Poster Session 1: Wednesday, 3rd November, From 15:30 To 19:00, Exhibition Hall.

PS1-01

Netrin-1/DCC Signaling System Differentially Regulates the Migration of Pax7, Nkx6.1, Irx2, Otp, and Otx2 Neuronal Populations in the Developing Interpeduncular Nucleus

Ms. Isabel M. García-Guillén[1], Dr. Antonia Alonso[1], Dr. Nicanor Morales-Delgado[2], Ms. Belén Andrés[3], Dr. Luis Puelles[1], Dr. Guillermina López-Bendito[3], Dr. Faustino Marín[1], Dr. Pilar Aroca[1]
[1]Universidad de Murcia, Murcia, Spain, [2]Universidad Miguel Hernández, Alicante, Spain, [3]Instituto de Neurociencias de Alicante, CSIC, Universidad Miguel Hernández, Alicante, Spain

The interpeduncular nucleus (IPN) is a hindbrain structure highly conserved among vertebrates. It is formed by three main subdivisions, the prodromal (Pro) domain located at the isthmus (Ist), and the rostral and caudal interpeduncular domains (IPR, IPC) within rhombomere 1 (r1). Various cell populations can be detected in the IPN through the expression of the Nkx6.1, Otp, Otx2, Pax7, and/or Irx2 transcription factors. These cell populations follow independent dorsoventral tangential and radial migratory routes targeting the ventral paramedian region of Ist and r1. Here we set out to examine the influence of the Netrin-1/DCC system on these migrations, since it is known to regulate other processes of neuronal migration in the brain. To this end, we analyzed IPN development in late gestational wild-type and DCC null mice, using mainly in situ hybridization (ISH) to identify the cells expressing each of the aforementioned genes. We found that the migration of Nkx6.1+ and Irx2+ cells into the Pro domain was strongly disrupted by the loss of DCC, as occurred with the migration of Pax7+, Irx2+, and Otp+ cells that would normally form the IPR. In addition, there was mild impairment of the migration of the Pax7+ and Otx2+ cells that form the IPC. These results demonstrate that the Netrin-1/DCC signaling pathway is involved in the migration of most of the IPN populations, mainly affecting those of the Pro and IPR domains of this nucleus. There are psychiatric disorders that involve the medial habenula (mHb)-IPN system, so that this experimental model could provide a basis to study their neurodevelopmental etiology.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-02

Characterization of different types of progenitor cells in the postnatal retina of sharks

Mr. Ismael Hernández Núñez[1], Dr. Alberto Docampo Seara[1], Dr. Diego Robledo[2], Dr. Sylvie Mazan[3], Dr. Antón Barreiro Iglesias[1], Dr. Fátima Adrio[1], Dr. Eva Candal[1]

[1]Universidade de Santiago de Compostela. CIBUS. Faculty of Biology., Santiago de Compostela, Spain, [2]The Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh, Edinburgh, United Kingdom, [3]CNRS, Sorbonne Université, UPMC Univ Paris 06, UMR7232, Observatoire Océanologique , Banyuls-sur-mer, France

Neurogenesis is the process by which progenitor cells persistently generate new neurons from neural progenitor cells (NPCs). Postnatal NPCs reside within well-defined neurogenic niches in the brain, which in mammals contain relatively quiescent radial glia-like progenitor cells (RGCs), transient intermediate progenitor cells (IPCs), and neuroblasts that subsequently differentiate into neurons. The study of the evolution of postnatal NPCs has gained significance, since they amplify the number of generated neurons and allow for the diversification of neuronal cell types. However, much of our understanding in this field is based in studies on mammals and zebrafish, a modern bony fish. The use of the cartilaginous fish Scyliorhinus canicula as a model expands the evolutionary scenario to a representative species of basal gnathostomes that shows significant neurogenic activity in the postnatal nervous system. In particular, the ciliary marginal zone (CMZ) of the retina constitutes an interesting neurogenic niche to identify different types of progenitors, since cells at different stages of commitment are spatially ordered from the most peripheral CMZ (where NPCs lie) to the central retina (comprised of differentiated cells). In this work, we have characterized different types of progenitors in the CMZ of juveniles by analysing the expression pattern of proliferation markers (proliferating cell nuclear antigen and phosphohistone-H3), a stem cell marker (ScSox2), glial markers usually found in RGCs (brain lipid-binding protein and the glial fibrillary acidic protein), the typical marker of IPCs ScTbr2 and markers of neuroblasts (doublecortin). By analysing their combined expression in the peripheral retina of juveniles, we identified the different types of NPCs (RGCs, IPCs and neuroblasts) previously described in mammalian brain neurogenic niches, which contributes to foster our knowledge about the evolution of postnatal neurogenesis in vertebrates.

Supported by Spanish MICINN grant BFU2017-89861-P and Xunta de Galicia Predoctoral Fellowship (IHN-ED481A-2018/216), both part-financed by the European Social Fund.

PS1-03

Neurogranin-like expression in the zebrafish brain during early stages of development and changes induced by Mn2+ exposure

Ms. Anabel Alba-González[1], Dr. Julián Yáñez-Sánchez[1], Dra. Mónica Folgueira-Otero[1]
[1]*Univerisity of A Coruña (CICA), A Coruña, Spain*

