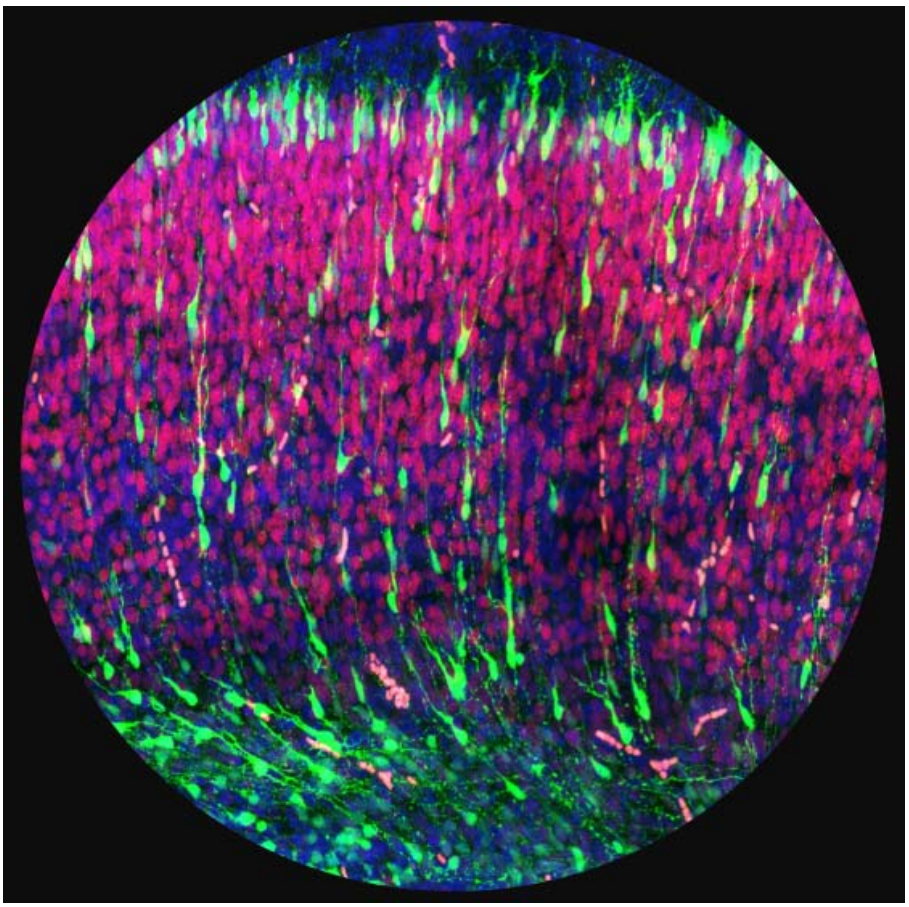
Instituto Universitario de Investigación Neuroquímica

III Reunión Científica IUIN



3 de Noviembre 2023
Sala Profesor Schüller

UNIVERSIDAD COMPLUTENSE MADRID

Recogida de documentación y acreditación desde las 9:00 de la mañana en la entrada del Aula Profesor Schüller - 2ª Planta – Pabellón Central – Facultad de Medicina, UCM

9:30 - 9:40	**PRESENTACIÓN DE LA JORNADA** Eva de Lago Femia y Onintza Sagredo Ezkioga
SESIÓN I **Moderadora: María Gómez Cañas**	
9:40 – 10:45	**PONENCIA INVITADA** **VÍCTOR BORRELL FRANCO – INSTITUTO DE NEUROCIENCIAS DE ALICANTE** Evolución de la neurogénesis y el plegamiento cortical
10:45-11:00	**O1 IRENE BERENICE MAROTO** Striatal GAP43 controls novelty-induced hyperactivity
11:00-11:15	**O2 LAURA EXPÓSITO BLÁZQUEZ** Los ARNs circulares como potenciales biomarcadores diagnóstico y pronóstico en el espectro ELA-DFT
11:15 - 11:30	**O3 ÁLVARO SIERRA TARAZONA** Estudio del proceso de mielinización en un modelo murino de Síndrome de Dravet: Implicaciones de los cannabinoides
11:30- 12:00	**COFFEE BREAK (Cafetería de la Facultad de Medicina)**

SESIÓN II Moderador: David Martín Hernández	
12:00-12:15	**O4 FRANCISCO JAVIER DE CASTRO MILLÁN** FeCL3 Stroke Model: Characterization of Post-Stroke Hippocampal Neurogenesis and Cognitive Impairment
12:15-12:30	**O5 ALBERTO SAMUEL SUÁREZ PINILLA** A positive allosteric modulator of mGluR4 rescues parallel fiber synaptic plasticity, motor learning and social behavior in a Fragile X Syndrome murine model
12:30-12-45	**O6 ANIBAL SÁNCHEZ DE LA TORRE** Cannabinoid CB1 receptor in NG2 cells is essential for myelin repair and functional recovery
12:45-13:00	**O7 ANA LAURA TORRES ROMÁN** Regulation of mitochondrial dynamics by endocannabinoids as a neuroprotective mechanism in vitro
13:00-13:15	**O8 ELISA NAVARRO GÓNZALEZ DE MESA** **E**xploring the effect of LRRK2 G2019S mutation on human derived microglia and monocytes
13:15-13:30	**O9 ALICIA ÁLVARO-BLÁZQUEZ** CB1R ubiquitination: towards an understanding of cannabinoid tolerance
13:30-13:45	**O10 MÓNICA MOVILLA PÉREZ** Modulación de la dinámica mitocondrial por la paliperidona en ratas macho y hembra
13:45-14:45	**COMIDA (Cafetería de la Facultad de Medicina)**
14:45-15:45	**SESIÓN DE POSTERS (Hall 3ª Planta)**

SESIÓN III Moderador: Manuel Navarro Oviedo	
15:45-16:00	**O11 TÀNIA GAVALDÀ-VIVES** Efectos de la señalización cannabinoide en alteraciones de la laminarización cortical: síndrome asociado a SATB2
16:00 - 16:15	**O12 SARA EZQUERRO** Astroglial monoacylglicerol lipase gene inactivation prevents cns demyelination
16:15 – 16:30	**O13 NOEMÍ ESTERAS GALLEGO** TAU inhibits mitochondrial calcium efflux and makes neurons vulnerable to calcium-induced cell death
16:30 - 16:45	**O14 RAQUEL MARTÍN BAQUERO** Exploring altered primary microglia and astrocytes responses to LPS from a TDP-43-related frontotemporal dementia mouse model
16:45-17:15	**O15 CLAUDIA GONZALO CONSUEGRA** Modulation of the endocannabinoid system as a disease-modifying therapy for frontotemporal dementia
17:15-17.30	**CLAUSURA Y ENTREGA DE PREMIOS**

SESIÓN DE POSTERS

P1 CARMEN NIETO VAQUERO. AHR deletion reduces amyloid plaque accumulation and axonal dystrophy in the APPNL-F Knock-in Alzheimer's mouse model

P2 NURIA ALFAGEME. Bacterial translocation after hemorrhagic stroke. detection by mri, effect of hematoma size and its inflammatory consequences

P3 JOSÉ ANTONIO GUIMARÉ. Evaluation of different doses of fenfluramine to reduce seizures in a mouse model of epilepsy induced by PTZ

P4 RAQUEL BAJO GRAÑERAS. Bidirectional modulation of inhibitory transmission by mGluR7 at CA1 pyramidal cells

P5 ADA QUINTERO PÉREZ. Modulation by PACAP-38, histamine, and serotonin of adrenomedullary catecholamine secretion in a neuropathic pain model

P6 SANDRA VAZQUEZ REYES. Effect of neutrophil circadian rhythms in mouse ischemic stroke

