previously identified the hormone prolactin (PRL), a peptide hormone secreted by the anterior pituitary gland, as a novel cytoprotective factor for astrocytes against oxidative stress. Here we define a mechanism by which PRL via its receptor promotes an antioxidant response in cortical astrocytes. We found that PRL promotes the activity of antioxidant enzymes and reduces both ROS generation and lipid peroxidation. Loss of PRL receptor signaling by genetic deletion of long PRL receptor isoform leads to higher susceptibility to oxidative damage and suppression of PRL-induced antioxidant response in astrocytes. These results reveal a mechanism through which PRL enables antioxidant response in astrocytes and suggest that PRL might represent a promising strategy for the treatment of brain pathologies associated with oxidative stress.

Unveiling the spatio-temporal profile and activation pathways that control reactive astrocyte pathological remodeling after brain injury

Alberto Javier Ramos
IBCN UBA-CONICET, Facultad de Medicina, Universidad de Buenos Aires, Argentina

Astrocytes rapidly respond to central nervous system damage with reactive astrogliosis. A long standing debate in the field has been focused in *good/bad* features of reactive astrogliosis. Studies of the last years showed that reactive astrocytes seem not to be "*bad*" or "*good*" per se, but under determinate circumstances, they may suffer a pathological remodeling accompanied of a pro-inflammatory gain of function that facilitates neurodegeneration. Our recent work combining *in vitro* primary cultures, *in silico* mathematical modeling and *in vivo* models of focal traumatic or ischemic brain injury has shown that pathologically remodeled astrocytes follow a specific spatial distribution from penumbra to injury core regions and they are more abundant at early time points after acute brain injury. Interestingly, these remodeled astrocytes co-exist with homeostatic astrocytes that support neuronal survival. We have also shown that TLR/NFkB pathways as well as microglia are essential requirements to achieve astroglial pathological remodeling following DAMP release from necrotic neurons. Moreover, we have proven some epigenetic modifications in reactive astrocytes that may confer a relatively stable phenotype to these pathologically remodeled astrocytes. The initiation of astroglial pathological remodeling is a potential target of intervention, and accordingly, our results disrupting DAMP-mediated signaling pathways have shown beneficial effects by reducing neuroinflammation and neurodegeneration in the injured brain. We propose that early treatment strategies aimed at blocking downstream DAMP-activated signaling pathways are likely to have a significant beneficial effect in neuroinflammation and neurodegeneration in the injured brain by controlling astroglial pathological remodeling.

Astrocytes, guardians of critical period plasticity in the visual cortex

Rouach Nathalie
College de France, France

Brain postnatal development is characterized by critical periods of experience-dependent remodeling. Termination of these periods of intense plasticity is associated with settling of neuronal circuits, allowing for efficient information processing. Failure to end critical periods thus results in neurodevelopmental disorders. Yet, the cellular processes defining the timing of these developmental periods remain unclear. Here we show in the mouse visual cortex that astrocytes control the closure of the critical period. We uncover a novel underlying pathway involving regulation of the extracellular matrix that allows interneurons maturation via an unconventional astroglial connexin signaling. Our results thus demonstrate that astrocytes not only influence activity and plasticity of single synapses, but are also key elements in the experience-dependent wiring of brain developing circuits.

S6M

Octopamine orchestrates a lactate shuttle between astrocytes and neurons to protect against a-synuclein proteotoxicity

Gabriela Caraveo Piso
Northwestern University, Chicago, IL, US

Octopamine acts as a neurotransmitter to regulate a variety of physiological functions in invertebrates. While Octopamine's role was taken over by epinephrine in mammals, its presence and deregulation in several neurological diseases including Parkinson's Disease (PD) suggests a distinct role yet to be elucidated. Through metabolomics, RNAseq, Ca^{2+}- imaging, utilizing primary cortical cultures and *in vivo* models of PD, we found a crucial role for Octopamine in the mammalian brain as an orchestrator of the metabolic communication between astrocytes and neurons. We found that calcineurin-dependent neuronal synthesis of Octopamine acts on astrocytes via a TAAR1-Orai1-Ca^{2+}-calcineurin-mediated signaling pathway to increase lactate secretion. Lactate uptake in neurons via MCT2 is utilized as an energy source to increase ATP and prevent neurodegeneration. Pathological increases of Octopamine in PD-like conditions, halts lactate production in astrocytes and short-circuits the metabolic communication to neurons. Our work provides an underappreciated function of Octopamine in astrocyte-neuron communication with implications to PD.

Serotonin directs microglia function in the adult rat brain

Friederike Klempin
Charité University Medicine Berlin, Germany

Microglia take an essential part in adult brain plasticity. As resident immune cells, microglia survey the environment, orchestrate an acute inflammatory response to injury, and engulf damaged cells to maintain neuronal homeostasis. Recent studies implicate microglia sense neurotransmission via the expression of various receptors, enabling circuit regulation. Serotonin (5-HT) is a crucial signal in the hippocampus and involved in antidepressant action. Our work established serotonin is required for exercise-induced neurogenesis accompanied by altered numbers of Iba1-positive microglia. Here, we explore microglia-serotonin interplay in the postnatal and young-adult hippocampus and cortex of *Tph2*$^{-/-}$ rats depleted of brain serotonin. Specifically, we determined 5-HT receptor expression on FACS sorted microglia, and the release of pro- and anti-inflammatory factors, e.g. BDNF, IL-6, TNF-□□ Our results reveal a significant increase in the population of CD11b-expressing microglia in the dissected brain areas of *Tph2*$^{-/-}$ rats. However, lack of brain serotonin does not affect microglia polarization, or leads to a decrease in other glial cell types, e.g. Glast1-positive astrocytes. Sorted microglia show an overall age- and sex-dependent expression of 5-HT1B, 2B, 5A and 5B receptor subtypes, with a surprising upregulation of microglial 5-HT2B in the prefrontal cortex of *Tph2*$^{-/-}$ rats. In contrast, immunohistochemistry *in vivo* reveals 5-HT2B is only expressed on neurons. Further results show increased BDNF signaling and reduced TNF-□ mRNA levels in *Tph2*$^{-/-}$ rats. Our data indicate brain serotonin can direct microglia function. This finding is relevant to understanding the progression of neurodegenerative diseases where microglia-neuron communication is altered causing prolonged inflammation and neuron death.

Not just corpse removal: How microglial phagocytosis maintains tissue homeostasis

Amanda Sierra
Achucarro Institute, ES

Microglia are the brain professional macrophages and they efficiently remove dead cells and other forms of cell debris, both during development and in pathological conditions. But what happens to microglia after engulfing and degrading apoptotic cells? In this talk, I will argue that phagocytosis is not a dead-end process but rather the begging of a new life for microglia. I will discuss that the events triggered in microglia by phagocytosis have an impact on the surrounding tissue, using as a model the adult neurogenic cascade, where microglia engulfs the excess of newborn cells. We are currently learning how phagocytosis affects microglial metabolism, transcription, and cell function, with the goal of developing pharmacological approaches to harness microglial phagocytosis in the diseased brain.

S9M

Neuron-astrocyte communication in sensorimotor processing and behavior

Axel Nimmerjahn

Waitt Advanced Biophotonics Center
The Salk Institute for Biological Studies,
10010 North Torrey Pines Road, La Jolla, CA 92037, USA

Studies over the past two decades have demonstrated that astrocytes are tightly associated with neurons and play pivotal roles in neural circuit operation and adaptation in health and disease. Nevertheless, precisely how astrocytes integrate diverse neuronal signals, modulate neural circuit structure and function at multiple temporal and spatial scales, and influence animal behavior or disease through aberrant excitation and molecular output remains unclear. This presentation will discuss how new and state-ofthe-art imaging approaches, fluorescence indicators, genetic targeting tools, quantitative behavioral assays, and computational methods may help resolve these longstanding questions. It will also address complicating factors in interpreting astrocytes' role in neural circuit regulation and animal behavior, such as their heterogeneity and inter-glial communication. Further research on these topics promises to provide a deeper mechanistic understanding of astrocyte-neuron communication in neural circuit function, complex behaviors, and disease.

Oral Presentations

Distinct endocannabinoids specifically signal to astrocytes and neurons

Noriega-Prieto Jose Antonio[1], Falcon-Moya Rafael[2], Araque Alfonso[1]
[1] University of Minnesota, [2] Universidad Pablo de Olavide

The endocannabinoid (eCB) system is an important intracellular signaling that plays relevant neuromodulatory roles in brain physiology. Endocannabinoids (eCBs) are retrograde messengers released from postsynaptic neurons that, directly acting on presynaptic neuronal CB1Rs, inhibit neurotransmitter release synapses — a phenomenon called depolarization-induced suppression of excitation, DSE. In addition, they can potentiate adjacent synapses — a phenomenon called lateral regulation of synaptic transmission or eCB-induced synaptic potentiation, eSP— through activation of CB1Rs in astrocytes and stimulation of gliotransmission. In contrast to most, if not all, neurotransmitter systems that involve a single ligand and numerous receptor types, the eCB system involves two distinct ligands (AEA and 2AG) and a single receptor (CB1Rs). The physiological meaning of this particularity remains unknown. We have monitored DSE and eSP in single CA3-CA1 synapses in hippocampal slices. Using pharmacological approach and transgenic mice for the synthesis enzyme of both eCBs, we have found that AEA specifically signals to astrocytes and 2-AG to neurons leading to distinct and contrasting synaptic regulation in single hippocampal synapses. In addition, the distinct astrocyte-driven signaling impacts synaptic plasticity induced by spike-timing dependent plasticity (STDP) which further supports the idea that astrocyte function influences synaptic activity.