Neurogranin (Nrgn) is a small peptide that seems to participate in neuroplasticity through, at least, interactions with calmodulin and Protein Kinase C (PKC) phosphorylation. Altered levels of Nrgn correlate with cognitive decline in aging and neurodegenerative disorders such as Parkinson or Alzheimer's disease. In this study, we determine the distribution of Nrgn in the brain of zebrafish (Danio rerio) embryos and larvae by using a polyclonal antibody (AB5620, Merk-Millipore). As a first approach to understand how Nrgn levels are affected in neurodegenerative diseases, we analysed its expression after exposure to Mn2+, a cation that can lead to Parkinsonism. Immunocytochemistry analysis showed that Nrgn expression is first observed by 2 days post fertilization and is maintained throughout adulthood. By 6dpf, Nrgn expression is observed in the telencephalon (olfactory bulbs and pallium), diencephalon (pineal, preoptic area, posterior tubercle, hypothalamus, and adenohypophysis), optic tectum, medulla oblongata and spinal cord. Zebrafish embryos exposed to a sublethal concentration of manganese dichloride (500 µM) from 2.5 to 120 hours post fertilization (hpf) show a significant decrease in Ngrn expression compared to controls. This includes a very strong reduction in the olfactory bulbs and pallium. Shorter exposure (from 2.5 to 48 hpf) to the same concentration of manganese dichloride rescues by 5dpf Nrgn expression to control levels. These results suggest there is Mn2+ mediated cytotoxicity in the zebrafish olfactory system, as described previously in humans and other vertebrates, affecting Nrgn expression. Further studies will be necessary to characterize in more detail Mn2+ cytoxicity and its direct or indirect role on neurogranin levels.
AA-G is supported by the Xunta de Galicia and the European Union through a predoctoral fellowship.

PS1-04

Intramodal functional plasticity in the developing somatosensory system

Ms. Mar Aníbal-Martínez[1], Mr. Luis Rodríguez-Malmierca[1], Mr. Francisco José Martini[1], Ms. Guillermina López-Bendito[1]

[1]*Instituto De Neurociencias De Alicante. Universidad Miguel Hernández de Elche-CSIC, San Juan De Alicante, Spain*

Sensory systems are represented in the primary sensory areas of the brain, organized in anatomical and functional maps. Understanding how the brain adapts to the sensory loss might help us to better decipher the role of intrinsic and extrinsic mechanisms involved in cortical maps development. A paradigm extensively used to unravel the role of the afferent input during the development of the cortex is the deprivation of one sensory modality, which leads to an adaptive reorganization of the deprived and non-deprived sensory circuits. We are interested in understanding the mechanisms that trigger the establishment of territories during sensory systems development. To this end, we developed a mouse model in which whisker pad is cauterized unilaterally at the embryo stage (embWPC) to induce changes in the territories representing the distinct body sensory maps. These mice showed an intra-modal enlargement of the antero-lateral barrel subfield (ALBSF) area both in the thalamus and primary somatosensory cortex (S1) before the onset of sensory experience. Furthermore, dye tracing studies and in vivo calcium imaging in the embWPC mice showed severe structural changes of the somatosensory point-to-point axonal topography from embryonical stages suggesting that prenatal whiskers deprivation, before experience-dependent activity, induces functional rearrangements within a critical window. Finally, blockade of the patterned spontaneous activity in the thalamus of the embWPC mice revealed that these reorganizations of sensory territories are independent of thalamic activity. In sum, our results showed that the territories and sensory maps designated to distinct peripheral representations within a sensory system rely on prenatal mechanisms that are mainly based on axonal competition rules while patterns of spontaneous activity would play a crucial role in their later refinement.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-05

APOE genotype and postnatal chlorpyrifos exposure affect mice cerebral lipid profile

Dra. Laia Guardia-Escote[1], Ms. Judit Biosca-Brull[1,2], Ms. Mikaela Mladenova-Koleva[1], Dra. Pia Basaure[1], Dr. Jordi Blanco[1,3], Dra. Maria Cabré[1,4]

[1]Universitat Rovira i Virgili, Research in Neurobehavior and Health (NEUROLAB), Tarragona, Spain, [2]Universitat Rovira i Virgili, Psychology, Research Center for Behavioral Assessment (CRAMC), Tarragona, Spain, [3]Universitat Rovira i Virgili, Basic Medical Science, Reus, Spain, [4]Universitat Rovira i Virgili, Biochemistry and Biotechnology, Reus, Spain

The brain is an organ rich in lipids, which requires different lipid molecules for its proper development and maturation. Lipids are involved in both structural and functional roles, including signaling in the brain. Apolipoprotein E (APOE) is important for the distribution of lipids and its different isoforms may lead to differences in lipid content in brain. In addition, the different isoforms of APOE confer different vulnerabilities to the toxic effects of the pesticide chlorpyrifos (CPF) that impact the brain, during development. The aim of this study was to assess the differences in the cerebral lipidic content depending on the APOE genotype and early exposure to CPF. We used C57BL/6, apoE3- and apoE4-TR male mice, which were orally exposed to 1 mg/kg/day of CPF from postnatal day (PND) 10 to 15, whereas the control group was exposed to the vehicle (corn oil). Four hours after treatment, at PND 15, mice were sacrificed and the whole brain dissected to study the cerebral lipidome by means of LC-MS. Our results showed that lactating mice presented differences in the lipid profile of the brain depending on APOE genotype. General screening showed differences between genotypes in some cholesteryl esters, diglycerides, lysophosphocholines, phosphatidylcholines, sphingomyelin and triglycerides. General treatment effects and some genotype x treatment interactions were also observed. Differences in lipid profile present during the developmental period could explain some functional and maturation variances between genotypes, which are present at very early ages. Overall, this study provides more information on the relationship between the APOE genotype and the brain lipid composition.

PS1-06

The development of the cerebello-cortical connectivity

Ms. Raquel Murcia-Ramón[1], Ms Belén Andrés[1], Dra Guillermina López-Bendito[1], Dr. Juan Antonio Moreno-Bravo[1]

[1]*Instituto De Neurociencias, San Juan De Alicante, Spain*

Classically, the cerebellum has been considered a pure motor brain structure. However, mounting evidence has suggested that it also has essential contributions to nonmotor functions, such as cognition and emotion. The cerebellum is well poised to contribute to these complex behaviors because it is connected with the cerebral cortex which controls these functions. In addition, the cerebellum receives afferent input from the cerebral cortex through the pons. The closed-loop circuits between these two regions is the anatomical substrate by which the cerebellum could modulate the activity pattern of distal cortical regions.