P7 CARLOS PARRA PÉREZ. NETosis is involved in chronic post-stroke outcome

P8 ALBA MÉRIDA CORONEL. Embryonic cannabinoid CB1 receptor knockdown alters the neurogenic gene expression program and functional maturation of pyramidal neurons

P9 JAIME GARCÍA MALO. C9orf72 in the Spanish ALS-FTD spectrum

P10 SARA IZQUIERDO. La quinolilnitrona QN6 como agente único y multivalente para la terapia del ictus y las enfermedades neurodegenerativas

ABSTRACTS
COMUNICACIONES ORALES

COMUNICACIÓN ORAL 1

STRIATAL GAP43 CONTROLS NOVELTY-INDUCED HYPERACTIVITY

Irene B. Maroto[1], Carlos Costas-Insua[1], Carlos Montero-Fernández[1], Alba Hermoso-López[1], Cristina Blázquez[1], Margaux Lebouc[2], Raquel Bajo-Grañeras[1], Ricardo Martín[1], Jérôme Baufreton[2], Ignacio Rodríguez-Crespo[1], Luigi Bellochio[2] & Manuel Guzmán[1]

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Keywords*:* novelty-induced hyperactivity, growth-associated protein of 43 kDa, corticostriatal circuit

Growth-associated protein of 43 kDa (GAP43) is a key cytoskeletal-associated component of the presynaptic terminal. Upon activation by PKC-mediated phosphorylation, it contributes to axonal growth during brain development, as well as to nerve regeneration, vesicular recycling and neuronal plasticity in the hippocampal formation in the adult brain. Homozygous GAP43 knocking out in mice is lethal shortly after birth, while heterozygous GAP43 knocking out leads to memory impairments and connectivity-related affections. However, little is known about the role of GAP43 in other brain structures and the precise mechanisms in excitatory *vs.* inhibitory inputs that may underlie those phenotypes. We have generated GAP43-floxed mice and, subsequently, conditional GAP43-knockout mice specifically in telencephalic glutamatergic neurons (Glu-GAP43$^{-/-}$ mice) or forebrain GABAergic neurons (GABA-GAP43$^{-/-}$ mice) by Cre-LoxP recombination. Compared to their WT littermates, Glu-GAP43$^{-/-}$ mice showed a striking hyperactivity in a novel environment habituated over time, which was not observed in GABA-GAP43$^{-/-}$ animals. In addition, Glu-GAP43$^{-/-}$ mice showed an unaltered home-cage spontaneous activity. These motor activity alterations in Glu-GAP43 $^{-/-}$ mice were associated with an increased neuronal activation (as assessed by c-Fos staining) of striatal medium spiny neurons after exposure to a novel open field compared to their WT littermates indicating that hyperactivity may be caused by an alteration in the corticostriatal circuitry. Moreover, corticostriatal LTD was abolished in Glu-GAP43 $^{-/-}$ mice compared to their WT littermates, and this occurred by a presynaptic mechanism. Taken together, these findings support an unprecedent role of GAP43 in striatal function and provide a robust behavioral phenotype reliant on glutamatergic neurons, which may constitute a useful tool for studying novelty-induced hyperactivity, thus mimicking some phenotypic abnormalities found in attention deficit hyperactivity disorder.

COMUNICACIÓN ORAL 2

LOS ARNs CIRCULARES COMO POTENCIALES BIOMARCADORES DIAGNÓSTICO Y PRONÓSTICO EN EL ESPECTRO ELA-DFT.

Laura, Expósito Blázquez[1], Daniel Borrego Hernández[2], Leticia Moreno García[2], Janne Markus Toivonen[2], Ana Cristina Calvo[2], María del Carmen Herrero Manso[3], Pilar Cordero Vázquez[1], Alberto Villarejo Galende[4], Sara Llamas Velasco[4], Marta González Sánchez[4], Miguel Ángel Martin Casanueva[5], Jesús Esteban[1], Rosario Osta[2] y Alberto García Redondo[1].

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Keywords: Esclerosis Lateral Amiotrófica; Demencia Frontotemporal; Biomarcadores; ARNs circulares; Expresión génica.

Introducción: La identificación de mutaciones en *C9orf72*, *TARDBP* y *FUS*, proteínas implicadas en el procesamiento, transporte y traducción de ARN, conduce a la idea de que el metabolismo aberrante del ARN contribuye en la patogénesis de la ELA.
Los ARN circulares (ARNcirc) son un tipo de ARNs no codificantes que se generan durante el *splicing* y que están aumentados en procesos de neuroenvejecimiento, por lo que son buenos candidatos como biomarcadores en ELA[1].

Objetivo: Evaluación de la capacidad diagnóstica y pronóstica de 6 ARNcircs previamente seleccionados en el modelo transgénico murino *G93ASOD1* como posibles biomarcadores en ELA y DFT.

Materiales y métodos: La cohorte de estudio está formada por 53 pacientes de ELA, 23 de DFT y 35 controles sanos. El análisis de expresión se ha realizado mediante qPCR en muestras de plasma y PBMCs. Seguidamente se ha estudiado la relación entre los niveles de expresión y los parámetros clínicos como la edad de inicio de los síntomas, ALSFRS-r o el retraso diagnóstico. Además, se construyen curvas ROC con el fin de determinar la sensibilidad diagnóstica de estos biomarcadores.

Resultados: Los ARNcirc 1 y 3 presentan gran potencial diagnóstico como biomarcadores en ELA, obteniéndose valores de sensibilidad por encima del 75%. Por otro lado, la sobreexpresión del ARNcirc 3 en ELA se asocia con una progresión más rápida de la enfermedad y una menor supervivencia.
En el caso de la DFT, la expresión de los ARNs circulares 1 y 4 se relaciona con la presencia de una historia familiar hereditaria; mientras que la sobreexpresión del ARNcirc 4 se asocia con un mayor retraso diagnóstico.
Conclusiones: Los ARNcirc podrían constituir un nuevo abordaje en el campo de los biomarcadores para los pacientes de ELA. Además, cabe destacar que se está replicando este análisis en otro centro colaborador con el fin de confirmar el potencial de estos.

Bibliografía:

1. Dolinar A, *et al.* Circular RNAs as Potential Blood Biomarkers in Amyotrophic Lateral Sclerosis. Mol Neurobiol. 2019 Dec;56(12):8052-8062.
2. Archbold HC, *et al.* TDP43 nuclear export and neurodegeneration in models of amyotrophic lateral sclerosis and frontotemporal dementia. Sci Rep. 2018 Mar 15;8(1):4606.

COMUNICACIÓN ORAL 3

ESTUDIO DEL PROCESO DE MIELINIZACIÓN EN UN MODELO MURINO DE SÍNDROME DE DRAVET: IMPLICACIONES DE LOS CANNABINOIDES

Sierra A.[1,2], Satta V.[1,2,3], Guimaré JA[1,2,3], Hernández-Fisac I[1,2], Fernández-Ruiz J.[1,2,3] y Sagredo O.[1,2,3.]

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El Síndrome de Dravet (DS) es un síndrome epiléptico causado por mutaciones en el gen *Scn1a* que codifica la subunidad α1 del canal de sodio Nav1.1. Estas mutaciones se asocian con convulsiones febriles que progresan a convulsiones tónico-clónicas graves y comorbilidades como deterioro cognitivo y rasgos autistas. El objetivo del estudio es conocer el impacto que produce el DS sobre la oligodendrogénesis y las proteínas de la vaina de mielina. También se ha querido valorar el efecto que produce sobre estos procesos el tratamiento con los compuestos cannabinoides cannabidiol (CBD) y beta-cariofileno (BCP), administrados solos o en combinación. Para dicho estudio se ha empleado un modelo murino knock-in con una mutación en el gen *Scn1a* que codifica para el canal de sodio dependiente de voltaje Nav1.1. El estudio incluye un tratamiento intraperitoneal con los compuestos CBD y BCP, análisis de expresión génica y ensayos de inmunofluorescencia.