Oligodendroglial $GABA_B$ receptors regulate remyelination

Laura Bayón-Cordero[1,2,3], Blanca I. Ochoa-Bueno[1,2,3], Vanja Tepavcevic [1,2,3], Xianshu Bai [4], Frank Kirchhoff [4], Estibaliz Capetillo [1,2,3], Raffaela Cipriani [1], Alfredo Rodríguez-Antigüedad [3,5], Carlos Matute [1,2,3] and María Victoria Sánchez-Gómez [1,2,3]

[1] Achucarro Basque Center for Neuroscience; [2] Department of Neurosciences, University of the Basque Country (UPV/EHU), Leioa, Bizkaia, Spain; [3] Instituto de Salud Carlos III, CIBERNED, Leioa, Bizkaia, Spain; [4] Department of Molecular Physiology, Center for Integrative Physiology and Molecular Medicine (CIPMM), Homburg, Germany; [5] Biocruces, Barakaldo, Bizkaia, Spain

Oligodendrocytes (OLs) drive myelination in the central nervous system and remyelination after demyelinating insults, such as in multiple sclerosis (MS). For that, OLs must differentiate from oligodendrocyte progenitor cells (OPCs) in a process guided by many factors, including γ-aminobutyric acid (GABA). Recently, we have demonstrated that GABAB receptor (GABABR) selective agonist baclofen promotes myelin protein generation in cultured OPCs, whereas GABABR antagonist CGP55845 reverts this effect. Here, given the little information available describing GABABR-mediated mechanisms in oligodendroglia, we first evaluated GABABR-induced calcium activity in OPCs, using conditional knockout mice for GABAB1 subunit in NG2-positive cells, and observed a reduction in the frequency of calcium signals. We then delved into oligodendroglial GABABR-mediated effect on myelination, using polycaprolactone nanofibers to assess myelin sheath formation by OPCs after treatment with baclofen or CGP55845. Baclofen is administered to MS patients as a spasticity treatment but its role on neuroprotection or remyelination has not been assessed yet. Therefore, we checked its remyelinating potential by administration of baclofen to adult mice following lysolecithin-induced spinal cord demyelination. In this model, we observed a significant acceleration of myelin regeneration within the lesions. Finally, using SIMOA technology, we determined changes in axonal damage and inflammation biomarkers in plasma samples of MS patients clinically treated or not with baclofen. Overall, our results provide relevant information about GABABR contribution to OPC functionality and identify baclofen as a powerful candidate for remyelinating therapies in MS.

Contribution of microglial exosomes to retinal neuroinflammation

Aires Inês Dinis [1,2,3], Boia Raquel [1,2,3], Ribeiro-Rodrigues Teresa [1,2,3], Girão Henrique [1,2,3], Ambrósio António Francisco [1,2,3,4], Santiago Ana Raquel [1,2,3,4]

[1]University of Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, Coimbra, Portugal; [2] University of Coimbra, Center for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal; [3] Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal; [4] Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal.

Glaucoma is a leading cause of blindness worldwide and is characterized by progressive degeneration of retinal ganglion cells and damage to the optic nerve. Elevated intraocular pressure is the main risk factor. Chronic neuroinflammation plays an important role in glaucoma. Microglia become reactive when challenged with elevated pressure, releasing cytotoxic factors that contribute to retinal ganglion cell death. The control of microglia-mediated neuroinflammation in experimental glaucoma is sufficient to protect retinal ganglion cells from damage. Exosomes are nanovesicles constitutively released by most cells and are important vehicles of intercellular communication, conveying lipids, proteins and genetic material. Exosomes derived from microglia exposed to elevated hydrostatic pressure, to mimic elevated intraocular pressure, trigger a pro-inflammatory response in naïve microglia, reflected by increased production of proinflammatory cytokines, microglia motility, phagocytosis, and proliferation. These exosomes also increase cell death and impact the survival of retinal ganglion cells. The depletion of retinal microglia halted neuroinflammation induced by exosomes isolated from microglia at elevated pressure, suggesting that microglial exosomes preferentially interact with microglia. Exosomes isolated from microglia challenged with elevated pressure are enriched in proteins associated with inflammatory signaling and RNA processing and in miRNAs that modulate the NFKB pathway. Our results show that microglial exosomes have an autocrine function and propagate the inflammatory signal, contributing to retinal degeneration. The elucidation of the signaling mechanisms triggered by exosomes may reveal new targets for treatment. Funding: FCT, Portugal (UID/NEU/04539/2019; UIDB/04539/2020; UIDP/04539/2020), COMPETE-FEDER (FCOMP-01-0124-FEDER-028417; POCI-01-0145-FEDER-007440), Centro 2020 Regional Operational Programme (CENTRO-01-0145-FEDER-000008: BRAINHEALTH2020).

Astrocytes activity mediate the duration of working memory

Rivera-Villaseñor A. [1,2], Calero-Vargas I. [1,2], and López-Hidalgo M. [2]

[1] Laboratorio de Fisiología de las interacciones Neuro-Gliales, [2] ENES Juriquilla, UNAM, Instituto de Neurobiología, UNAM

Astrocytes integrate, process, and store information of the underlying neural circuitry in the form of changes in [Ca+2], acting as a "memory" of synaptic activity. This allows astrocytes to regulate the activity of neuronal circuits on different time scales through the release of gliotransmitters and thereby participate in cognitive functions such as working memory (WM). To evaluate if astrocytes Ca+2 activity from the mPFC is associated with the duration of WM, we use C57BL6/J male mice (3 months old). The animals were injected into the mPFC with AAV5-GFAP-GCaMP6f and pAAV-GFAP-hM3D(Gq)-mCherry and were trained to choose either left or right depending on the frequency of a vibrotactile stimuli (20/80Hz). Once the mice reached a performance of ~80%, the delay in the opening of the door was increase (1, 3, 6, 9, 12, 15, 18, 25, 40, 60 and 90s) to evaluate duration of WM. The performance was evaluated in three conditions, control, saline and in the presence of the ligand of the DREADDs (CNO) to modify calcium levels in astrocytes. In control and saline conditions, the animals decreased their performance when the delay increase becoming a random choice 15s. The activation of DREADDs in astrocytes with CNO significantly improved their performance in the WM task increasing the duration of working memory being a random choice at 40s.These results show that astrocytes activity in the prefrontal cortex play a pivotal role in maintain behaviorally important sensory information over short periods of time in a vibrotactile WM paradigm.

Tuesday

October 4th, 2022

R. Thóra Káradóttir
University of Cambridge, UK

Activity dependent myelination - a mechanisms for learning and regeneration?

María Cecilia Angulo
Institute of Psychiatry and Neuroscience of Paris, FR

Early interneuron-oligodendroglia interactions shape cortical inhibition and behavior

Abraham Cisneros-Mejorado
Universidad Nacional Autónoma de México, MX

β-carbolines in focal and systemic demyelination-remyelination models

Raúl Russo
Clemente Estable Biological Research Institute, UY

Connexin signaling in the awakening of endogenous progenitors after spinal cord injury

Cristina García-Cáceres
University of Munich Helmholtz Zentrum,, DE

Beyond neurons in the hypothalamic control of systemic metabolism

Gerardo Bernabé Ramírez-Rodríguez
Instituto Nacional de Psiquiatría, MX

Repetitive transcranial magnetic stimulation reverses microglia modifications in the hippocampal neurogenic niche in chronically stressed mice

Ana María Estrada-Sánchez
Instituto Potosino de Investigación Científica y Tecnológica, MX

Contributions of astrocytes to the neuronal alterations observed in Huntington's Disease

Blanca Díaz-Castro
The University of Edinburgh, UK

Architecture of astrocyte-vasculature interactions

Alfonso Araque
University of Minnesota, US

Tripartite synapses: Astrocyte regulation of synaptic function, network activity and animal behavior.

Early interneuron-oligodendroglia interactions shape cortical inhibition and behavior

Maria Cecilia Angulo, PhD
Institute of Psychiatry and Neuroscience of Paris (IPNP)
INSERM U1266, Paris, France

Oligodendrocyte precursor cells (OPCs) represent the only non-neuronal cells that receive *bona fid*e synapses from neurons in the CNS. The function of these synapses remains poorly understood. We previously showed that OPCs in the cerebral cortex are primarily and transiently innervated by fast-spiking parvalbumin-expressing (PV) interneurons. Interestingly, PV interneurons represent the largest proportion of cortical myelinated GABAergic neurons. To investigate the role of PV interneuron-OPC synapses, we genetically inactivated γ2-mediated GABAergic synaptic signaling in OPCs during early postnatal development. This inactivation does not affect OPC proliferation and differentiation or the global cortical developmental myelination pattern. However, the disruption of GABAergic synaptic signaling of OPCs prior to myelination onset resulted in severe PV interneuron myelination defects characterized by longer internodes and nodes and a proximal axon malformation. Consequently, high-frequency PV interneuron discharges as well as PV interneuron-dependent postsynaptic latencies and strengths of excitatory neurons were reduced during postnatal development. These dysfunctions generated a strong excitation-inhibition imbalance that was associated with whisker-dependent texture discrimination impairments. We concluded that, during cortical development, the inactivation of γ2-mediated OPC synapses have profound consequences in the myelination of PV interneurons, affecting the function of mature cortical inhibitory circuits. PV interneuron-OPC synaptic activity during postnatal development constitute a key step in the construction of cortical circuits involved in rapid and strong inhibition during sensory processing. We are presently investigating the effect of these synapses in cognitive processes.