Importantly, early abnormalities of these circuits have been related with different neurodevelopmental disorders, such as autism spectrum disorders. Thus, understanding how the cerebello-thalamo-cortical pathway develops is the initial step to understanding the cerebellar contribution to high-order neurodevelopmental disorders.

Here we have developed diverse in utero strategies to specifically target the cerebellum and its long-range projections. This approach, together with tissue clearing methods and 3D light-sheet microscopy, has allowed us to study the development of cerebellar connectivity in three-dimensions.

The data shows that cerebellar axons invade the contralateral thalamus as early as embryonic day (E)17. At E18, these axons target multiple motor and non-motor thalamic nuclei. Strikingly, at postnatal stages, the cerebellar axons recross the thalamic midline to innervate the ipsilateral thalamus.

This broad innervation suggests a potential bilateral influence of the cerebellum over immature motor and non-motor thalamocortical networks. Hence, we have stablished the anatomical basis by which the cerebellum could impact the development and/or function of cortical circuits.

PS1-07

Motor Neuronal Conversion of Human Mesenchymal Stem Cells by Application of Small Molecules

Mr. Antonio Almenar[1], Ms. Alicia Estirado[1], Ms. Francisca Almagro[1], Dr. Salvador Martínez[1]
[1]*Instituto De Neurociencias-CSIC-UMH, Alicante, Spain*

Mesenchymal Stem Cells are a good alternative to the induced pluripotent Stem Cells in different areas of developmental biology as well as in translational medicine. Its easy extraction, manipulation and maintenance, no teratoma risk transplantation or beneficial properties (immunomodulatory) after the transplantation are some examples of the advantages of its usage.

Apart from the mentioned properties, mesenchymal stem cells are able to produce non-classical differentiation processes. One important differentiation trajectory observed in mesenchymal stem cells is a general neuronal differentiation which could produce neuron-like cell types.

In this study we try to extend this idea, and see whether the manipulation of the differentiation process of mesenchymal stem cells derived from adipose tissue by the application of cocktail of different small molecules (without genetic manipulation) could open the possibility of formation of motor neuron-like cell types. Furthermore, we analyse whether this non-classical differentiation could be useful to produce a cellular model to study Amyotrophic Lateral Sclerosis.

Our results based on the analysis by immunofluorescence and quantitative PCR of different specific markers point to the idea that: first, the conversion to motor neuronal-like progenitors is possible starting from mesenchymal stem cells by the application of a sequence of cocktails of different small molecules. And second, that further analysis should be made to confirm its application for the production of a cellular model of Amyotrophic Lateral Sclerosis.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-08

CHARACTERIZATION OF THE PARALAMINAR NUCLEUS IN THE MICE: AN AMYGDALAR REGION WITH PROTRACTED MATURATION

Ms. Lucía Inés Torrijos Saiz[1], Dr. Vicente Herranz Pérez[1], Dr. Shawn Sorrells[2], Professor Jose Manuel García Verdugo[1]

[1]Instituto Cavanilles De Biodiversidad Y Biología Evolutiva, University Of Valencia-CIBERNED, Valencia, Spain, [2]University Of Pittsburgh, Pittsburgh, United States Of America

The paralaminar nucleus (PL) is a region located in the ventral amygdala which has been little studied and whose cells in humans and non-human primates show a late maturation profile. Despite its heterogeneous composition, a large population of cells in the PL present simple morphology, dense clustering, and expression of the microtubule-associated protein doublecortin (DCX) and PSA-NCAM, both markers of immature neurons. Since the PL has been described in several species, including the rat, our main hypothesis is the existence of a homologous region to the PL in the mice brain, a species with no evidence in the matter.

In this work, we studied the cellular dynamics of the PL during four stages of postnatal development in C57BL6 mice (P7, P14, P21 and P28). First, we delimited its anatomical localization by Cresyl violet staining in sagittal brain sections and we characterized the PL cell populations by immunohistochemistry against several molecular markers. The ultrastructural characteristics of the PL cells were studied by transmission electron microscopy and pre-embedding immuno-gold for DCX.

Our results indicate that, in mice, the PL is a discrete region of the amygdala and extends in a frontal-posterior direction as dense clusters of small cells around the basolateral amygdala. It is characterized by the presence of neurons in different maturational stages in juvenile individuals. Ultrastructurally most of DCX+ cells located in the PL presented immature morphology, with compacted heterochromatin and reduced cytoplasmatic volume. However, we found low expression of DCX in bigger neurons with a more developed cytoplasm, suggesting an active maturation process of these cells.

In conclusion, the presence of immature DCX+ cells in the PL of mice which mature at juvenile postnatal stages supports the idea that protracted maturation could provide neuronal plasticity at an important time in the development of the amygdala.