Tras el tratamiento combinado con los cannabinoides CBD y BCP, los niveles de mielinización en la corteza prefrontal y el hipocampo de ratones con DS es similar al de los animales WT. El estudio también mostró que la oligodendrogénesis estaba alterada en estos animales, con un aumento de los oligodendrocitos maduros, posiblemente como mecanismo compensatorio contra la desmielinización sufrida. En conclusión, nuestros resultados proporcionan pruebas sólidas de los efectos relevantes ejercidos por la combinación de BCP y CBD contra el daño a la mielina, lo que puede ayudar a mejorar el tratamiento terapéutico de la DS

COMUNICACIÓN ORAL 4

$FeCL_3$ STROKE MODEL: CHARACTERIZATION OF POST-STROKE HIPPOCAMPAL NEUROGENESIS AND COGNITIVE IMPAIRMENT

F.J. Castro-Millán[1], M.I. Cuartero[2], A. García-Culebras[3], P. Villatoro-González[1], A. Rodríguez-Llave[1], C. Torres-López[1], T. Jareño-Flores1 y M.Á. Moro[1].

1Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Laboratorio de Fisiopatología Neurovascular, Madrid, España, 2Universidad Complutense de Madrid, Departamento de Farmacología, Madrid, España, 3Universidad Complutense de Madrid, Departamento de Biología Celular, Madrid, España.

Keywords: stroke, cognitive impairment, vascular dementia, adult neurogenesis, hippocampus

Stroke is the second leading cause of death worldwide and is now considered a chronic disease, being the principal cause of vascular cognitive impairment and dementia. Previously, a mouse model of brain ischemia with surgical permanent occlusion of the middle cerebral artery (pMCAO) and of the ipsilateral carotid by ligature has shown a neurogenic response in the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus, with an increase in proliferation, aberrant morphology of post-stroke newborn neurons, that is causally related to cognitive deficits. Now, we are exploring the hippocampal neurogenic response after focal cerebral ischemia in a mouse model with pMCAO induced by topical application of ferric chloride (FeCl3), affecting neither carotid blood flow nor meningeal integrity.

Two-month C57BL/6 mice underwent either pMCAO or sham surgery. After 7 or 30 days, we analyzed the number and morphology of the DCX+ neuroblasts by immunofluorescence. Another group of animals was used to study acute (24h) and chronic (5 weeks) brain lesions after pMCAO by T2 magnetic resonance imaging and arterial spin labelling, also behavioural tests were conducted to assess anxiety, motor and cognitive deficits.

Our results show that this model produces a cortical acute lesion which results in a long term cortical ipsilateral atrophy and hypoperfusion. Even though the infarct lesion did not directly affect the hippocampus, it did result in an ipsilateral hypertrophy of this structure. Furthermore, we observed an increase in the number of neuroblasts in the SGZ of the DG 7 and 30 days after ischemia, with the appearance of aberrant morphology in both hemispheres. In addition, part of the animals developed motor and cognitive deficits, and anxiety-like behaviour. These results suggest that FeCl3 induced stroke is a suitable and accessible experimental model for the study of adult hippocampal neurogenesis and post-stroke cognitive impairment.

COMUNICACIÓN ORAL 5

A POSITIVE ALLOSTERIC MODULATOR OF mGluR4 RESCUES PARALLEL FIBER SYNAPTIC PLASTICITY, MOTOR LEARNING AND SOCIAL BEHAVIOR IN A FRAGILE X SYNDROME MURINE MODEL

Alberto Samuel Suárez-Pinilla[1,2,3], Nuria García-Font[1,4], Raquel Bajo-Grañeras[1,2,3,5], María Luisa Laguna-Luque[6], Juan Carlos López-Ramos[6], María Jesús Oset-Gasque[2,3,7], Agnes Gruart[6], José María Delgado-García[6], José Sánchez-Prieto[1,2,3], Magdalena Torres[1,2,3] and Ricardo Martín [2,3,5]

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Keywords: Parallel Fiber-Purkinje cell synapse, β adrenergic receptor, RRP size, *Fmr1* KO, classical conditioning, vestibulo-ocular reflex

Fragile X syndrome (FXS), the most common inherited intellectual disability, is caused by the loss of expression of the Fragile X Messenger Ribonucleoprotein (FMRP). FMRP is an RNA-binding protein that negatively regulates the expression of many postsynaptic as well as presynaptic proteins involved in action potential properties, calcium homeostasis and neurotransmitter release. FXS patients and mice lacking FMRP suffer from multiple behavioral alterations, including deficits in motor learning for which there is currently no specific treatment.

We performed electron microscopy, whole-cell patch-clamp electrophysiology and behavioral experiments to characterise the synaptic mechanisms underlying the motor learning deficits observed in *Fmr1*KO mice and the therapeutic potential of positive allosteric modulator of mGluR4.

We found that enhanced synaptic vesicle (SV) docking of cerebellar parallel fiber to Purkinje cell *Fmr1*KO synapses was associated with enhanced asynchronous release, which not only prevents further potentiation, but it also compromises presynaptic parallel fiber long-term potentiation (PF-LTP) mediated by β adrenergic receptors. A reduction in extracellular Ca^{2+} concentration restored the readily releasable pool (RRP) size, basal synaptic transmission, β adrenergic receptor-mediated potentiation, and PF-LTP. Interestingly, VU 0155041, a selective positive allosteric modulator of mGluR4, also restored both the RRP size and PF-LTP in mice of either sex. Moreover, when injected into *Fmr1*KO male mice, VU 0155041 improved motor learning in skilled reaching, classical eyeblink conditioning and vestibulo-ocular reflex (VOR) tests, as well as the social behavior alterations of these mice.

Our study shows that an increase in SV docking may cause the loss of PF-LTP and motor learning and social deficits of *Fmr1*KO mice and that the reversal of these changes by pharmacological activation of mGluR4 may offer therapeutic relief for motor learning and social deficits in FXS.

COMUNICACIÓN ORAL 6

CANNABINOID CB_1 RECEPTOR IN NG2 CELLS IS ESSENTIAL FOR MYELIN REPAIR AND FUNCTIONAL RECOVERY

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Keywords: NG2 cells, Remyelination, CB1 receptor.

Regeneration of the oligodendroglial population through differentiation of NG2 cells is essential for myelin repair under demyelinating conditions. In this context, cannabinoid compounds have been shown to modulate oligodendrocyte regeneration, CNS remyelination and functional recovery in different animal models of demyelination. However, the cell-autonomous role of cannabinoids in NG2 cells mediating their remyelinating actions has never been determined. In this work, by using genetic mouse models and the cuprizone model of demyelination, we found that selective CB1 receptors inactivation in NG2+ cells following demyelination blocks cell differentiation and disrupts oligodendrocyte regeneration, CNS remyelination and motor function recovery, by perturbing the mTORC1 and RhoA/ROCK signaling pathways. Moreover, CB1 receptor deficiency in NG2 cells exacerbates axonal damage, gliosis and neuroinflammation during remyelination. Conversely, Δ9-tetrahydrocannabinol (THC) administration following demyelination induces oligodendrocyte regeneration and functional remyelination in wt but not in Ng2-CB1 deficient mice. Finally, pharmacological ROCK inactivation rescues the defects in oligodendrocyte regeneration and functional remyelination of NG2-CB1 deficient mice. Overall, this study identifies CB1 receptors as essential modulators of NG2 cells differentiation under demyelination and confirms the therapeutic potential of cannabinoids for promoting functional remyelination.