β-carbolines in focal and systemic demyelination-remyelination models

Abraham Cisneros Mejorado
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Demyelinating damage, which is often a major cause of progressive and neurodevelopmental disabilities, is typically characterized by subsequent remyelination, which promotes the development of mature oligodendrocytes (OLs) from precursor cells, although this event is usually incomplete. Modulation of remyelination is an important target for designing effective therapeutic strategies against white matter lesions. The use of experimental models is a fundamental element to advance in this area, so the use of models based on the use of toxins has proven to be very useful for remyelination studies. Here, we have addressed a model of focal demyelination (with the injection of 0.05% ethidium bromide in the caudal cerebellar peduncle of rats) and another systemic demyelination (with the intake of 0.3% cuprizone in mouse). In both, demyelination has been characterized transversally, through histology using Black-Gold II (BGII) stain, and longitudinally through diffusion-weighted magnetic resonance imaging (dMRI), by computing fractional anisotropy (FA) and diffusivity parameters to infer microstructural changes. In both models, the dMRI analysis revealed FA decrease and radial diffusivity (R_D) increase after demyelination, findings that correlate with histological observations by BGII (in the caudal peduncle in case of focal demyelination and in the corpus callosum, internal capsule or cerebellum in case of systemic demyelination). Later, we evaluated the effect produced by the following β-carbolines, allosteric $GABA_A$ receptor ($GABA_AR$) modulators in the focal demyelinzation: N-butyl-β-carboline-3-carboxylate (β-CCB), 4-Ethyl-6,7-dimethoxy-9H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester (DMCM) and Ethyl 9H-pyrido[3,4-b]indole-3-carboxylate (β-CCE). The results indicates that daily systemic β-CCB (1mg/Kg) administration for two weeks in lesioned animals increased FA and decreased R_D, suggesting myelination improvement, supported by histological analysis as has been observed in our previous studies. However, nor DMCM (0.25mg/Kg) or β-CCE (1mg/Kg) had not promyelinating effect, which was also supported by histological analysis. Next, we tested whether the promyelinating effect of β-CCB observed in the focal demyelination model was also observed in the systemic demyelination. At the moment, administration of β-CCB (1mg/Kg) during three weeks after to six weeks of cuprizone intake, the histological analyzes with BGII revels that, at least in regions of cerebellum but not in corpus callosum, β-CCB also promotes remyelination. Thus, in a focal and systemic demyelination it was observed a promyelinating effect stimulated by β-CCB, a potent positive modulator of the $GABA_AR$ in OLs. This indicates that both models can be monitored longitudinally by MRI and it suggests that remyelination is enhanced by β-CCB treatment.

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Connexin signaling in the awakening of endogenous progenitors after spinal cord injury

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The ependyma of the mammalian spinal cord is a stem cell niche in stand-by mode that is reactivated by spinal cord injury (SCI) thereby helping scar formation. How this stem cell niche is reactivated by injury remains poorly understood. Gap junctions and connexin hemichannels are key regulators of the biology of neural progenitors during development and in adult neurogenic niches. Non-mammalian vertebrates with remarkable self-repair capabilities have a sub-population of active ependymal stem cells that are coupled via gap junctions. We hypothesize that communication via connexins among ependymal cells in mammals is developmentally regulated and may play a part in the reactivation of this latent stem cell niche after injury. By combining patch clamp recordings of ependymal cells with immunohistochemistry for various connexins in the neonatal and the adult normal and injured spinal cord of mice, we demonstrated that coupling among ependymal cells is down-regulated during post-natal development. However, communication via gap jucntions increases after injury, resembling that of immature animals. The increase in gap junction coupling in adult ependymal cells was paralleled by up-regulation of connexin 26 which correlated with the resumption of proliferation and a reduction of connexin hemichannel activity. Connexin blockade in vivo reduced the injury-induced proliferation of ependymal cells. Our study suggests that connexins are involved in the early reaction of ependymal cells to injury, representing a potential target to improve the contribution of the ependymal stem cell niche to self-repair.

S5T

Beyond neurons in the hypothalamic control of systemic metabolism

Cristina García-Cáceres

Helmholtz Zentrum, DE

My research work is focusing on highlighting the emerging paradigm shift in researching the hypothalamic control of systemic metabolism from a comparatively 'neurocentric' view towards a more holistic approach in which is required an appropriate functioning of astrocytes. Hypothalamic astrocytes are embedded in the framework surrounding neurons key involved in metabolic control, and function to convey blood-borne hormone and nutrient signals within the brain for the coupling between feeding behavior and metabolism with metabolic demand. Impairment in the functionality of hypothalamic astrocytes results in pathological astroglia-neuronal communication leading to a dysregulation in neuronal network activity and impairing the control of metabolism, inducing an overall mishandling of energy that favors metabolic diseases such as obesity.

S6T

Repetitive transcranial magnetic stimulation reverses microglia modifications in the hippocampal neurogenic niche in chronically stressed mice.

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Repetitive transcranial magnetic stimulation (rTMS) as a therapeutic intervention for depression has been shown to have interesting effects on patients suffering from major depression, especially in patients resistant to pharmacological treatment. There is a close relationship between neurogenesis and the effects of rTMS. In rodents exposed to chronic unpredictable mild stress (CUMS) treated with rTMS (5Hz), the stimulation is linked to the pro-neurogenic impacts in the hippocampus and a decrease in depressive-like behaviors such as anhedonia and hopelessness. However, although the relationship between hippocampal neurogenesis in the antidepressant effect of rTMS is known, the molecular and cellular mechanisms that lead to the persistence of its antidepressant and plastic level effects in the hippocampus have not been fully elucidated. In this sense, it was of interest to know whether rTMS can modulate other cell types, such as microglia, since the overactivation of these cells has been correlated with the generation of a pro-inflammatory environment in the depressive disorder, which affects the production of factors that modulate the proliferation or survival of different cells within the neuronal lineage. Therefore, it was important to determine whether 5Hz rTMS can reverse the morphological alterations of microglial cells in the hippocampus of rodents exposed to CUMS, and whether these modifications persist over time. We used Balb/c females exposed to CUMS for 15 continuous weeks, treated with the first set of stimulation at 5Hz for four weeks, then started maintenance sessions at 5Hz for five more weeks. We performed immunolabeling for IBA-1 and TMEM119 to identify microglial cells. Thus, we quantified the number of IBA-1 or TMEM119 positive cells in the hippocampal dentate gyrus. Also, we estimated the morphometry of these cells. Our results indicate that 5Hz rTMS reverses the alterations in microglial cells caused by chronic stress on the number and length of processes. This effect is maintained for at least seven weeks, despite continued exposure to chronic stress. In addition, the alterations produced by CUMS and the benefits of rTMS on hippocampal neurogenesis will be shown.

S7T

Contributions of astrocytes to the neuronal alterations observed in Huntington's Disease

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Huntington's disease is an inherited neurodegenerative condition caused by the increased repeats of CAG in the huntingtin gene, leading to the presence of a protein with an increased poly-glutamine section at the N-terminus. This mutation will lead to psychiatric and cognitive symptoms, accompanied by the progressive development of involuntary generalized movements. Although huntingtin is ubiquitously expressed throughout the body, significant damage occurs in the caudate-putamen, where the medium spiny neurons are the most vulnerable. As this neuronal population receives prominent glutamatergic innervation from the motor cortex and thalamus, it has been suggested that glutamatergic-mediated damage or excitotoxicity lies as the main cause of neuronal death. However, most of the research has centered on understanding the neuronal changes that might contribute to excitotoxicity, leading the astrocytes' contribution out of the picture. In this talk, I will describe how astrocytes emerge as a key component in the neuropathology of Huntington's disease, in which the astrocytic glutamate transporters 1 (GLT-1) and glutamate aspartate transporter (GLAST), proteins in charge of glutamate uptake during glutamatergic neurotransmission, might contribute to dysregulated neuronal processing as well as neuronal vulnerability to excitotoxicity.

Architecture of astrocyte-vasculature interactions

Blanca Díaz-Castro

University of Edinburgh

Blood-brain barrier (BBB) dysfunction is one of the earliest observations in neurodegenerative diseases, preceding neuronal death, and it is associated with cognitive decline. Astrocytes, with specialized structures called astrocyte endfeet, are part of the BBB. However, astrocyte-vasculature interactions and their contribution to BBB dysfunction is remarkably understudied. Here, I present our investigations towards understanding the morphological and molecular architecture of astrocyte endfeet in young mice and how it is altered by conditions that relate to dementia like neuroinflammation or ageing.

S9T

Tripartite synapses: Astrocyte regulation of synaptic function, network activity and animal behavior.

Alfonso Araque

Dept. of Neuroscience, University of Minnesota.