PS1-09

Deregulation of the epithelial-to-mesenchymal transition process underlies Zic2-linked holoprosencephaly

Dra. Aida Giner de Gracia, Dra. Cruz Morenilla, Ms. Maria Teresa López-Cascales, Dr. Gerald Muça, Dr. Angel Barco, Dra. Eloisa Herrera
[1]*Instituto De Neurociencias, Alicante, Spain*

Holoprosencephaly (HPE) is a congenital brain malformation resulting from incomplete separation of the two hemispheres. Mutations in the Zic2 gene cause holoprosencephaly type 5, but the mechanisms that translate Zic2 mutations into this devastating pathology remain unclear. Here, we report that Zic2 is expressed in a few epiblast cells during gastrulation to become transiently upregulated in the primitive streak. Later, during neurulation, Zic2 is re-expressed in neural crest cells and downregulated as they delaminate from the neural tube. In combination with transcriptomic data from mutant embryos, chromatin occupancy profiles in gastrula and neural crest cells reveal that Zic2 regulates a large number of genes associated with the Wnt, cadherin and TGF-β pathways. In proliferating cells exposed to Wnt, Zic2 prevents the translocation of β-catenin to the nucleus, subsequently accumulating in the cytoplasm. This blocks activation of the canonical pathway inducing a non-canonical Wnt response necessary to initiate EMT. Our results elucidate the role of Zic2 in early development and provide an explanation for the wide variety of developmental alterations in HPE5 patients that, unlike other HPE patients, include many other mesoderm-derived defects.
Altogether, these analyses identify cell types, signaling cascades, and genomic regions implicated in the etiology of Zic2-linked neurodevelopmental disorders.

PS1-10

The transcription factor Zic2 participates in adult neurogenesis at the hippocampal subgranular zone (SGZ)

Dr. Carlos Sanchez Huertas[1], Ivan Guzman[1], Prof. Eloisa Herrera[1]
[1]*Instituto de Neurociencias (CSIC-UMH), Alicante , Spain*

Neurogenesis is the process whereby new postmitotic neurons are produced by neural progenitors during the formation and maturation of the nervous system. In the adult mouse, neurogenic process is largely restricted to discrete brain regions, such as the subgranular zone (SGZ) of the hippocampal dentate gyrus, and plays a key role in brain function. Adult neurogenesis in the SGZ generates new cohorts of granular neurons, which contribute to learning and memory events, and a malfunction of this process has been associated to depression or epilepsy. It is known that the Wnt signaling pathway is an important regulator of adult neurogenesis in mice, but the cellular and molecular mechanisms driving neuron generation in adult brain still remain obscure. The transcription factor Zic2, formerly identified as a neuron-intrinsic axon guidance regulator during retinothalamic circuit development, is expressed in neurogenic niches of the adult brain and was recently described to modulate the Wnt-β-catenin signaling pathway. We found that Zic2 is expressed in the radial glia-like (RGL) progenitors of the SGZ. In particular, we uncovered that Zic2 specifically localizes to quiescent RGLs. Following Zic2 overexpression in adult neural progenitors, we observed a decreased proliferation in the hippocampal SGZ, marked with Ki67 and BrdU labelling. Conversely, the downregulation of Zic2 led to an increase in intermediate type2a progenitors in the SGZ, labelled by Ascl1. These results suggest that Zic2 acts as a regulator of the transitions between quiescence and proliferation in the RGL progenitors. Our data support a possible role of Zic2 in the acquisition and maintenance of quiescence in adult neural stem cells.

PS1-11

IMPLICATION OF SFRP1 IN ALTERED SYNAPTIC PLASTICITY ASSOCIATED WITH ALZHEIMER'S DISEASE

Ms. Guadalupe Pereyra Gómez[1], Dr. Inés Mateo Ruiz[1], Ms. María Jesús Martín Bermejo[1], Mr. Jose María Delgado-García[2], Ms. Pilar Esteve[1,3], Ms. Paola Bovolenta[1,3]

[1]Centro de Biología Molecular Severo Ochoa, UAM-CSIC, Madrid, Spain, [2]Universidad Pablo de Olavide, Sevilla, Spain, [3]Centro de Investigación Biomédica en Red de Enfermedades Raras, CIBERER, Madrid, Spain

We have demonstrated that SFRP1 is a novel, promising therapeutic target for Alzheimer Disease (AD). SFRP1 acts as a secreted endogenous regulator of ADAM10, a brain α-sheddase, which controls the activity of several substrates including APP and proteins regulating synaptic plasticity and neuroinflammatory crosstalk. Astrocyte-derived SFRP1 is upregulated in the brain of AD patients, localizing to amyloid plaques and interacting to Aβ peptides. Neutralization of Sfrp1 activity in AD-like mouse models decreases the formation of Aβ peptides, counteracts brain inflammation and maintains synaptic plasticity. Here we aimed at determining if Sfrp1 has a direct effect on synaptic plasticity.

We generated a transgenic mouse model overexpressing Sfrp1 in astrocytes (GFAP-tTA;TRE-Sfrp1) and analysed it by immunohistochemistry and RT-qPCR to determine the possible presence of neuroinflammatory and molecular alterations. Mice were further characterized for cognitive abilities with behavioural tests and analysed for possible dendritic and spine modification via viral-mediated visualization of their morphology.

We show that GFAP-tTA;TRE-Sfrp1 mice present an allele-dependent increase in Sfrp1 expression, which is associated with a decrease in dendritic and spine density already at two months of age. These defects are associated with an age-dependent appearance of cognitive decline and alterations in LTP.

Our data support the idea that Sfrp1 has a direct impact on synaptic plasticity which is not secondary to its effect on APP processing, indicating that it might have a pleiotropic effect in AD.