COMUNICACIÓN ORAL 7

REGULATION OF MITOCHONDRIAL DYNAMICS BY ENDOCANNABINOIDS AS A NEUROPROTECTIVE MECHANISM IN VITRO

Ana Laura Torres-Román[1,2,3], Samuel Simón-Sánchez[2,3], Tania Gavalá-Vives[2,3], Alette Ortega-Gómez[1,3], Abel Santamaría[1,3], Ismael Galve-Roperh[2,3]

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Keywords: Anandamide, Energy metabolism, Mitochondrial fission, PPARγ receptor

The mitochondrial network defines the cellular metabolic state and is crucial to meet energy demand while regulating oxidative stress and controlling survival signals. Hence the alteration of mitochondrial dynamics is one of the main characteristics of many neurodegenerative diseases associated with increased oxidative stress, excitotoxicity, and energy deficit. The transcriptional activity of the peroxisome proliferation-activated receptor gamma (PPARγ) play key roles in the regulation of mitochondrial dynamics and energy metabolism by interacting with its coactivator PGC1α. In this regard, it has been shown that endocannabinoid signaling can promote PPARγ transactivation, however, the mechanism associated with the activation of PPARγ receptors, mitochondrial biogenesis and neuroprotection remains poorly investigated.

This project aims to evaluate whether endocannabinoid system signaling through the PPARγ/PGC1α pathway can regulate mitochondrial biogenesis and mitochondrial dynamics exerting a neuroprotective action in neurodegenerative models. Primary cortical neuronal cultures derived from E14 mouse embryos were treated with the neurotoxins quinolinic acid and 3-nitropropionic acid generating a model that combines excitotoxicity and energy deficit, as observed in neurodegenerative diseases. Neurons were challenged with the acylethanolamines anandamide and oleamide that exerted a neuroprotective effect increasing cell viability. Pharmacological manipulation experiments with receptor antagonists indicate the involvement of PPARγ receptor in anandamide induced neuroprotection. Ongoing experiments evaluating anandamide-induced changes in mitochondrial dynamics, metabolic state, and mechanism of action will be presented.

COMUNICACIÓN ORAL 8

EXPLORING THE EFFECT OF LRRK2 G2019S MUTATION ON HUMAN DERIVED MICROGLIA AND MONOCYTES

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Keywords: microglia, monocytes, *LRRK2*, G2019S, lipid metabolism, transcriptomics

Parkinson's disease (PD) is the second most common neurodegenerative disease that causes motor and cognitive impairment. A number of loci have been identified to modify the risk, being variants in the *LRRK2* (Leucine-rich repeat kinase 2) gene the most common genetic cause of late-onset PD. LRRK2 codes for a ubiquitously expressed kinase and variants in the gene have been reported to alter its expression and activity in myeloid cells, although its exact function and contribution to the disease remains elusive. Given the role of LRRK2 in myeloid cells, our goal is to understand the transcriptional and functional effect of the G2019S variant (the most frequent mutation in *LRRK2*) in human derived microglia and monocytes. For this goal, we have generated large-scale transcriptomic profiles and functional validation of isogenic human induced microglial cells (iMGLs) and patient derived monocytes carrying the G2019S mutation under baseline culture conditions and following exposure to proinflammatory factors IFNγ and LPS. Our results demonstrate that the G2019S mutation does not confer transcriptional differences in untreated iMGLs or monocytes but elicits a profound impact on transcriptomic profile upon proinflammatory stimulation. Pathway analyses revealed that iMGLs carrying the G2019S mutation showed an upregulation in genes related to lipid metabolism and phagolysosomal pathways under LPS and IFNγ stimulation, which was accompanied by an increased phagocytic capacity. Among the downregulated genes in G2019S cells we observed the E2F transcription factor, which controls cell cycle and has been previously linked to PD. Patient derived monocytes carrying the G2019S mutation confirmed alteration in lipid metabolism associated genes. Altogether, these findings reveal that G2019S mutation profoundly affects gene expression in myeloid cells upon pro-inflammatory environment. Moreover, these results open the door to a crucial role of lipid homeostasis alteration as a pivotal factor contributing to the observed functional disturbances in myeloid cells harboring the G2019S mutation

COMUNICACIÓN ORAL 9

CB_1R UBIQUITINATION:TOWARDS AN UNDERSTANDING OF CANNABINOID TOLERANCE

Alicia Álvaro-Blázquez[1,2], Carlos Costas-Insua[1,2,3], Carlos Montero-Fernández[1,2], Alba Hermoso-López[1,2], Ignacio Rodríguez-Crespo[1,2,3], Manuel Guzmán[1,2,3]

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Keywords: *CB_1R, ubiquitination, tolerance*

Δ^9-Tetrahydrocannabinol (THC), the main psychoactive component of the plant *Cannabis sativa,* exerts a plethora of actions in the central nervous system mainly by engaging the type-1 cannabinoid receptor (CB_1R). Repeated administration of THC produces tolerance to most pharmacological effects in both animal models and humans, which is believed to rely on the downregulation of CB_1R. Ubiquitin-dependent degradation by the ubiquitin-proteasome system (UPS) is the major pathway controlling protein degradation in eukaryotic cells. Therefore, we asked whether CB_1R ubiquitin-dependent degradation contributes to the development of tolerance to THC. We show that CB_1R undergoes constitutive and agonist-induced ubiquitination in HEK293T cells. Pharmacological inhibition of the UPS or genetic mutation of either all the lysine residues (CB_1R-0K) or solely the eight cytoplasmic-facing ones (CB_1R-8KR) of CB_1R prevented agonist-induced receptor degradation. In mice, a 5-day sustained treatment with 10 mg/kg THC reduced CB_1R protein levels, which was prevented by co-administration of the proteasome inhibitor MG-132 in a brain region-specific manner. Co-treatment with MG-132 also prevented the development of tolerance to the hypokinetic, analgesic and cataleptic effects of THC. Altogether, our results highlight CB_1R ubiquitin-dependent degradation as a molecular mechanism contributing to the development of tolerance to THC.

COMUNICACIÓN ORAL 10

MODULACIÓN DE LA DINÁMICA MITOCONDRIAL POR LA PALIPERIDONA EN RATAS MACHO Y HEMBRA

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Keywords: mitofagia, fusion/fisión mitochondrial, biogenesis mitochondrial, paliperidona, neurodesarrollo

Abstract:

Estudios en pacientes y modelos animales de enfermedad psicótica revelan la presencia de un entorno pro-inflamatorio y un exceso de estrés oxidativo causado por daños a nivel celular. Las mitocondrias son orgánulos fundamentales y de naturaleza dinámica, ya que pueden fusionarse, dividirse o sintetizarse de novo. Alteraciones en las vías de reciclaje mitocondrial indican una homeostasis afectada. La prevención de este desequilibrio en la red mitocondrial podría contribuir a la terapia actual de las enfermedades neuropsiquiátricas.

Las acciones del antipsicótico paliperidona sobre la homeostasis mitocondrial no están estudiadas. Ante la emergente importancia de la mitocondria en enfermedad psiquiátrica, se plantea el análisis de su posible alteración en el modelo de estudio y modulación por la paliperidona.

Ratas Wistar macho y hembra fueron expuestas a dos estresores (deprivación materna y aislamiento social) en momentos clave del neurodesarrollo con la hipótesis de que “la paliperidona revierte, al menos parcialmente, los cambios en vías mitocondriales en la corteza frontal y el hipocampo inducidos por un modelo de alteración del neurodesarrollo” y se analizaron los niveles de expresión génica (RT-qPCR) y proteica (Western blot) de las proteínas implicadas en la fusión/fisión, biogénesis mitocondrial y mitofagia.