Astrocytes, a major type of glial cells, are recognized as key supportive elements in neuronal function, providing structural and metabolic support for neurons, and controlling brain homeostasis mechanisms. Historically, they were ignored as being active players in cellular processes underlying brain function. However, accumulating evidence indicate that astrocytes and neurons establish bidirectional communication. Astrocytes respond to synaptically-released neurotransmitters and, in turn, release gliotransmitters that influence neuronal and synaptic activity. This evidence has led to the establishment of the tripartite synapse concept, a novel view of synaptic physiology in which astrocytes are integral elements involved in synaptic function.
I will present and discuss current evidence regarding the mechanisms and functional consequences at synaptic, circuit and behavioral levels of the bidirectional astrocyte-neuron signaling in different brain areas, including striatum, hippocampus, cortex and amygdala. Specifically, I will present results indicating: 1) the existence of functional astroglial-neuronal networks comprising subpopulations of astrocytes, neurons, and synapses; 2) the synapse-specific astroglial control of synaptic function in these brain areas; 3) the neuronal activity-dependent ability of single astrocytes to release distinct gliotransmitters; 4) the contribution of astrocytes to hippocampal synaptic plasticity; 5) the astrocyte-mediated lateral synaptic regulation in the somatosensory cortex; 6) the layer- and column specific astrocyte-neuron signaling in the cortex. Finally, I will also present recent evidence showing the behavioral consequences of the eCB signaling to astrocytes in hippocampus- and amygdala-associated animal behaviors. I will discuss how this evidence supports a paradigm shift in our understanding of the cellular basis of brain function, which would result not solely from the neuronal activity, but from the coordinated activity of astrocytes and neurons.

Oral Presentations

Hypothalamic astrocyte remodeling of purinergic signaling during obesity impacts on glucose metabolism and food intake

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Obesity is a significant public health problem, resulting from disturbed energy balance. The hypothalamus is regarded as an essential player in body weight regulation. The paraventricular nucleus (PVN) of the hypothalamus is an integrator of autonomic and neuroendocrine information, containing distinct pre-autonomic neurons that directly influence energy and glucose metabolism. Synaptic transmission and activity of hypothalamic neurons are regulated by astrocytes, whose role in the control of energy metabolism remains to be addressed. Astrocytes form extensive networks connected through connexin (Cx)-based gap junctions. Non-junctional Cx hemichannels (HC) mediate the release of neuroactive molecules for inter-cellular communication during acute and chronic inflammatory responses. We have investigated the impact of diet-induced obesity on astrocyte network activity in the PVN, with a particular interest in the role of purinergic signaling in the pathophysiology of obesity. We showed that obesity leads to exacerbated ATP release from PVN astrocytes mediated by increased activity of Cx43 HC. The heightened ATP availability in the PVN modified both the spontaneous and GPCR-dependent astrocyte activity. In addition, in vivo metabolic profiling showed decreased glucose tolerance and increased food intake specifically in obese mice. In vivo blocking of astrocytic hemichannel activity, by PVN infusion of TAT-Cx43L2 peptide, ameliorated the deleterious metabolic effects of ATP over-release. The aberrant ATP release was accompanied by dysregulation of purinergic and adenosine receptor signaling, which translated into development of insulin resistance. Our data revealed functional purinergic adaptation of hypothalamic astrocytes in diet-induced obesity, being implicated in the development of hyperphagia and insulin resistance states.

Sustained activation of GABA receptors attenuates AMPA-mediated apoptotic excitotoxicity in oligodendrocytes

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Oligodendrocytes (OLs) are the myelinating cells of the central nervous system (CNS). Excitotoxic damage produced by overactivation of glutamate receptors (GluR) triggers OL death and contributes to the pathogenesis of multiple sclerosis and possibly other neurodegenerative diseases. In addition to GluRs, oligodendrocytes express GABA receptors (GABARs) that are involved in their survival and differentiation. The interaction between Glu and GABAergic systems are well-documented in neurons but this potential cross-talk in oligodendrocytes has not been studied in depth yet. Here, we evaluated the protective effect of GABAR agonists baclofen (GABAB) and muscimol (GABAA) against AMPA-induced excitotoxicity in cultured rat oligodendrocytes. We observed that both baclofen and muscimol reduced oligodendrocyte death and caspase-3 activation after AMPA insults, proving their oligoprotective potential. Interestingly, GABAergic agonists significantly reduced also calcium-impermeable GluR2 internalization induced by AMPA. Furthermore, we detected that baclofen and muscimol attenuated AMPA-induced intracellular calcium increase and subsequent events as mitochondrial membrane potential alteration, ROS generation and calpain activation. Finally, we determined that AMPA stimulus significantly modified the activation state of relevant signaling molecules for oligodendrocytes as Src, Akt, JNK and CREB, which could indicate their involvement in this excitotoxic process. However, neither baclofen nor muscimol alter these AMPA-triggered modifications suggesting that GABA agonists-mediated protection is independent of these molecules. Overall, our results suggest that GABAR activation attenuates AMPA-mediated apoptotic excitotoxicity in oligodendrocytes by interfering with GluR subunits membrane expression and with calcium-dependent intracellular signaling pathways. Together, these findings provide evidence of the potential of GABAR agonists as oligodendroglial protectants in CNS disorders.

Evaluation of Remyelination by Ganaxolone Treatment in a Cuprizone Demyelination Model

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UNAM-Campus Juriquilla, Instituto de Neurobiología, Laboratorio de Neurofisiología Celular (D-14)

Neurodegenerative diseases, which cause damage to the white matter, are health problems in which repair of the damage is sought through pharmacological strategies. Thus, several investigations have addressed the modulation of GABAeric signaling as a possible therapeutic target for the recovery of myelin sheaths in models of experimental demyelination. In this sense, the use of neurosteroids as modulators of the GABAAR receptor has been used as a systemic treatment to promote remyelination. Some findings, using animal models of focal lesions, indicate that neurosteroid treatment promotes remyelination and these involve the GABAergic system. With this background, the effects of the neurosteroid Ganaxolone (Gnx, the synthetic analog of allopregnanolone) are being investigated in this project. Using a murine model of systemic demyelination with cuprizone, we evaluate the degree of demyelination/remyelination transversally through histology using Black-Gold II (BGII) staining, and longitudinally through T2-weighted imaging by magnetic resonance. Using this characterization we evaluated, in demyelinated regions, the effect of daily systemic administration for 3 weeks of Gnx (2.5mg/Kg). Initially, a hyperintensity in some regions like the corpus callosum (cc) has been observed during the demyelination phase in T2 images, compared with the control group ($P<0.05$). Interestingly, the Gnx promotes a heterogeneous dose-dependent effect, being deleterious in regions such as the cc or the cerebral cortex, while it is promyelinating in the hippocampus and striatum; these data supported with histology using BGII. These data suggest that remyelination associated with the modulator of GABAergic signaling, Gnx, promotes remyelination in different brain regions in a different manner.

Posters

(virtual presentations)

Monday & Tuesday

October 3rd – 4th, 2022

P1

The activity of intracellular calcium in brain endothelial cells is increased by astrocytes

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Brain endothelial cells (BEC) made up part of the cerebral vascular network and the blood brain barrier. BEC can trigger diverse metabolic pathways that involve intracellular Ca2+ signaling. Yet, their roles in brain physiology are scarce. Here, we investigated if meningeal BEC and corpus callosum astrocytes of postnatal (P0-P21) Wistar rats, alter their intercellular Ca2+ communication in primary cell co-cultures. Through Ca2+-imaging records, we found that 13.6% (n = 36/264) of BEC, and 7.1% (n = 7/98) of astrocytes, presented spontaneous intracellular Ca2+ events. These Ca2+ events were sensitive to 50 µM 2-APB, 10 µM CPA and extracellular Ca2+. Also, in primary cell co-cultures of BEC and astrocytes, spontaneous Ca2+ events were observed in a greater number of cells (19.7%, n = 37/188). These results suggest that BEC and astrocytes may communicate with each other in primary cell cultures by diverse physical or molecular mechanisms that involve altering their intracellular Ca2+ metabolism.

P2

Ginkgo biloba extract improved astrocytic recruitment and reduced microglia reactivity and oxidative stress in the hippocampus of ovariectomized rats

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Several studies have demonstrated that menopause leads to the development of psychological disturbances and obesity. However, even being observed improvement in these conditions after hormonal replacement therapy (HRT), alarming side effects are associated with this treatment, limiting its use by women with a history of breast cancer and cardiovascular disease. We have previously observed that Ginkgo biloba Extract (GbE) attenuated ovariectomy-related obesity, and anxious/depressive-like behaviors, as well as improved the effectiveness of the hippocampal and hypothalamic serotonergic system. Thus, the present study investigated the GbE activity on microglia reactivity, astrocytes recruitment, and oxidative stress in the hippocampus of ovariectomized rats. 2-month-old Wistar female rats were ovariectomized (OVX) or Sham-operated. After 2 months, daily oral gavages were performed once a day with 500 mg.kg−1 of GbE or vehicle for 14 days. GbE decreased ovariectomy-induced microglia reactivity in CA3 and DG of the dorsal hippocampal formation. Moreover, GbE increased GFAP-positive cells in the CA1 and DG of the ventral hippocampal formation. OVX increased superoxide dismutase activity, which was reverted by GbE. Additionally, GbE increased the glutathione peroxidase activity in comparison to the Sham group. In summary, the present findings indicated that GbE exerted a modulatory action on microglia and astrocytes activities that may be related to the antioxidant effects observed since both astrocytes and microglia produce high amounts of reactive oxygen species. Therefore, GbE might be used to ameliorate menopausal-related hippocampal disorders, offering an alternative therapeutic approach, particularly for those women that HRT is contraindicated.

The role of class IIa HDACs in remyelination of ageing peripheral nerves

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Nerve regenerative capacity and remyelination are impaired in aged animals by a poorly understood mechanism. Repair Schwann cells are necessary for peripheral nerve regeneration and remyelination after nerve damage. It is known that after injury there is an upregulation of Jun, a transcription factor pivotal for the switch to the repair Schwann cell phenotype. It has been recently reported that Jun induction is lower in the aged nerves, which causes defects in the activation of the repair Schwann cell phenotype delaying axonal growth [2]. Class I Histone Deacetylases (HDACs) play a central role in myelin development and maintenance [2]. Among them, HDAC3 has been shown to be important for maintaining myelin homeostasis in aged nerves [3]. This work aims to study if class IIa HDACs are also involved in the remyelination of aged peripheral nerves. To this aim, we explore if there was any difference in myelin homeostasis and remyelination after injury in aged mice lacking Hdac4, Hdac5 and Hdac7.