PS1-12

HYPERAMMONEMIA ALTERS THE FUNCTION OF AMPA, NMDA AND GABAA RECEPTORS AND EXTRACELLULAR cGMP REVERSES SOME OF THESE ALTERATIONS

Ms. María Sancho-Alonso[1], Dr. Vicent Teruel[2], Dr. Andrea Cabrera-Pastor[3], Dr. Vicente Felipo[1]

[1]Neurobiology Laboratory, Centro De Investigación Príncipe Felipe, Valencia, Spain, [2]Neuronal Circuits Laboratory, Universidad de Valencia, Valencia, Spain, [3]Neurological Impairment Group - INCLIVA, Valencia, Spain

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome caused by liver disease. Liver failure leads to hyperammonemia (HA) and inflammation, which act synergistically to induce neuroinflammation which alters neurotransmission leading cognitive and motor impairment. Extracellular cGMP levels are decreased in the hippocampus of hyperammonemic rats and increasing extracellular cGMP to normal levels normalizes neuroinflammation and cognitive and motor impairment, through the modulation of membrane expression of some glutamate and GABA receptor subunits. However, the effect of HA and extracellular cGMP on the function of these receptors are not known. The aim of this work was to analyze the function of AMPA, NMDA and GABAA receptors in the hippocampus of rats with chronic HA, and assess if extracellular cGMP modulates their function. Rats were sacrificed after four-five weeks of ammonium rich diet and we obtained transversal hippocampal slices. The MEA2100-system was used for postsynaptic Input-Output (I/O) curve recordings in the Schäffer Collaterals. One of the 120 available planar microelectrodes was selected in the distal part of CA1/CA3 border for tetanic stimulation. The recording electrode was in CA1 area. We perfused the slices with ACSF or with ACSF with different inhibitors (CNQX, AP5 and picrotoxin) to analyse the contribution of AMPA, NMDA and GABAA receptors to I/O curves separately. To assess the effect of extracellular cGMP, hippocampal slices were perfused with solutions containing or not extracellular cGMP. We analysed the effect of HA and extracellular cGMP on different parameter of the I/O curves at different times and stimulation intensities. The results show that HA reduces the function of AMPA receptors and results in a hyperfunctionality of NMDA and GABAA receptors. Extracellular cGMP reverses some of these alterations.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-13

EARLY SYNAPTIC IMPAIRMENT IN THE HIPPOCAMPUS OF A RAT MODEL OF PROGRESSIVE PARKINSONISM

Arantzazu Belloso-Iguerategui[1], Marta Zamarbide-Gónzalez[1], Leyre Merino-Galan[1], Aleph Prieto[2], Carl W Cotman[2], Joaquín Fernández-Irigoyen[3], Enrique Santamaría-Martínez[3], Ana Quiroga-Varela[1,5], María Cruz Rodríguez-Oroz[4,5]

[1]CIMA-Universidad de Navarra, Pamplona, Spain, [2]Institute for Memory Impairments and Neurological Disorders, University of California-Irvine, Irvine, USA, [3]Centro de Investigación Biomédica Navarrabiomed, Pamplona, Spain, [4]Clínica Universidad de Navarra, Pamplona, Spain, [5]Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain

The loss of dopaminergic neurons and the aggregation of α-synuclein in intracytoplasmic Lewy bodies are key pathological features of Parkinson´s disease (PD). Although considered a predominantly motor disorder, PD patients often present non-motor signs, which could be related to alterations in limbic brain regions. The aim of our study was to evaluate synaptic plasticity and differential protein expression in the main limbic nucleus, the hippocampus, at different time-points in the neurodegenerative progress using an animal model of progressive parkinsonism. Rats were inoculated in the substantia nigra compacta with an adeno-associated viral vector coding for A53T mutated human α-synuclein (AAV-hαsyn) or empty viral vector as a control group (AAV-EVV), and evaluated at 1-, 2-, 4-, and 16-weeks post inoculation (p.i.). Synaptosomes were isolated from hippocampus and synaptic plasticity was evaluated by chemical stimulation of long-term potentiation (cLTP), double-staining of postsynaptic-GluA1 and presynaptic-Neurexin1β, and flow cytometry analysis, whereas protein expression was assessed by SWATH-MS proteomics. The effect of pramipexole and L-DOPA on cLTP were also tested. In the AAV-hαsyn group, a significant inhibition of cLTP was observed since 1w p.i. ($p<0.01$) coinciding with the presence of hαsyn in midbrain, confirmed by western blot. Incubation with pramipexole showed a recovery of cLTP in AAV-hαsyn group at all time points ($p<0.05$), whereas L-DOPA only recovered cLTP at 4 weeks p.i. ($p<0.05$). Of note, pramipexole partially inhibited hippocampal cLTP in AAV-EVV animals ($p<0.05$). The proteomic study identified a total of 7958 proteins, of which 131 were statistically differentially expressed in the AAV-hαsyn group (58 up-regulated, 73 down-regulated). Bioinformatic analysis revealed alterations related to synaptic structure and transport at early time-points, and related to membrane potential and plasticity at later time-points. Our results indicate that hαsyn impairs synaptic function and structure in the hippocampus of parkinsonian rats, which could be functionally recovered by dopaminergic treatment.

PS1-14

Astrocytes exert negative modulation on hippocampal neuron excitability

Ms. Sara Expósito Reguero[1], Mr. Samuel Alberquilla[1], PhD Rosario Moratalla[1], Mr. Alfonso Araque[1], Mr. Eduardo D. Martín[1]
[1]*Instituto Cajal, CSIC, Madrid, Spain*

Neuronal firing is the essential element of neuronal networks as action potentials are the end product of synaptic integration. Therefore, brain neurons adjust their intrinsic membrane excitability to maintain the firing rate within their own optimal operational range. A principal homeostatic factor of neuronal excitability in the mammalian hippocampus is the postburst afterhyperpolarization (AHP). AHP exerts a negative control predominantly through a Ca2+-dependant K+-current that contributes to the slow AHP (sIAHP) responsible for the spike-frequency adaptation, and can be dynamically influenced by neuronal modulators. Accumulating evidence indicates that astrocytes respond to neurotransmitters released by synaptic terminals and-modulate neuronal activity and synaptic transmission through the release of gliotransmitters. However, little is known about the direct effect of astrocyte signalling on neuronal intrinsic properties and the excitability of neuronal networks beyond synapses. To address this issue, we used electrophysiological and Ca2+ imaging techniques in mouse hippocampal slices, as well as chemogenetic, electric and optogenetic stimulation of astrocytes and/or GABAergic interneurons. We saw that chemogenetic stimulation of astrocytes with Clozapine-N-oxide (CNO) in CA1 hippocampal region decreases pyramidal neuron excitability through increasing sIAHP and the reduction of action potential firing. Both effects were blocked by using specific adenosine 1 receptor (A1R) antagonist. We next hypothesized that GABAergic interneurons may play an important role regulating ATP/adenosine release from astrocytes. Therefore, we used high frequency stimulation and optogenetic protocols to specifically stimulate hippocampal interneurons. In these experimental conditions, we found that GABA released from interneurons activates astrocytic GABAB receptors. Consequently, astrocytes release ATP/adenosine, which acts on pyramidal neurons A1 receptors increasing sIAHP and reducing neuronal excitability. Present results uncover the role of astrocytes in the regulation of neuronal intrinsic properties and reveal a novel mechanism involved in network dysfunctions and brain disorders related with neuronal hyper-excitability.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-15