Los resultados muestran que en este modelo de alteración del neurodesarrollo la situación en diferentes regiones cerebrales varía. En la corteza frontal, predomina la síntesis de mitocondrias de novo, posiblemente por daños irreparables que haya sufrido el tejido y no hayan sido compensados por las mitocondrias existentes. En el hipocampo, con menos cambios, la balanza parece inclinada hacia el reciclaje de mitocondrias. La paliperidona ejerce efecto sólo en algunas proteínas de las vías estudiadas, por lo que la búsqueda de fármacos que puedan modular estas vías mitocondriales merece mayor investigación.

COMUNICACIÓN ORAL 11

EFECTOS DE LA SEÑALIZACIÓN CANNABINOIDE EN ALTERACIONES DE LA LAMINARIZACIÓN CORTICAL: SÍNDROME ASOCIADO A SATB2

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Keywords: corteza cerebral, neurodesarrollo, SAS, sistema endocannabinoide.

El sistema endocannabinoide (SEC) juega un importante papel regulador durante el neurodesarrollo prenatal. En particular, los receptores de cannabinoides CB1 regulan diferentes procesos entre los que se incluyen la migración y diferenciación de las neuronas piramidales de la corteza. Evidencias previas demuestran que alteraciones en el balance en la generación de neuronas piramidales de capas profundas y superficiales de la corteza pueden suponer uno de los mecanismos responsables para el desarrollo de
alteraciones neuropsiquiátricas. Entre ellas se incluye el síndrome asociado a SATB2 (SAS), caracterizado por retraso intelectual, características de trastornos del espectro autista (TEA). El SAS se produce por mutaciones en el locus del gen SATB2, un factor regulador de transcripción esencial para la especificación de las neuronas de proyección interhemisférica características de las capas superiores de la corteza. Por tanto, hipotetizamos que la regulación de la señalización cannabinoide mediante el antagonismo de los receptores CB1 en etapas prenatales podría corregir algunas de las alteraciones neuronales implicadas en la etiopatología del SAS y/o reducir algunos de sus síntomas.

Como primera aproximación experimental, hemos silenciado SATB2 en cultivos neuronales primarios de ratón mediante la nucleofección de plásmidos de expresión shSATB2 y shControl y hemos tratado estas células con SR141716 (SR1), antagonista de los receptores CB1. La aplicación de SR1 en estos cultivos parece ser capaz de recuperar parcialmente los niveles de SATB2 determinados por inmunofluorescencia en las células shSATB2, efecto que no se observa en las neuronas shControl.

También hemos electroporado los plásmidos shSATB2 en ratones en E14.5, el momento de máxima generación de neuronas de las capas superiores de la corteza, y hemos observado inicialmente que el silenciamiento de SATB2 interfiere con su migración radial.

Actualmente estamos analizando el efecto del tratamiento con SR1 (días E15 y E16) en embriones electroporados, para determinar el posible rescate de las alteraciones inducidas por el silenciamiento de SATB2 en la expresión de diferentes factores de transcripción, en la migración neuronal y en su arborización dendrítica.

COMUNICACIÓN ORAL 12

ASTROGLIAL MONOACYLGLICEROL LIPASE GENE INACTIVATION PREVENTS CNS DEMYELINATION

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Key words: demyelination, 2-arachidonylglycerol, monoacylglycerol lipase, oligodendrocyte

Demyelination is caused by the loss of the myelin sheath that surrounds the axons of neurons, which leads to an impaired transmission of the nerve signal. Previous studies have demonstrated that the endocannabinoid system can modulate the pathological process of demyelination. In particular, it has been shown that pharmacological blockade of the primary enzyme responsible for the degradation of the endocannabinoid 2-arachidonylglycerol (2-AG), monoacylglycerol lipase (MGL), can prevent myelin loss in animal models of demyelination. However, the cellular target of such pharmacological blockade responsible for the neuroprotective actions have never been identified.

To address this, we utilized the cuprizone animal model of demyelination and a mouse line with a selective deletion of the MGL gene in astrocytes. We found that deletion of astroglial MGL prevents oligodendrocyte cell death and myelin loss, and attenuates glial activation and axonal damage in the *corpus callosum* during cuprizone-induced demyelination. Therefore, astroglial MGL may represent a promising therapeutic target for the treatment of neurological disorders that suffer from oligodendrocyte dysfunction or myelin loss.

COMUNICACIÓN ORAL 13

TAU INHIBITS MITOCHONDRIAL CALCIUM EFFLUX AND MAKES NEURONS VULNERABLE TO CALCIUM-INDUCED CELL DEATH

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Keywords: Mitochondria, calcium, NCLX, tau, neurons, astrocytes, frontotemporal dementia

Tauopathies comprise a heterogeneous group of neurodegenerative disorders including Alzheimer's disease or frontotemporal dementia, in which aggregated tau protein is accumulated into neurofibrillary lesions. Although misfolded tau has strong familial and histopathological association with neurodegeneration, the cellular mechanisms of tau-induced pathology remain controversial. Importantly, the interplay between mitochondria and calcium signaling imbalance is often a hallmark in these and other neurodegenerative disorders. Beyond its role in bioenergetics, mitochondria are fine regulators of the cytosolic calcium homeostasis by rapidly buffering and shaping cytosolic calcium transients that modulate neuronal activity. However, when mitochondrial buffering capacity is compromised, such as by impaired calcium influx or efflux, it might become overloaded. Indeed, neuronal death is often triggered by a common downstream mechanism: the excessive accumulation of calcium in mitochondria.

We have recently described a new mechanism by which tau impairs the interplay between calcium and mitochondria. We employed as a model primary cortical neurons and astrocytes treated with extracellular tau protein and iPSC-derived neurons bearing the 10+16 mutation in MAPT gene -encoding tau- linked to frontotemporal dementia. We have shown that tau directly alters mitochondrial calcium homeostasis by inhibiting its efflux through the mitochondrial sodium/calcium exchanger NCLX both in neurons and astrocytes. This inhibition led to mitochondrial depolarisation in response to physiological and pathological cytosolic calcium stimuli, and made these cells more vulnerable to calcium-induced neuronal cell death.

Importantly, mitochondrial antioxidants were able to prevent excitotoxicity and caspase-3 activation triggered by mitochondrial calcium overload in all the models tested, thus pointing at new disease-modifying approaches to target calcium homeostasis.

COMUNICACIÓN ORAL 14

EXPLORING ALTERED PRIMARY MICROGLIA AND ASTROCYTES RESPONSES TO LPS FROM A TDP-43-RELATED FRONTOTEMPORAL DEMENTIA MOUSE MODEL: IMPLICATIONS FOR CANNABINOID MODULATION

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Keywords: Neuroinflammation, frontotemporal dementia, astrocytes, microglia, cannabinoids

Neuroinflammation, involving microglia and astrocyte activation, protects the central nervous system from harmful stimuli. However, prolonged inflammation contributes to neuronal death in various neurodegenerative disorders such as Parkinson's disease and amyotrophic lateral sclerosis. Yet, less is known about the role of neuroinflammation in the pathophysiology of frontotemporal dementia (FTD), a neurodegenerative disease characterized by degeneration in the frontal and temporal brain lobes, leading to
behavioral, cognitive, and language impairments.

To further investigate the contribution of neuroinflammation to FTD pathology, this study aims to characterize astrocytes and microglia from an FTD model. For this purpose, cortical primary microglia and astrocytes from CaMKII-TDP43 FTD mice pups were cultured to investigate their response to lipopolysaccharide (LPS 100 ng/ml), an inflammatory stimulus. Additionally, as we previously observed in the TDP43-FTD mouse model that cannabinoids reduced glial reactivity *in vivo*, we were interested in assessing the wellknown anti-inflammatory effect of cannabinoids in these FTD-glial cells and Investigating the mechanism of action involved in this response by using the non-selective CB1/CB2 receptors agonist, WIN 55212-2.