P4

Microglia distribution promoted by lipopolysaccharide in rat substantia nigra

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Advancing microscopy and algorithm-based image analysis leads to understand the morphology, dynamics, and distribution of microglia. Lipopolysaccharide (LPS) is an endotoxin that is able to induce neurodegeneration and neuroinflammation in catecholaminergic brain nuclei, which are highly susceptible to cellular stress. In this histological study, we evaluate the microglia distribution in rat substantia nigra pars compacta (SNpc), pars compacta dorsal (SNcd) and pars reticulata (SNpr). Using immunostaining against TH and OX42, and image processing techniques; we qualitatively evaluated the loss of dopaminergic neurons by immunoreactivity, and determined the microglia distribution patterns in substantia nigra of 50, 300, 500 µg/kg and 5 mg/Kg of LPS-induced rats. The dosage of 500 µg/kg and 5 mg/kg of LPS caused the loss of dopaminergic neurons in SNpc and microglia migration in a dose-dependent manner in SNpc, SNcd, and SNpr. This study will add more details regarding microglial distribution in LPS-induced cellular stress in rats.

Role of astroglial Cx43 hemichannel-mediated gliotransmission in memory & depression

Stehberg Jimmy

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Connexin 43 (Cx43) hemichannels are among the main mechanisms for astroglial release of gliotransmitters. Recent studies have shown that the astroglial Cx43 hemichannel-mediated release of glutamate and D-serine is necessary for memory, by regulating post-synaptic NMDA receptor (NMDAR) activity in the basolateral amygdala. Moreover, astroglial Cx43 hemichannel activity is increased in the ventral hippocampus in response to chronic stress, mediating the release of glutamate and ATP, and appear to be critical in the development of depressive-like symptoms induced by chronic stress, through the release of glutamate and D-serine, and the subsequent overactivation of postsynaptic NMDARs. All the above evidence has led to targeting astroglial Cx43 hemichannels for the development of novel antidepressants.

Cannabinoid CB_1 receptors in oligodendrocytes: modulation of energetic metabolism and role during autoimmune demyelination

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). MS symptomatology is caused by the demise of mature oligodendrocytes (OLs) that produce and maintain CNS myelin and provide metabolic support to axons. These cells originate during development and adulthood from a population of oligodendrocyte precursor cells (OPCs). The endocannabinoid system has protective effects in MS associated to the activation of CB1 receptors. OLs and OPCs express low levels of CB1Rs that mediate protection from excitotoxicity and promote lineage progression in vitro and pharmacological in vivo studies suggest that the CB1Rs in oligodendroglia engages myelin repair in MS. However, bona-fide evidence supporting the involvement of CB1Rs expressed by OLs and OPCs in the myelin repair and regenerating effects of (endo)cannabinoids is still lacking. Here we investigated the role of oligodendrocyte CB1Rs in MS by addressing 1) the effects of cannabinoid-modulating drugs on energy metabolism in OLs and OPCs and 2) the phenotype of conditional mutant mice lacking oligodendrocyte CB1Rs in the experimental autoimmune encephalomyelitis (EAE) model of the disease. Metabolic analyses in rat oligodendrocyte cultures showed that the cannabinoid agonist ACEA and the endocannabinoid hydrolysis inhibitor JZL184 reduce mitochondrial respiration and glycolysis. On the other hand, PLP-CB1R-KO mice displayed slightly attenuated clinical scores during EAE progression whereas NG2-CB1R-KO animals showed increased EAE severity as compared to their control littermates. Taken together, these preliminary results suggest a complex role of oligodendrocyte CB1Rs during autoimmune demyelination and point to (endo)cannabinoids modulate oligodendrocyte energy metabolism.

Metabolic reprogramming of reactive astrocytes: implications for multiple sclerosis

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Recent studies suggest the existence of reactive astrocytes that exhibit transcriptional programs destructive to synapses and oligodendrocytes in response to pro-inflammatory signals. These cells are abundant in demyelinating lesions of multiple sclerosis (MS) patients and proposed to play a relevant role during disease progression. Astrocytes depend on metabolic reprogramming to meet their bioenergetic demands during activation and it is postulated that astrocytic metabolic switch accelerates neurotoxicity. However, the metabolic signature of neurotoxic astrocytes has not been investigated in detail. This study addresses astrocyte metabolic reprogramming as pathogenic mechanism in MS through a combination of bioenergetic, Ca2+ imaging and gene expression studies applied to rodent astrocytes in vitro. Cells purified from the mouse forebrain were maintained in a serum free manner and activated to a neurotoxic phenotype by incubation with the pro-inflammatory factors (PIFs) IL-1α, TNFα and C1q. Astrocytes incubated with PIFs showed increased expression of neurotoxic phenotype related genes and down-regulated levels of genes related to neuroprotection and synaptogenesis. In parallel, we measured attenuated Ca2+ responses, associated to changes in different Ca2+ handling genes. At the metabolic level, neurotoxic astrocytes displayed enhanced glycolytic activity, as supported by increased levels of extracellular lactate. In summary, our research shows that astrocytes activated in vitro towards a neurotoxic phenotype display Ca2+ signaling and metabolic defects that affect mitochondria-glycolytic interplay and may contribute to the pathophysiology of MS.

White matter ensembles in the developing cerebellum

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Glial cells predominate in the white matter of the cerebellum. Here, astrocytes have neurogenic activity earlier in the postnatal (PN) neurodevelopment (PN 2-12) giving rise to interneurons of the molecular layer, while myelination starts with oligodendrocyte precursor cells (OPCs) that differentiate into oligodendrocytes (PN 12-23). Prenatal exposure to valproate is a well-known model of autism that disturbs neurodevelopment of the cerebellum. On the other hand, depolarization of the white matter results in calcium transients that can spread to neighboring cells resulting into functional ensembles. Calcium signaling is involved in proliferation, migration, and differentiation of glioblasts and neuroblasts. Thus, we tested prenatal exposure to VPA on functional ensembles of the cerebellar white matter. Pregnant mice were injected intraperitoneally at embryonic day 12.5 with a unique dose of VPA (500 mg/kg) or saline solution (0.9%) (CTRL). Latency to reach the nest was delayed in the VPA male pups (-62.59%) suggesting sensorimotor deficits at PN 8. Subsequently, sagittal slices of the cerebellum were obtained from these animals (PN 8-12) and depolarization of white matter evoked a calcium wave that recruited a group of cells, revealing a functional ensemble. The mean amplitude of the evoked calcium transients, the functional extension of the ensembles and the number of recruited cells were analyzed. All of these parameters were significantly reduced in the VPA model (63.16%, 49.92% and 60.48%, respectively). We conclude that prenatal exposure to VPA reduce ensemble function in the cerebellar white matter.

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Human iPSC-derived astrocytes as novel model to study multiple sclerosis

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Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) caused by autoimmune responses against myelin followed by neuroinflammation and neurodegeneration. Astrocytes are crucially involved in MS initiation and progression and regarded as potential cellular targets for the development of novel therapies. However, astrocyte pathophysiology in MS has been studied in rodent models that do not recapitulate the complexity and specific functional features of human cells. Assessing the relevance of findings in animal models using human astrocytes is therefore crucial for better-adapted translational applications to treat MS. Here we aim at differentiating astrocytes from MS patients and control subjects for functional studies using the human induced pluripotent stem cell (hiPSC) technology. In particular, we will generate astrocytes from 4 hiPSC lines with 2 different genotypes (TT and CC) of the polymorphism rs1800693 that affects the TNFRSF1A gene and confers an increased risk for MS. Differentiation of hiPSCs to astrocytes is carried out in 3 consecutive steps that include 1) generation of neural progenitor cells (NPCs), 2) astrocyte induction in the presence of EGF and LIF and 3) maturation of astrocyte progenitors in the presence of CNTF. NPCs generated from hiPSCCC and hiPSCTT MS lines were 9-98% positive for the neuronal progenitor markers Pax6, Sox2 and Nestin. We also corroborated that mature astrocytes differentiated from 1 hiPSCCC line display cytosolic Ca2+ transients in response to ATP. Our results support the utility of generating human astrocytes from MS patients as novel model to study disease pathogenesis and therapy.

P10

Evidence for a neuroinflammatory process in the hippocampus of the C58/J mouse model of autism

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Autism spectrum disorder (ASD) comprises a complex and heterogeneous array of neurodevelopmental disorders that feature communication and language impairments, as well as repetitive behaviors or restricted interests. Recently, neuroinflammatory cues have been linked to the onset and maintenance of neurodevelopmental disorders, such as ASD. Individuals with ASD display higher microglial densities and microglia cells with hypertrophic morphologies, besides an elevated content of inflammatory mediators across different areas of the brain. However, the relation between microgliosis and the observed neuronal and behavioral traits in autistic individuals remains to be fully understood. Several animal models have been proposed for studying the molecular alterations implicated in the development of autistic-like traits. The inbred mouse strain C58/J shows a low social preference along with repetitive behaviors. Here we found that male adult mice of the C58/J strain show a significant increase in the density of microglia in the CA1 hippocampal region as well as in the dentate gyrus. We also found that there are distinct subsets of morphological types of microglia in the CA1 hippocampal region. We observed there is a significant increase in the hippocampal content of the cytokines IFN-γ and TNF-α, and the chemokine MCP-1. We discovered there is an increase in the hippocampal content of the enzyme arginase-1 (Arg-1), suggesting an ongoing shift in the immune response in the hippocampus of C58/J mice, providing further evidence of a deregulated immune phenotype concurrent with behavioral and synaptic changes in this murine model of autism.