Modelling microscale diffusion in geometrically resolved brain extracellular space in live tissue

Ms. Paula Giménez Mínguez[1,2], Mr Konstantinos Chatzimichail[2], Dr. Jan Tønnesen[1,2]
[1]Universidad Del Pais Vasco, Getxo, España, [2]Achucarro Basque Center for Neuroscience, Leioa, España

The extracellular space (ECS) is emerging as an important regulator of brain function involved in metabolite clearance and volume transmission signaling. It consists of highly convolved channels and reservoirs filled with interstitial fluid that facilitates diffusional spreading of molecules. However, state-of-the-art methods for investigating diffusional properties in brain neuropil do not reconcile sub-micron optical resolution with live tissue experiments. Consequently, it remains largely unknown how diffusion is shaped around individual cellular sub-structures. Knowing this is important for understanding how ECS structure can regulate signaling and metabolism, and how aberrant changes in the ECS properties may disrupt these processes.

Recently developed Super Resolution Shadow Imaging (SUSHI) reveals the nanoscale organization of the ECS in live tissue [1]. SUSHI images therefore provide new opportunities to model diffusion in the interstitial fluid channels around individual cellular structures. Accordingly, we aim to establish a numerical computational model of nanoscale ECS diffusion based on live tissue images, which is highly robust to image acquisition parameters and allows modelling differently sized molecules. In addition, we are using 2-Photon microscopy-based shadow imaging [2] to study how osmotic changes affect the ECS volume and consequently the concentration of neurotransmitters in live brain slices.

We will test the hypothesis that the local ECS geometry around a given synapse will channel away released transmitters in preferred directions, which may conceivably modulate extracellular crosstalk between neighboring synapses, and shape extrasynaptic transmission.

The proposed models are likely to facilitate groundbreaking new insights into the role of ECS structure in shaping diffusion and signaling on micro-scales, which remains a poorly understood phenomenon.

[1] Tønnesen J, et all. Super-Resolution Imaging of the Extracellular Space in Living Brain Tissue. Cell, 2018

[2] Kuo, S. P., et all. Spatial Organization and Dynamics of the Extracellular Space in the Mouse Retina. J. Neurosci. 40, 7785–7794 (2020).

PS1-16

Cell to cell communication mediates the neurodegeneration caused by glioblastoma

Dr. Sergio Casas Tinto[1], Dr. María Losada-Pérez, Dr. Patricia Jarabo, Dr. Marta Portela, Dr. Francisco A Martín
[1]*Instituto Cajal CSIC, Madrid, Spain*

Glioblastoma (GB) is the most aggressive and frequent primary brain tumor. Current treatments include radio-, chemotherapy and surgical resection of the solid core of the tumor. However, GB infiltrative cells cause that almost 100% of the patients undergo relapses and cause death in 16 months. GB cells produce cellular protrusions known as Tumor Microtubes (TMs) or cytonemes, which facilitate tumor expansion and cellular interaction among GB cells and with healthy surrounding neurons.

We use a Drosophila melanogaster GB model to study glia-neuron cellular interactions that contribute to the neurodegeneration induced by GB signals. TMs expand through the brain and connect GB cells, and with the healthy neurons through synapses.

As a consequence of GB-neuron interaction, WNT pathway and Insulin Receptor (InR) signaling attenuation play a central role in the neurodegeneration associated to GB. TMs accumulate specific Frizzled receptors that contribute to the depletion of WNT from surrounding neurons. This imbalance in WNT pathway causes JNK pathway activation and Matrix Metalloproteases (MMPs) secretion, MMPs degrade extracellular matrix and facilitates further TMs expansion. In consequence of WNT depletion, neurons undergo synapse loss and neurodegeneration that contribute significantly to the premature death caused by GB.

Besides, GB cells also produce ImpL2, an antagonist of the Insulin receptor known as IGFBP7 in humans. ImpL2 is secreted and impact on neighboring neurons, in consequence Insulin pathway is repressed, causes mitochondrial defects and synapse loss. Restoration of InR signaling in neurons counteracts neurodegenerative effects of GB.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-17

GSK-3β S9A overexpression leads murine hippocampal neural precursors to acquire an astroglial phenotype in vivo.