FTD-microglia displayed a differential response to LPS compared to WT counterparts, showing increased expression of pro and anti-inflammatory cytokines and inflammasome components such as NLRP3, as well as Toll-like receptor 4 (TLR-4), indicating heightened cell reactivity. Furthermore, FTD-microglia displayed alterations in some diseaseassociated microglia (DAM) markers under basal conditions, evidenced by a downregulation in Trem2 and Cx3cr1 expression, as well as in CB2 receptor, whose expression was also reduced compared to control cells. In contrast, FTD-astrocytes showed reduced reactivity to LPS stimulation, as evidenced by downregulated expression of pro-inflammatory cytokines, TLR-4, and glutamate transporter-1 compared to control cells. In addition, basal FTD-astrocytes exhibited downregulated expression of CB1 receptor.

Both types of glial cells, when pre-treated with WIN 55212-2, demonstrated a reduction in pro-inflammatory cytokines expression and nitrites production after LPS stimulus, confirming the anti-inflammatory potential of this compound in the glial cells of the FTD model. Further studies are needed to study the pathways involved in this effect.

In summary, FTD microglia and astrocytes exhibit altered responses to inflammatory stimulation, potentially contributing to FTD pathology. Modulating these responses with cannabinoids may represent a promising strategy for addressing this disorder

COMUNICACIÓN ORAL 15

MODULATION OF THE ENDOCANNABINOID SYSTEM AS A DISEASE-MODIFYING THERAPY FOR FRONTOTEMPORAL DEMENTIA

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The endocannabinoid system (ECS) is a cell-signaling system involved, among others, in the maintenance of neuronal homeostasis. The ECS becomes dysregulated in the CaMKII-TDP43, where TDP43 overexpression, which recapitulates FTD-like cognitive, social behavior, and emotional impairment, which were associated with relevant neurodegeneration and elevated glial reactivity in the medial prefrontal cortex (mPFC) and the hippocampus (HPC). ECS dysregulation is observed by an upregulation of the CB_1 receptor (CB_1R) in the mPFC and a downregulation of the fatty acid amide hydrolase (FAAH) enzyme in the mPFC and HPC. The upregulation of the anandamide-synthesizing enzyme NAPE-PLD is also upregulated in the HPC, resulting in an increased endocannabinoid tone, whose pharmacological enhancement has resulted in neuroprotective effects. Thus, we hypothesized that these effects are mediated by CB_1Rs and that their activation may be validated as a disease-modifying therapy. Presymptomatic CaMKII-TDP43 transgenic mice (PND45) were treated with the selective CB_1R agonist ACEA or vehicle for 45 days. Recognition memory was measured by the novel object recognition test (PND60 and PND90). Animals were euthanized (PND90), and brain hemispheres were processed for immunohistochemistry and biochemical analysis. The activation of CB_1Rs prevented the cognitive deficits of CaMKII-TDP43 mice, which was associated with the preservation of CA1 pyramidal neurons and reduced glial reactivity in the mPFC and HPC. Moreover, the activation of CB_1Rs stimulated the removal of TDP43 pathogenic species.

Additionally, we were interested in studying a possible dysregulation of the ECS in FTD, as observed in other neurodegenerative diseases, affecting its endogenous neuroprotective role, and then contributing to disease progression. Human sample cohorts included fixed and fresh-frozen *postmortem* samples of the frontal cortex (FC) and HPC from patients with TDP43 (n=5) or Tau pathology (n=5), and control cases (n=6). Once FTD-related alterations were confirmed, we studied the expression of CB_1Rs and FAAH enzyme by immunohistochemistry and western blot techniques, where we noticed a decrease in CB_1R and a subtle increase in FAAH immunoreactivity in patients' FC and hippocampal dentate gyrus compared to controls.

Our preclinical study validates the activation of CB_1Rs as a disease-modifying therapy against TDP43-induced neuropathology in FTD. Moreover, our ongoing work reveals the dysregulation of CB1Rs and FAAH enzyme in human *postmortem* samples of FTD patients, endorsing CB1Rs and FAAH enzyme as therapeutic targets for the treatment of FTD. These results suggest an association of the status of the ECS with FTD pathogenesis, and that pharmacological modulation of the ECS may open new therapeutic avenues for FTD that deserve further examination.

ABSTRACTS
SESIÓN DE POSTERS

PÓSTER 1

AHR DELETION REDUCES AMYLOID PLAQUE ACCUMULATION AND AXONAL DYSTROPHY IN THE APP^{NL-F} KNOCK-IN ALZHEIMER'S MOUSE MODEL

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Keywords:

Abstract: An interaction between intrinsic and environmental factors probably contributes to the molecular processes that drive Alzheimer Disease (AD). Although variation in specific genes increases the risk of AD, one of the main risk factors is age. However, how molecular processes of aging predispose to, or become deregulated in AD, still remains to be understood. Studies in different organisms from invertebrates to humans show that the Aryl Hydrocarbon Receptor (AhR), that integrates environmental stimuli (from pollutant to diet components with agonist properties) into transcriptional changes, is implicated in the aging process. Therefore, we decided to investigate the role of AhR in the development of age-associated neurodegeneration. To address this issue, we characterized the effect of AhR deletion and activation by specific agonists in the APP^{NL-F} knock-in mouse model of AD. First, we found that the expression of AhR increase in the APP^{NL-F} mouse with age and importantly, that this increase was mostly associated with astrocytes and microglia. Our data also demonstrated that AhR plays a deleterious role in AD since AhR deletion reduced amyloid plaque formation and plaque-associated dystrophic neurites. Correlation network analysis and functional enrichment from proteomic data identified a set of pathways associated with mitochondrial metabolism, neuron projection and synaptic vesicles among others. By the opposite and corroborating the key role of AhR in the AD development, we found that activation of AhR by the I3S agonist increased amyloid plaque formation and dystrophic neurites.
Therefore, we can conclude that AhR plays a pivotal role in the development and progression of AD and suggests that the AhR pathway and/or its modulation by exogenous or endogenous agonists can be explored for AD therapy.

PÓSTER 2

BACTERIAL TRANSLOCATION AFTER HEMORRHAGIC STROKE. DETECTION BY MRI, EFFECT OF HEMATOMA SIZE AND ITS INFLAMMATORY CONSEQUENCES.

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Keywords: Hemorrhagic Stroke, Bacterial Translocation, Inflammation, Poststroke infections

Abstract:
Background/aim: Hemorrhagic Stroke (HS) is one of the most devastating types of Cerebrovascular Disease. One of the most frequent complications after stroke is the development of infections. In this setting, it has been demonstrated only in ischemic stroke, gut barrier damage (GBD), bacterial translocation (BT), alterations in the immune response, processes that favor the occurrence of infections. In addition, the use of imaging techniques would be very useful to early detect these processes. Therefore, we explored the effect of the hematoma size in GBD/BT, their inflammatory consequences and we have developed a new MRI-protocol to detect these processes.
Methods: In naïve and at 72h in sham/HS two-months old male Wistar rats, we determined the GBD by T1W-images enhanced with mannitol+$MnCl_2$ as contrast agents (CA), hematoma volume in T2W-images, BT by microbiological culture and different immune cell populations by flow cytometry.
Results: Our results showed that the hematoma size determined the BT, by increasing this process from 62% of BT after moderate HS vs. 100% of BT after severe HS. Our GBD-MRI-protocol was able to detect CA extravasation inside the peritoneal cavity in the same animals that underwent BT. In addition, GBD/BT after HS altered the T, B lymphocytes and neutrophils populations in different organs.
Conclusions: Our study shows that the greater is the severity of HS, higher is the occurrence of GBD/BT and more altered is the immune response. Furthermore, our GBD-MRI protocol suggests that it would be very useful to detect this process early and noninvasively in stroke patients.