Glial fibrillary acidic protein (GFAP) isoforms expression in neural regeneration promoting cells

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Repairing the central nervous system (CNS) has always been a challenge. It possesses a limited capacity to repair and restore itself to the pre-damaged state; CNS can contain the degeneration, though, through reactive gliosis. The damage to the CNS could originate from an acute lesion (e.g., spinal cord injury), or neurodegenerative diseases, among others. Olfactory ensheathing cells (OEC) are capable of promoting CNS reparation, but due to the difficulty of their obtention and purification for cell therapy, we are proposing a model based on bone marrow-derived mesenchymal stem cells (BMMSC) differentiated to a phenotype like the OEC or Schwann-like (BMMSC-SC). The aim was to evaluate the differential expression of the mRNA of GFAP isoforms between the distinct cell types. Primary cultures of OEC and BMMSC-SC of Wistar rats were used. By immunofluorescence, we were able to characterize OEC with p75 and GFAP; BMMSC with CD90; and BMMSC-SC with p75, GFAP, and CD90 markers. Our end-point PCR and qPCR results show that the GFAP isoforms we were evaluating are expressed in the OEC and, in general, express more total GFAP, as anticipated. We also found that BMMSC and BMMSC-SC express all the GFAP isoforms evaluated. Finding that GFAP and its isoforms are expressed in BMMSC, unfolds the possibility to study this cytoskeletal protein more deeply in regeneration-promoting cells, regardless of their differentiation state. However, if it is expressed in many of these cell types, it is necessary to delve deeper into the role of this protein in the neural regeneration process.

Analysis of density and distribution of microglial cells at the prefrontal cortex of autistic-like C58/J mice

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Autism Spectrum Disorder (ASD) comprises a set of neurodevelopmental disorders, which affects communication, social interaction and presents repetitive behaviors. Although ASD etiology remains unclear, there is increasing evidence indicating that glial cells, such as microglia, are functionally deregulated in ASD, promoting its pathology. Indeed, some findings show that these cells present anomalous overactivation and spatial distribution patterns in ASD across different brain areas, including the prefrontal cortex (PFC). This region is important due to the functions it houses, such as working memory and executive functions, that involve decision-making, planning, among others; some of which have been reported to be impaired in individuals with ASD. Recent findings from our laboratory showed an increased density and an altered distribution of astrocytes and microglial cells in the hippocampus of the autistic-like C58/J mouse strain. To further characterize microglial cells in other brain areas, we aimed to evaluate the density and spatial distribution of this cell population in the PFC of C58/J adult male mice. Our data showed an increase in the mean fluorescence intensity of Iba-1 besides an increase in the density of microglial cells in the PFC of C58/J mice. Interestingly, microglial distribution showed a more contiguous spatial distribution of this cell population in the PFC of C58/J mice. Furthermore, we found a decrease in the PFC content of TNF-α and IFN-ɣ cytokines in the autistic-like mice; suggesting that these changes in inflammatory cytokines could be related to the onset of microglial alterations and autistic-like traits.

Schwann-like cells and their functional participation in the myelination process in cortical neurons in in vitro co-culture

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The central nervous system has a limited repair response to injury, however, regions that house cells with plasticity and promoting properties for neuronal regeneration stand out. These cells are similar to Schwann cells, which is why they are called Schwann-like, which includes tanycytes, pituicytes, Müllerian glia, and enveloping glia (EG) of the olfactory bulb (Gudiño, 1999). GE is the main characterized and used to favor regeneration in spinal cord injury models, where it has been reported that it increases the release of neurotrophic factors and growth factors that promote cell proliferation and the wrapping of neuronal axons (Jessen and Mirsky, 2016; Yijian, 2021). Based on the above, cells with a Schwann-like phenotype have been proposed as a therapeutic strategy for neuronal regeneration (Boyd, 2004). However, for its application in humans, it is important to analyze its ability to myelinate cortical neurons in vitro by establishing a cell co-culture. For this purpose, we used primary co-cultures of GE cells from the olfactory bulb and cortical neurons, which were maintained for 7 days, for subsequent analysis by fluorescence microscopy. The results show the establishment of the co-culture of cortical neurons and Schwann-like cells, demonstrating that the latter promote neurite growth and the expression of MBP, a protein characteristic of myelin, favoring the survival and growth of cortical neurons, which offers an experimental alternative for the analysis of neural regeneration.

P14

Olfactory bulb transplantation with systemic drugs: summatory synergy

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Multiple therapeutics looking for functional motor reconnection in spinal cord injury have been reported with unpromising results; they are not yet acceptable for clinical application. They have been studied individually or in combinations looking for synergy mostly on therapeutic attempts of chronic injury and on few experimental acute injury models. Materials and methods: a model of acute spinal cord injury on mice was used, with application of heterologous olfactory bulb graft (TBO) and intraperitoneal systemic drugs: paclitaxel (T), ambroxol (A) and colchicine (C), applied individually (TA) (TAC) or in combination (TBO-TA) (TBO-TAC) compared with control groups without treatment. Motor recovery was assessed with a simplified Tarlov ´s scale and BBB (Basso, Beathie, Bresnahan) scale, at baseline and up to 12 weeks post-injury, done for to blind evaluators. Video-Tracking process with the Tox Track program was made, measuring parameters of speed, acceleration, and liftings on hind limbs. A histological study was performed with light and transmission electron microscopy. Results were analyzed by comparing standard means and errors, as well as percentage proportions using the SPSS 25.0 package. Results: very significant motor recovery was demonstrated at 12 weeks in the groups combining TBO and triple drug (TBO-TAC). In the groups with TBO and only drugs separately, recovery was shown on less degree; but greater than controls. The Sham group had no motor deficit. Histological evidence of increased myelination was obtained in combination therapy. Conclusions: The results indicate that all the treated groups, TBO, drugs and the combination of both were superior to the controls, being more important and spectacular in the group with combination.

γ-secretase inhibitor in the amino acids: D257, L268, D385, I387, F388 and L432. The development of a drug against Alzheimer's disease

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The γ-secretase is formed by a complex consisting of four individual proteins: PSEN-1, nicastrin, APH-1, and PEN-2. In Alzheimer's disease, several mutations in PSEN-1 have been reported, favoring the production of β-amyloid peptides. There are compounds that inhibit beta and γ-secretase, but they are not selective, since they affect the function of γ-secretase with the NOTCH peptide, since it is introduced into the cavity in which the APP is being cut. In 2019, the crystallographic structure of the γ-secretase complex with APP was published, where the amino acids D257, L268, D385, I387, F388 and L432 are demonstrated in the γ-secretase are important to make the cuts in the APP in the amino acids I718, T719 and L720 to produce the β-amyloid peptides, it can also be identified the differences of interaction in APP and NOTCH, to propose specific sites for APP that avoid interaction with NOTCH and that these amino acids do not have reports of being mutated in any sector of the population worldwide . In this study, we will select by molecular docking compounds directed to the amino acids D257, L268, D385, I387, F388 and L432 in the γ-secretase, to propose a compound that avoids cutting the APP in the amino acids I718, T719 and L720. The compounds selected will be tested in vitro tests (APP Processing Assay and Gamma secretase activity assay), with which the effect of the compounds on the formation of APP peptides and the activity of gamma secretase will be evaluated.

P16

Morphometabolic effects of high glucose concentration in the C6 astrocyte model

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Diabetes mellitus is a risk factor for cognitive impairment and dementia. Alterations in astrocyte functions are an important part of this link, mainly neuroinflammation and glucose metabolism. Glioma-derived C6 cells exhibit morphological and functional characteristics analogous to astrocytes. Using C6 cells exposed to a glucose concentration of 6mM (control) or 35mM (high glucose/HG) for 72 hours (subacute lapse), we aimed to evaluate the effect of HG on morphometabolic functions in C6 cells as an astrocyte model. A trypan blue exclusion viability assay was performed. The "incidence of spindle morphology", "soma/cell index" and "cell area" were evaluated using Image J software. Cellular glucose uptake was evaluated by measuring residual glucose concentration (RGC) in the culture medium. Mitochondrial activity and intracellular ROS generation were assessed by MTT assay and DCFH-DA assay, respectively. Each assay was performed in triplicate. The results were analyzed using JASP software. The HG group showed a lower incidence of spindle morphology ($p<0.001$), higher mean cell area ($p=0.011$), lower RGC when both groups were exposed to HG ($p=0.0240$), higher mitochondrial activity ($p<0.001$) and higher intracellular ROS concentration ($p=0.0289$). No statistically significant differences were observed in the other assays. Our findings suggest that exposure of the C6 astrocyte model to HG modifies cell morphology and is associated with increased glucose uptake and metabolism, linked to increased intracellular ROS generation, a mechanism related to the development of oxidative stress and the damage it causes to brain cells.