Mr. Miguel Flor-García[1,2,3], Dr. Jesús Ávila[1,3], Dr. María Llorens-Martín[1,3]

[1]Department of Molecular Neuropathology, Centro de Biología Molecular "Severo Ochoa", CBMSO, CSIC-UAM, Madrid, Spain, [2]Department of Molecular Biology, Faculty of Sciences, Universidad Autónoma de Madrid, Madrid, Spain, [3]Center for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), Madrid, Spain

The addition of new neurons to the existing hippocampal circuitry persists in the adult dentate gyrus (DG). During this process, named adult hippocampal neurogenesis (AHN), adult hippocampal progenitor cells (AHPs) give rise to newborn dentate granule cells (DGCs). The acquisition of a neuronal lineage by AHPs is tightly regulated by numerous signaling molecules and transcription factors. In this regard, glycogen synthase kinase 3β (GSK-3β) is a master regulator of the maturation of AHPs in vitro. Here we analyzed the cell-autonomous effects of overexpressing a constitutively active form of GSK-3β (GSK-3β S9A) in AHPs in vivo. To this end, we stereotaxically injected a GSK-3β S9A-encoding retrovirus (GSK-3β-V5) into the DG of young adult C57BL6/J Ola Hsd female mice and studied the cell lineage acquisition, migratory and marker expression patterns, and the morphological maturation of the infected cells over time. Strikingly, GSK-3β S9A-transduced cells expressed glial fibrillary acidic protein (GFAP) and NG2, thereby acquiring an immature astroglial phenotype, which differed markedly from the neuronal phenotype observed in cells transduced with a control retrovirus that encoded GFP. Accordingly, the morphology and migration patterns of cells transduced by the two retroviruses are remarkably divergent. These observations support the role of GSK-3β as a cornerstone that regulates the balance between new astrocytes/neurons generated in the adult murine DG.

PS1-18

Astroglial CB1 mediates synaptic plasticity in the Nucleus Accumbens

Dr. Ana Covelo[1,2], Ines Filipa Dinis[1,3], Dr Giovanni Marsicano[1,2]
[1]Inserm, Bordeaux, France, [2]University of Bordeaux, Bordeaux, France, [3]University of Lisbon, Lisbon, Portugal

The Nucleus Accumbens (NAc) has a prominent role in the reward system and its activity is critical for the correct processing of relevant emotional information being involved in positive and negative reinforcement. Type-1 cannabinoid receptors (CB1), the main elements of the endocannabinoid system (ECS), participate in reward processing in part by its direct impact on synaptic plasticity in the NAc. Indeed, impaired endocannabinoid (eCB) signaling contributes to dysregulated synaptic plasticity, increased stress response, negative emotional states and cravings that propel addiction. Astrocytes play active roles in information processing by sensing synaptic activity and releasing neuroactive molecules – called gliotransmitters – that activate neuronal receptors. Through the release of gliotransmitters, astrocytes have been found to modulate neuronal activity and synaptic transmission in several brain areas and to impact animal behavior. CB1-mediated astrocyte-neuron communication has been shown in different brain regions, but the functional astrocyte-neuron interactions and its underlying mechanisms in the nucleus accumbens (NAc) are unknown. We used electrophysiology, pharmacology and cell-type specific transgenic mouse lines to investigate the role of astroglial CB1 in synaptic plasticity in the Nucleus accumbens core. We found that CB1 specifically expressed in astrocytes, but not in neurons, are necessary for spike-timining-dependent long-term depression (t-LTD) in the NAc, a form of plasticity critically involved in memory formation. We also found that astrocytes release purines downstream of the CB1 activation, which is a key step for t-LTD. Synaptic modifications in the NAc are important for appetitive/aversive-dependent learning. Here we show that astroglial CB1 mediate long-term synaptic depression in the NAc and reveals astrocytes as new potential targets for treatment of motivational disorders.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-19

In silico screening of GMQ-like compounds reveals guanabenz and sephin1 as new allosteric modulators of acid-sensing ion channel 3

Dr. G Callejo[1,2], Mr LA Pattison[1], Mr JC Greenhalgh[1], Dr S Chakrabarti[1], Ms E Andreopoulou[1], Dr JRF Hockley[1], Dr E St. John Smith[1], Dr T Rahman[1]

[1]Department of Pharmacology, University of Cambridge, Cambridge, United Kingdom, [2]Institut de Neurociències, Universitat de Barcelona, Barcelona, Spain

Acid-sensing ion channels (ASICs) are voltage-independent cation channels that detect decreases in extracellular pH. Dysregulation of ASICs underpins a number of pathologies. Of particular interest is ASIC3, which is recognised as a key sensor of acid-induced pain and is important in the establishment of pain arising from inflammatory conditions, such as rheumatoid arthritis. Thus, the identification of new ASIC3 modulators and the mechanistic understanding of how these compounds modulate ASIC3 could be important for the development of new strategies to counteract the detrimental effects of dysregulated ASIC3 activity in inflammation. Here, we report the identification of novel ASIC3 modulators based on the ASIC3 agonist, 2-guanidine-4-methylquinazoline (GMQ). Through a GMQ-guided in silico screening of Food and Drug administration (FDA)-approved drugs, 5 compounds were selected and tested for their modulation of rat ASIC3 (rASIC3) using whole-cell patch-clamp electrophysiology. Of the chosen drugs, guanabenz (GBZ), an α2-adrenoceptor agonist, produced similar effects to GMQ on rASIC3, activating the channel at physiological pH (pH 7.4) and potentiating its response to mild acidic (pH 7) stimuli. Sephin1, a GBZ derivative that lacks α2-adrenoceptor activity, has been proposed to act as a selective inhibitor of a regulatory subunit of the stress-induced protein phosphatase 1 (PPP1R15A) with promising therapeutic potential for the treatment of multiple sclerosis. However, we found that like GBZ, sephin1 activates rASIC3 at pH 7.4 and potentiates its response to acidic stimulation (pH 7), i.e. sephin1 is a novel modulator of rASIC3. Furthermore, docking experiments showed that, like GMQ, GBZ and sephin1 likely interact with the nonproton ligand sensor domain of rASIC3. Overall, these data demonstrate the utility of computational analysis for identifying novel ASIC3 modulators, which can be validated with electrophysiological analysis and may lead to the development of better compounds for targeting ASIC3 in the treatment of inflammatory conditions.

PS1-20

Loss of TRESK background potassium channel enhances acute and chronic itch.