PÓSTER 3

EVALUATION OF DIFFERENT DOSES OF FENFLURAMINE TO REDUCE SEIZURES IN A MOUSE MODEL OF EPILEPSY INDUCED BY PTZ

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Keywords: Dravet syndrome, epilepsy, fenfluramine, PTZ Abstract:

Dravet syndrome (DS) is a rare form of infantile epileptic encephalopathy characterized by mutations in the SCN1A gene, responsible for encoding the α subunit of the voltage- dependent sodium channel Nav1.1. This genetic disorder is notorious for its association with febrile seizures that eventually evolve into severe tonic-clonic seizures, resulting in lifelong motor and cognitive impairments for affected individuals.

Recent advancements in medical research have brought forth a novel treatment option for DS: fenfluramine. This medication has received approval for its efficacy in reducing convulsions in DS patients. Fenfluramine exerts its therapeutic effects by modulating the serotoninergic system, leading to increased serotonin levels, which in turn play a pivotal role in managing seizures in DS.

The aim of our study was to determine the optimal dosage of fenfluramine for reducing epileptic seizures in a murine model of DS exposed to the proconvulsive agent pentylenetetrazole (PTZ). Once the optimal dose of fenfluramine has been selected, combination treatments with other drugs acting on different pharmacological targets will be explored in order to improve therapies for DS.

We administered PTZ to the mice, along with varying doses of fenfluramine (5, 7.5, and 10 mg/kg) via intraperitoneal injection. Subsequently, we conducted a battery of behavioural tests to evaluate the treatment's effectiveness.

Our findings revealed that the 7.5 mg/kg dosage exhibited the most promising anticonvulsant properties, striking a favourable balance between seizure suppression and hypolocomotion compared to the 10 mg/kg dose.

In summary, our study concluded that the 7.5 mg/kg dosage of fenfluramine is the most suitable for in vivo experiments involving a murine genetic model of DS. This dosage minimizes interference with behavioural test results while maximizing its potential therapeutic benefits in managing seizures associated with this debilitating condition. These results represent a significant step forward in the pursuit of more effective treatments for individuals grappling with DS.

PÓSTER 4

BIDIRECTIONAL MODULATION OF INHIBITORY TRANSMISSION BY mGluR7 AT CA1 PYRAMIDAL CELLS.

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Keywords: hippocampal synaptic transmission, synaptic vesicle docking, Munc 13-2 protein, *mGluR7*KO, epilepsy

mGluR7 is a G protein-coupled glutamate receptor located at the presynaptic active zone that modulates neurotransmitter release. Brief activation of mGluR7 with the agonist L-AP4 activates $G_{i/o}$ proteins and reduces neurotransmitter release blocking voltage-gated Ca^{2+} channels. It is also known that both prolonged activation with L-AP4 and the endogenous activation with high frequency stimulus (HFS) potentiate synaptic transmission at the Schaffer Collateral–CA1 synapses by a novel signaling pathway involving the Phospholipase C activation by a pertussis toxin-resistant G protein and the diacylglycerol mediated activation of synaptic vesicle docking by Munc13-2. Since mGluR7 is also expressed on GABAergic boutons, we studied its ability to bidirectionally modulate neurotransmitter release at GABAergic inputs on CA1 pyramidal cells.

Recording IPSCs from CA1 pyramidal cells induced by *Stratum Radiatum* stimulation, we have demonstrated that prolonged L-AP4 application causes an initial reduction followed by a potentiation of IPSC amplitude. As it occurred with excitatory synaptic transmission, the first inhibitory phase is sensitive to $G_{i/o}$ protein blocker Pertussis toxin, while the potentiation phase is abolished by DAG union blocker calphostin C. This response was accompanied by an increase in the coefficient of variation and in the frequency but not in the amplitude of miniature IPSCs as well as an increase of the synaptic vesicle docking, and was insensitive to AMPA and NMDA antagonists, confirming that it was mediated by direct mGluR7 activation at GABAergic boutons. We also found that endogenous activation of mGluR7 by HFS on Schaffer Collateral also potentiates GABAergic synaptic transmission and this response was absent in the presence of Group-III-mGluR antagonist, MSOP, of calphostin C and in slices from *mGluR7*KO mice. This novel role of mGluR7 in inhibitory transmission could be decisive to understand the regulation of neuronal excitability and pathological conditions such as epilepsy, where mGluR7 is a target for anticonvulsant drugs.

PÓSTER 5

MODULATION BY PACAP-38, HISTAMINE, AND SEROTONIN OF ADRENOMEDULLARY CATECHOLAMINE SECRETION IN A NEUROPATHIC PAIN MODEL

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Keywords: catecholamines, chromaffin cell, neuropathic pain, stress, histamine, PACAP-38, serotonin

Abstract: Neuropathic pain manifests as heightened sensitivity to painful stimuli (hyperalgesia) and nociceptive responses to non-painful stimuli (allodynia), The central pathophysiological mechanism underlying this condition is the dysfunction of the nociceptive nerve system. We have used a rat model of neuropathic pain consisting of the chronic constriction of the sciatic nerve (CCI), which gives rise to functional remodeling of channels and receptors involved in the excitation-secretion coupling of chromaffin cells from the adrenal medulla. This leads to an increased exocytotic response with augmented release of catecholamines to the bloodstream. To further investigate the molecular pathophysiology of this process, patch-clamp and amperometry techniques were used to study the effect of PACAP-38, histamine and serotonin on the catecholaminergic secretory response elicited by acetylcholine while evaluating possible changes in nAChRs and voltage-dependent sodium (Na_v), potassium (K_v), and calcium (Ca_v) channels. The results show, for histamine and serotonin, a differential modulation of Na_v, K_v, and Ca_v currents in chromaffin cells from CCI animals and Control ones, whereas PACAP-38 could modify currents through low voltage-activated (T-type) Ca_v channels in a neuropathy-independent manner.

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PÓSTER 6

EFFECT OF NEUTROPHIL CIRCADIAN RHYTHMS IN MOUSE ISCHEMIC STROKE

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Keywords: stroke, circadian rhythms, neutrophil, neuroinflammation

Abstract:

Ischemic stroke is a devastating disease that is currently the second leading cause of death worldwide and one of the most significant contributors to disability. Circadian rhythms are postulated as one of the possible causes responsible for the translational failures in most neuroprotective strategies under development. Due to the pivotal role played by neutrophils in the pathophysiology of this disease, our study investigated the circadian regulation of these immune cells, their phenotypic characterization, and their involvement in NETosis concerning susceptibility to cerebral ischemia. Our results suggest that the time of day at which the stroke occurs determines the infarct size in mice. Furthermore, circadian effects on stroke outcomes are eliminated with the use of the CXCR4 agonist ATI and also in BMAL KO mice, supporting the crucial role of neutrophils. Additionally, NETosis is implicated in infarct size after a stroke, being higher when the stroke occurs during the inactive period (ZT5) in mice. These findings could provide novel therapeutic and diagnostic targets, potentially explaining the lack of success in translating research findings into effective stroke clinical trials.