P17

Effect of Peroxiredoxin 5 overexpression in a cellular model of Parkinson´s disease

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Oxidative stress is considered one of the pathological mechanisms that cause Parkinson´s Disease (PD). The main pathological characteristic of PD is the progressive degeneration of dopaminergic neurons. An imbalance of reactive oxygen species (ROS) production and reactive intermediates detoxification generates oxidative stress (OS), this affects cellular function by targeting different macromolecules. Dopaminergic neurons are susceptible to oxidative damage due to dopamine's inherent metabolism, which is oxidized and generates ROS. The association between PD and oxidative stress is supported by post-mortem studies of PD patients' brains, where increased oxidative activity was found in dopaminergic neurons, also a decrease of antioxidant enzymes. We previously found, in an in vitro model of PD, that the thiol-dependent enzymes Peroxiredoxins (Prx) were in their hyperoxidized form, this form is catalytically inactive and perpetuates the state of oxidative stress. In the present study, we evaluate the redox state of the Prx 2-Cys typical subgroup. We found by eastern blot that there is a compartmentalization of oxidative stress in different organelles, reflected in the hyperoxidation pattern of these enzymes. Studies in mammals have shown that 2-Cys Prxs are most vulnerable to hyperoxidation, while Prx5 2-Cys atypical is resistant. That's why we induced Prx5 overexpression in the SHSY 5Y cell line, using the adenoviral vector Ad-Prx5. Prx5 overexpression was confirmed by immunofluorescence, and we observed using a mitochondrial Superoxide Indicator, that this overexpression decreases mitochondrial oxidative stress. On the other hand, flow cytometry showed that oxidative stress in the cytoplasm also decreased when Prx5 is overexpressed. This decrease in oxidative stress in the main subcellular compartments led to overall cell protection against death in this model of PD, which was demonstrated by flow cytometry using Annexin V labeled and propidium iodide. Prs 5 is more resistant to hyperoxidation than Prx 2-Cys typical, and is expressed in multiple organelles,. These make Prx5 an interesting therapeutic target for PD. In addition, its overexpression protects dopaminergic-like cells from oxidative stress and death, which justifies the study of this effect in in vivo models of PD, for its subsequent application in clinical trials

Autophagy Inducers Trehalose and Metformin Prevent Cognitive and Motor Dysfunction by Protecting Dopaminergic Neurons from Paraquat Toxicity

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Parkinson's Disease (PD) pathological characteristics include dopaminergic neuronal loss, 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 its impairment leads to neurodegeneration. Therefore, studying the potential neuroprotective effect of autophagy-inducing molecules such as trehalose and metformin is crucial. We previously demonstrated that autophagy induction with trehalose and metformin has an antioxidant effect and improves mitochondrial activity on SH-SY5Y dopaminergic cells treated with paraquat (PQ). Hence, we evaluated the effect of both autophagy inducers in C57BL6 mice were pretreated with trehalose (2%) or metformin (500 mg/kg) in drinking water ad libitum one week before PQ (10 mg/kg) intraperitoneal co-administration for seven weeks. Cognitive function was evaluated through the nest building test. Trehalose and metformin-pretreated mice followed by PQ treatment built higher quality nests (full dome-shaped) than those that received only PQ. The gait test assessed the motor function; PQ-treated mice showed a smaller stride length compared to mice from the control group. Therefore, trehalose and metformin prevent cognitive and motor functions deterioration in the PD animal model. Notably, pretreatment with trehalose and metformin protected from PQ-induced dopaminergic neuronal death, demonstrated through tyrosine hydroxylase detection by immunofluorescence and confirmed by western blot. Astrocytes were also analyzed, observing that PQ induces astrocytosis, which was prevented by pretreatment with both autophagy inducers. Therefore, trehalose and metformin represent autophagy inducers with a promising potential for treating neurodegenerative diseases such as PD.

P19

Metformin improves health and quality of life in middle and late aged mice

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Although it is not considered a disease, the inevitable aging process is directly linked to life expectancy and causes the development of multiple diseases. Like the rest of the organs, the functional capacities of the brain progressively decrease with aging, and this manifests in different ways, such as decreased memory and learning capacity, decreased attention, low speed of reasoning, and changes in sensory perception and motor coordination. Metformin is the most prescribed biguanide for the treatment of type 2 diabetes. It has been in use for 60 years and, in addition to its hypoglycemic effect, it has been observed that has effects on other diseases such as cancer, hepatic dysfunction and, kidney diseases. And its users appear to have slower cognitive decline and have a reduced incidence of dementia as they age. This work describes the results of a battery of behavioral and motor tests in mice that model age-associated changes. Where we were able to observe that treatment with usual hypoglycemic doses of metformin, improves the cognitive and motor function of middle-aged and late-aged female and male mice. This adds evidence to the senostatic effect of metformin and places it as a promising adjuvant and therapeutic drug whit multiple applications in age-related diseases. Keywords: aging, metformin, behavior and motor tests.

Recently, it has been proposed to classify the inevitable aging process as a disease directly linked to life expectancy and causing the development of multiple diseases. Like the rest of the organs, the functional capacities of the brain progressively decrease with aging, which manifests in different ways, including decreased memory, learning and attention capacities, low speed of reasoning, and changes in sensory perception and motor coordination. Metformin is the most prescribed biguanide for the treatment of type 2 diabetes. It has been in use for 60 years, and, in addition to its hypoglycemic effect, it has been shown to affect other diseases such as cancer, hepatic dysfunction, and kidney diseases. Furthermore, its users appear to have slower cognitive decline and have a reduced incidence of dementia as they age. Herein, we describe the results of a battery of behavioral and motor tests in middle-aged and late-aged female and male C57BL/6J mice treated with metformin 500 mg/kg/day in the drinking water ad libitum for 15 weeks, modeling age-associated changes. We observed that treatment with usual hypoglycemic doses of metformin significantly improves the cognitive and motor function of middle-aged and late-aged female and male mice. Our results add evidence to the senostatic effect of metformin and place it as a promising adjuvant and therapeutic drug with multiple applications in age-related diseases. Keywords: aging, metformin, behavior, motor tests.

P20

D-serine effect on cognitive flexibility depends on the cognitive status of the senescent rats

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NMDA receptors (NMDAR) play a pivotal role in many cognitive functions. During aging, the levels of the NMDAR co-agonist, D-serine, are decreased which is linked to NMDAR hypofunction and cognitive deficits. Previous results from our lab, have shown that D-serine supplementation in senescent rats restores cognitive flexibility (CF) and functional brain connectivity. However, it's unclear if the D-serine effect depends on the severity of the cognitive impairment. To answer this, we did a longitudinal study using 12-month-old rats (middle-aged) that were trained in a reversal-learning task and the number of perseverations was quantified as an inverse measure of CF. After this, the rats were assigned into two groups: one supplemented with D-serine (300 mg/kg) in the drinking water (two months), and the control group that received a vehicle. The CF was then re-evaluated at 18 months (late middle-aged) and functional brain connectivity was analyzed during resting state with fMRI. Middle-aged rats had more perseverations than young rats (6 months), indicating that at this age CF is affected. We found that good performers rats receiving D-serine, but not control rats, significantly decreased their CF when they were evaluated in late middle-aged. Also, we observe an increase in functional brain connectivity in brain areas associated with CF. These results suggest that the effect of D-serine supplementation depends on the cognitive status and that supplementation in high performers is detrimental to cognitive functions.

Macro- and microstructural correlation in chronic ethanol consumption in Wistar rats

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Alcohol use disorder (AUD) is an affliction which impairs motivational circuits, involving several brain regions such as prelimbic cortex, infralimbic cortex, caudate-putamen, globus pallidus, anterior amygdala, ventral tegmental area, hippocampus, and cerebellum. Magnetic resonance imaging (MRI) through whole-brain volumetric analysis has identified changes in gray matter volume (GMV) compromised by AUD in humans and animal models. However, the cellular components related to volume changes in AUD remained unclear. Here, we used an intermittent access 2-bottle choice model at 20% ethanol concentration which consists of 20 sessions of alcohol (45 days), 10 days of withdrawal, and 10 sessions of alcohol relapse (23 days) with male and female Wistar rats (n=90). After the alcohol sessions, we used deformation-based morphometry (DBM) in ex-vivo MRI whole brain images to compare local volume between ethanol and control groups. Then, we use immunofluorescence to measure density and volume alterations in cells of 8 regions of interest (ROI): neurons (NeuN), astrocytes (GFAP), and microglia (Iba1). Lastly, we ran a multiple regression model of macro and microstructural measures to find their relationship. Our preliminary results showed lower DBM local volume mainly in the left thalamus, left caudate-putamen, and left dentate gyrus. We also found a region-specific pattern of reduced number of NeuN-positive neurons with a lower volume, an increased number of astrocytes with a higher volume, and an increased number of microglia with a higher volume. Finally, the multiple regression model will explain a great percentage of the GMV variance.

P23

GABA Modulate VEGF-A Expression in Retinal Müller Glial Cells

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In diabetic retinopathy (DR), the concentrations of vascular endothelial growth factor (VEGF) increase in the vitreous of patients exacerbating the angiogenic processes in the retina and facilitating the progression of the disease. Studies show the presence of GABA in the vitreous of patients with DR, however, the pathophysiological contribution to DR is currently unknown. In the retina, Müller cells (MG) are the most abundant glial cells. One of MG homeostatic functions is the regulation of the synthesis and release of trophic factors such as VEGF. Experimental evidence suggests a possible relationship between GABA and the angiogenic processes. The gold of this study is to explore if the exogenous application of GABA modulates the expression of VEGF-A in MG cultures. Primary cultures of MG were generated isolated from CD-1 mouse eyes (P5-7 days). Cells were exposed to GABA at several concentrations (12.5 to 200 µM) for 48 hours. Protein and mRNA expression was determined and analyzed by immunofluorescence, western blot, and RT-PCR assays. Our results showed that VEGF expression in MG was modulated in a dose-dependent fashion, with a significant increase at GABA 100 µM. In addition, GABA also upregulates the VEGF mRNA in MG. These results suggest that GABA can modulate VEGFA expression in Müller glia, and therefore could play an important role in the development of the angiogenic processes and progression of diabetic retinopathy.