PÓSTER 7

NETosis IS INVOLVED IN CHRONIC POST-STROKE OUTCOME

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Keywords: stroke, neutrophile, NETosis, cognitive impairment, behaviour

Stroke is the second cause of death worldwide and a leading cause of chronic disability and cognitive deficits. Stroke causes a major inflammatory response, recruiting neutrophils to the insulted area. Neutrophils release their intracellular content, including their DNA accompanied by granular proteins in a web-like structure called Neutrophil Extracellular Traps (NETs). The release of NETs (known as NETosis) is linked to an increase in the infarcted volume, brain-blood barrier leakage, and worsen functional deficits in the acute phase of stroke. Here, we are exploring the effects of NETs on the functional recovery of animals two months after stroke.
Wild type C57BL/6, Dnase1$^{-/-}$Dnase1/3$^{-/-}$ (deficient in the enzyme responsible to break down NETs) and PAD4$^{-/-}$ mice (deficient in an enzyme key to the production of NETs) underwent the permanent occlusion of the middle cerebral artery (pMCAO) surgery. Infarct volume was measured by MRI after 24 hours. A battery of behavioural test was performed 60 days after stroke to assess changes in motor and sensory function, anxiety-like behaviour, and working and spatial memory.
Our results indicate on the one hand, that there were not significant differences in infarct volume among genotypes. On the other hand, we have shown that only the Dnase1$^{-/-}$Dnase1/3$^{-/-}$ isquemic mice exhibited a decline in sensory and motor ability, while all genotypes show a normal motor behaviour and they did not show differential anxiety-like behaviour. In addition, PAD4$^{-/-}$ ischemic mice showed a better performance in spatial memory compared to the rest of ischemic animals.
Overall, our results suggest that NETosis could be a potential factor affecting the recovery after stroke.

PÓSTER 8

EMBRYONIC CANNABINOID CB1 RECEPTOR KNOCKDOWN ALTERS THE NEUROGENIC GENE EXPRESSION PROGRAM AND FUNCTIONAL MATURATION OF PYRAMIDAL NEURONS

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Keywords: cortical development, gene expression program, neuronal differentiation, CB1 receptor, *in utero* electroporation, epileptic disorders

During embryonic development, a series of proliferation waves of neural stem cells and neuron precursor populations take place in spatiotemporally ordered manner. Progressive changes in the neurogenic program determine the specific differentiation, migration and neuronal maturation that will define the different projection neuronal populations fate and its characteristics of upper and deep cortical layers neurons. The endocannabinoid system (ECS) via CB1 receptor coordinates crucial steps of neurogenesis, hence disturbances by genetic alterations or exogenous prenatal cannabinoid exposure leads to alterations of long-range projection neurons and can contribute to developmental epilepsy and focal malformations. Acute prenatal silencing of CB1 cannabinoid receptors through the *in utero* electroporation (IUE) technique interferes the multipolar-bipolar neuronal transition required for radial migration, leads to ectopic delayed neurons with features resembling subcortical band heterotopias and increases seizure susceptibility in adulthood. Also, CB1 receptor regulates the signaling exerted by BCL11b/SATB2 transcription factors, whose balance favoring deep layer subcortical and subcerebral projection neuron development. To dissect the precise consequences of embryonic CB1 receptors silencing in deep layer neuronal development, we performed gene expression, electrophysiological patch clamp and behavioral analyses at different developmental times after electroporation of siCB1 and siControl constructs (E14.5 mouse embryos). FACS-sorting of GFP+ cells and microarray studies revealed changes in neurogenic transcriptomic program with conserved features of the described changes in intellectual disability and autism spectrum disorder. Neurons that migrate incorrectly were characterized by an altered firing pattern and less excitability compared to the control (siCB1 ectopic upper layer neurons located at L56 have smaller sag and lower firing rate compared to native L56 neurons). Finally, CB1 receptor embryonic knockdown induces changes in social interaction and hiperexcitability. These findings expand the knowledge of neurodevelopmental changes induced by prenatal interference with CB1 receptor that are essential in molecular and cellular mechanisms involved in cortical development and its implications in the etiopathology of neuropsychiatric and developmental epileptic disorders.

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PÓSTER 9

C9orf72 IN THE SPANISH ALS-FTD SPECTRUM

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Keywords: ALS, FTD, *C9orf72*, Expansion, Repeat-primed PCR

Background
Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) take part form a clinical, pathological and genetic continuum. Early detection of the *C9orf72* mutation may allow for earlier diagnosis of these diseases. Analysis of C9orf72 can identify patients and families at higher risk of developing these diseases.

Methodology
The study of GGGGCC repeat expansion in *C9orf72* included 1594 patients subdivided into 3 clinical groups: 1226 ALS patients, 201 ALS-FTD intermediate clinical patients, and 167 FTD patients. We performed a Repeat-Primed PCR with 6-FAM labeled primer which allows for quantification of each repeat up to approximately 100 repeats.

Results
The percentage of patients carrying the pathogenic expansion in *C9orf72* in the ALS group was 4.4%, 15.4% in the ALS-FTD group it was, and 5.4% in the FTD group. As expected, the majority percentage within each group came from the hereditary cases.

Discusion&Conclusion
The age of symptom onset is lower in groups with a family history, while survival is extended in these same groups. Patients with bulbar onset have a later disease onset and lower survival. The age of onset in C9+ patients in the ALS and ALS-FTD groups is higher than in other patients, most likely due to a higher number of patients with bulbar onset.

PÓSTER 10

LA QUINOLILNITRONA QN6 COMO AGENTE ÚNICO Y MULTIVALENTE PARA LA TERAPIA DEL ICTUS Y LAS ENFERMEDADES NEURODEGENERATIVAS

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Keywords: Enfermedades neurodegenerativas, Ictus, Isquemia cerebral, Neuroprotección, Nitronas.

Recientemente, se ha identificado el óxido de (Z)-N-bencil-1-(8-hidroxiquinolin-2-il)metanimina (**QN6**) como un potente inhibidor de la hBuChE (IC_{50} = 1,06 ± 0,31 nM) y de la hMAO-B (IC_{50} = 4,46 ± 0,18 µM), que presenta propiedades antioxidantes, actúa como quelante biometálico, es capaz de atravesar la barrera hematoencefálica y carece de citotoxicidad[1]. **QN6** también demostró efectos neuroprotectores en un modelo celular de 6-hidroxidopamina de la enfermedad de Parkinson y exhibió propiedades antiamnésicas en el modelo de ratón inducido por escopolamina de la enfermedad de Alzheimer[1]. Además, el tratamiento crónico de ratones doblemente transgénicos APPswe-PS1δE9 con **QN6** redujo la acumulación de placas amiloides en el hipocampo y la corteza cerebral[1].
En este trabajo se describe el potencial neuroprotector y antioxidante de **QN6** en la terapia del ictus. Estudios *in vitro* con un modelo de isquemia cerebral por privación de oxígeno y glucosa en células de neuroblastoma humano demostraron la potente capacidad neuroprotectora de **QN6**, que es capaz de preservar la actividad metabólica neuronal (EC_{50} = 3,97 ± 0,78 µM) y previene la muerte celular necrótica (EC_{50} = 3,79 ± 0,83 µM) y apoptótica (EC_{50} = 3,99 ± 0,21 µM)[2]. **QN6** también mostró una notable capacidad para disminuir la producción de anión superóxido (EC_{50} = 3,94 ± 0,76 µM)[2].
Además, en un modelo experimental de isquemia focal permanente, el tratamiento con **QN6** produjo una reducción significativa (75,21 ± 5,31%) del volumen de la lesión cerebral[2].
En conjunto, los hallazgos colectivos de las investigaciones previas y actuales subrayan que **QN6** es un agente terapéutico único y multivalente con potenciales aplicaciones en el tratamiento combinado de enfermedades neurodegenerativas y neurovasculares.

1. Knez D. et al. 8- Hydroxyquinolylnitrones as multifunctional ligands for the therapy of neurodegenerative diseases, Acta Pharmaceutica Sinica B, 2023, 13(5): 2152-2175. (https://doi.org/10.1016/j.apsb.2023.01.013).
2. Chamorro B. et al. Neuroprotective and antioxidant properties of new quinolylnitrones in in vitro and in vivo cerebral ischemia models. Sci Rep. 2023, 13, 2865. (https://doi.org/10.1038/s41598-023-29929-7).

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