Taurine promotes differentiation and maturation of neural progenitor cells from the subventricular zone through GABA receptors

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Neurogenesis occurs throughout the life of mammals, and two main neurogenic zones have been described in adult mammals, the hippocampal subgranular zone and the subventricular zone. Neuronal differentiation is a complex process characterized by the initial formation of immature neurites, commonly called "neurite outgrowth." Taurine, plays a central role in the proliferation, differentiation, and migration of neural progenitor cells. However, the mechanism of action of taurine is not well understood. In this work, we explored the interaction of taurine with the GABA receptors. Our results show that cultures exposed to differentiation conditions with taurine, the number of DCX+ cells was increased. Morphometric analysis revealed a significant difference in cell morphology. Compared to control and GABA-treated cells (positive control), taurine-treated cells exhibited increased dendritic branching and marked complexity in dendritic arborization. Taurine actions were sensitive to picrotoxin, indicating active participation of GABAA receptors. Also, the treatment with CGP55485 antagonist of GABAB receptors increased dendritic complexity and branching. Additionally, we determined the passive and active electrophysiological properties of the control, GABA, and taurine treated cells with patch-clamp whole-cell recordings. Our results provide information regarding the role of taurine as a morphogen in the neurogenic processes throughout the interaction with ionotropic and metabotropic GABA receptors and their role as a central player in the maturation processes of NPCs into functional neurons. This work represents an advance in the morphometric effect and suggests a functional effect of taurine in the neuronal differentiation process through GABA receptors.

P25

D-serine effect on the decrease in motivated behavior associated with aging

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D-serine, which is synthetized and released by astrocytes, acts as a co-agonist at NMDA receptors. It is located in brain regions with important glutamatergic activity mediated by NMDA receptors and participates in cognitive and emotional processes. In the aged brain, there is a decrease in both D-serine levels and NMDA receptor activity, which has been associated with cognitive decline as well as mood alterations. Previous results from our lab, have shown that D-serine supplementation in senescent rats restores cognitive flexibility and locomotor activity that is affected by age. However, we wonder if the effect of D-serine is mediated by changes in the motivated behavior. To test this, we used young (6 months) and aged (18 months old) male rats that were supplemented daily with D-serine (300 mg/Kg) in the drinking water for two months. We use elevated plus maze and open field test to evaluate the explorative and anxiety-like behavior. We analyzed their behavior using deep learning tools (DeepLabCut). Aged animals decreased the number of rearings, nose dips, traveled less distance in the arena, and expended more time in the open areas when compared to young rats. This indicates that aged animals have a decreased motivated behavior and an increased anxiety-like behavior in comparison with young ones. Animals supplemented with D-serine show a reverse in this tendency, whit aged individuals resembling young ones. These results suggest that D-serine increases motivated behaviors, which opens the possibility to use D-serine as a therapeutic target for mood-related changes in aged individuals.

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GABA increase Müller glial cell proliferation in vitro

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$GABA_A$ receptors ($GABA_AR$) are ionotropic receptors activated by GABA and have an important role in neuronal communication, typically inhibitory-hyperpolarizing responses. However, in glial cells, the participation of $GABA_AR$ involves other processes most related to homeostases, such as cell proliferation and migration in astrocytes and oligodendrocytes. Interestingly, the physiological function of $GABA_AR$ in retinal glia such as Müller cells has not been explored yet. The goal of this research was to study the effect of GABA on the proliferation of Müller glia. For this, primary cultures of Müller glia were obtained from CD-1 mice (5-7 postnatal days). At the third passage, the cultures were exposed to different concentrations of GABA (12.5-250 µM) for 48 hours. Cell proliferation was evaluated using CCK-8 metabolic activity, and bromodeoxyuridine (BrdU) incorporation assays. The results with CCK-8 indicate that GABA induces an increase in the number of cells after 48 hours of exposure, with a high percentage of viable cells (>90%). At a concentration of 100 µM, GABA was able to induce a significant increase, compared to the control conditions, in the number of BrdU positive cells. The results shown here indicate that GABA induces cell proliferation in these retinal glial cells.

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Astrocytes: an important player in vibrotactile discrimination?

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Astrocytes play an active role in neuronal circuits and cognitive functions. They respond to sensory stimulation with intracellular calcium transients in several sensory areas. In the somatosensory system, astrocytes encode features of the sensory stimulus. However, it is not clear if astrocytes are involved in the processing of somatosensory information. Here, we analyzed the role of astrocytes in the secondary somatosensory cortex (S2), in a vibrotactile discrimination task. We trained C57BL/6 male mice (8–12 weeks old to discriminate between low (20 Hz) and high frequencies (80 HZ) of vibrotactile stimuli. Once the mice reach the criterion, their performance was tested with stimuli of different frequencies (25, 32, 50, 63 Hz), and the mice had to compare and categorize them (as high or low) based on previously learned reference frequencies. Mice ability to discriminate vibrotactile stimulus decreased when the frequency was farther from the reference value. Then, we wonder if astrocyte calcium activity could modify the performance of mice in this task. First, astrocytes calcium activity in S2 was imaged with a Miniscope V4 using GCaMP6f under GFAP promoter. Astrocytes responded to mechanical forelimb stimulation with calcium increases. Astrocyte DREADDs activation with Clozopine N-Oxide (CNO) evoked calcium increases that last for up to 50 min. Mice receiving CNO improved their performance in the vibrotactile discrimination task suggesting that astrocyte activation is sufficient to modify the behavioral performance of rodents.

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Role of astrocytes in the processing of sensory information in the secondary somatosensory cortex of mice

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Information processing is not an exclusive property of neurons, this can also be mediated by astrocytes. Synaptic activity is integrated by astrocytes through calcium increases. This calcium activity can be evoked by sensory stimulation, as occurs in the primary somatosensory cortex. Here, astrocytes respond to somatosensory stimuli encoding the intrinsic properties of the stimulus. However, the role of astrocytes in the secondary somatosensory cortex (S2) it is not fully understood. The aim of this project was to analyze the participation of astrocytes in the processing of sensory information in S2. To do this, we performed extracellular recordings with multielectrodes in anesthetized mice (C47BL/6) in combination with chemogenetics (DREADDs- pAAV-GFAP-hM3D(Gq)-mCherry) to activate the astrocytes. Sensory responses were evoked by electrical stimulation in the forelimb (5Hz, 3 pulses). Using this protocol, we observed an adaptation of sensory-evoked neuronal responses with consecutive pulses. The activation of DREADDs (with CNO) expressed in astrocytes, evoked calcium activity that was monitored using GCaMP6f and a miniature microscope (Minoscope V4). CNO administration, significantly increased sensory-evoked neuronal responses, without affecting the spontaneous activity of the neuronal circuit. Furthermore, the activation of the astrocytes decreases the adaptation of sensory responses. These results point to a relevant role of astrocytes in the processing of sensory information in S2.

Human olfactory epithelium-derived astrocytes transplantation into the striatum of neonatal mice

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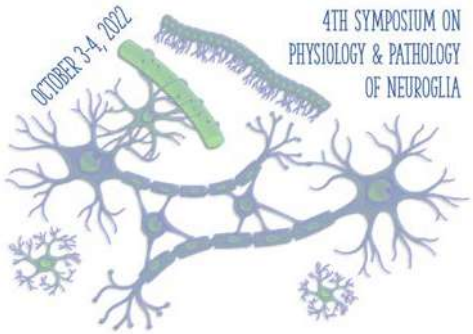
The human olfactory epithelium (hOE) is characterized by a continuous regeneration of olfactory sensory neurons and glial cells that persist into adulthood. Neuro and gliogenesis in the hOE, are possible due to the neural progenitor cells (NPC) known as the globose and the horizontal basal cells. A great advantage attributed to these basal cells is their easy access in the nasal cavity of adult human donors which prompts them for therapeutic applications such as autologous transplants. The aim of this work was to evaluate the potential of human OE NPC-derived astrocytes to survive and morphologically develop after grafting into the striatum of neonatal mice. To achieve this goal, cells were transduced with an adenovirus vector carrying the gen that codes for the green fluorescent protein (GFP) and their differentiation into astrocytes was induced using the ScienCell differentiation medium. Subsequently, the cells were transplanted into the striatum of neonatal P1-3 CD1 mice. The results obtained show the survival of these cells at least two months after transplantation, denoted by the presence of GFP+ cells. To evaluate the complexity of grafted cells, Sholl analysis was used through a time course (week 1 to week 8). It was observed that the grafted cells after 4 and 8 weeks are more complex since they have a greater number of processes, and these processes increased their length throughout time reaching a maximum at 4 weeks post-transplant. Additionally, grafted cells expressed the astrocytic marker GFAP (glial fibrillar acid protein), showing that hOE cells maintain their astrocytic identity after transplantation. These results allow us to consider hOE NPCs as astrocytes source and their use in cell therapy for neurodegenerative disorders, however, additional experiments are required. Key words: olfactory epithelium, neural progenitor cells, astrocytes. Acknowledgments: Dr. Benitez-King, A.E. Espino-Saldana. From PAPIIT-DGAPAUNAM IN205321 to AH and IN204520 to AMT. From CONACYT A1S7659 to A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