Dr. Alba Andrés-Bilbé[1], Dr. Aida Castellanos[1], Ms. Anna Pujol[1], Dr. Núria Comes[1,2], Dr. Gerard Callejo[1,2], Prof. Xavier Gasull[1,2]

[1]Institute of Neurosciences, Universitat de Barcelona, Barcelona, Spain, [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

TRESK (K2P18.1) is a background K+ channel expressed in sensory neurons, where it modulates the resting membrane potential, action potential firing and neuronal excitability. A subset of these sensory neurons, which express specific TRPs and Mas-related G protein-coupled receptors (Mrgprs), are activated by pruritogens and mediate itch sensations. Because TRESK is involved in somatosensitivity and pain perception, we evaluated the contribution of this channel to pruritic sensitivity and its potential as a target for the treatment of chronic itch pathologies including renal or liver failure, Hodgkin's lymphoma and different types of dermatitis. By combining, RNA in situ hybridization, calcium imaging, electrophysiological and behavioral approaches, we found that TRESK is involved in the modulation of non-histaminergic itch. TRESK colocalizes in MrgprD+ and MrgprA3+ sensory neurons. Different populations of primary cultured sensory neurons from both wild-type and TRESK knockout mice were activated by chloroquine (CQ), β-alanine, BAM8-22 or histamine in calcium imaging experiments. At the behavioral level, subcutaneous injection of chloroquine in the cheek model produced an acute scratching response, which was significantly enhanced in mice lacking TRESK. Interestingly, TRESK ko mice also showed alterations in mice models of chronic itch. Induction of Allergic Contact Dermatitis or Dry Skin showed a significantly higher scratching response in mice lacking TRESK compared to their wild-type counterparts. In the mouse model of imiquimod-induced psoriatic itch, the absence of TRESK produced a significantly enhanced scratching behavior, which developed earlier and was more robust. In summary, our data indicate that TRESK is involved in regulating the excitability of a subset of sensory neurons that mediate histaminergic-independent itch. Given the prominent role of this neuronal subpopulation in chronic itch diseases, TRESK appears as a new potential candidate for therapeutic intervention.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-21

TRESK background K+ channel regulates sensory neuron excitability and contributes to mechanical and cold pain

Dr. Aida Castellanos[1], Dr. Alba Andrés-Bilbé[1], Dr. Ahmed Negm[3,4], Dr. Gerard Callejo[1,2], Prof. Jacques Noël[3,4], Prof. Xavier Gasull[1,2], Dr. Núria Comes[1,2]

[1]Institute of Neurosciences, Universitat de Barcelona, Barcelona, Spain, [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [3]Université Côte d'Azur, CNRS UMR 7275, Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne, France, [4]LabEx Ion Channel Science and Therapeutics, Valbonne, France

TRESK (K2P18.1) is a background K+ channel highly expressed in spinal cord, dorsal root and trigeminal ganglia sensory neurons, where it has been involved in modulating sensory neuron excitability and firing. Changes in channel expression and function have been reported to enhance nociceptor excitability after injury or inflammation. To determine the role of TRESK in sensory transduction, we first compared the excitability and membrane properties of small/medium-sized sensory neurons in whole cell patch clamp recordings of cultured DRG neurons from wild type and TRESK knockout mice, which presented a reduced action potential threshold, increased membrane resistance and enhanced repetitive firing upon depolarization. Recordings of skin nociceptive fibers showed strong activation in response to cold in the absence of TRESK channel. In agreement, behavioral experiments in TRESK ko mice revealed a decreased mechanical threshold to von Frey hairs and an enhanced cold sensitivity. No significant changes were found for thermal sensitivity to warm or hot temperatures. Nocifensive behavior after capsaicin injection was unaltered while the response to AITC was slightly diminished. Interestingly, TRESK ko mice presented a reduced response to hypertonic and hypotonic stimuli even after sensitization with PGE2. During inflammation, ko mice showed a decreased phase I response in the formalin test, while phase II was unaltered. In the CFA-induced inflammatory model, both mechanical and thermal sensitivity were enhanced compared to wt animals. Mechanical and thermal hyperalgesia were also enhanced in the sciatic nerve cuffing model of neuropathic pain. Finally, the oxaliplatin-induced cold sensitization was absent in ko mice, probably due to the already enhanced cold sensitivity. In summary, our results indicate that TRESK has a significant contribution regulating the excitability of certain populations of sensory neurons mainly involved in mechanical and cold pain sensing. Moreover, a down-regulation of its expression as occurs after nerve injury might contribute to the generation of the hyperalgesia and allodynia observed during chronic pain.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-22

mGlu4 receptors rescue parallel fiber LTP and motor skilled reaching deficits in a mouse model of Fragile X Syndrome

Dr. Ricardo Martín[1,2,3], Dr. Nuria García-Font[1,2,3,4], Mr Alberto Samuel Suárez-Pinilla[1,2,3], Dr David Bartolomé-Martín[5], Dr María Jesús Oset-Gasque[1,2,3], Dr Magdalena Torres[1,2,3], Dr José Sánchez-Prieto[1,2,3]

[1]Universidad Complutense de Madrid, Madrid, España, [2]Instituto Universitario de Investigación en Neuroquímica, Madrid, España, [3]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos, Madrid, España, [4]University of Edinburgh, Edinburgh, United Kingdom, [5]Universidad de La Laguna, San Cristóbal de La Laguna, España

Fragile X patients and mice lacking the Fragile X Mental Retardation Protein (Fmr1 KO) suffer from multiple behavioral alterations including some motor deficits. We found that cerebellar parallel fiber to Purkinje cell Fmr1 KO synapses show an increase in synaptic vesicle (SV) docking and in spontaneous release that occludes further potentiation by β adrenergic receptors (β-ARs) and compromises parallel fiber Long Term Potentiation (LTP), a presynaptic form of synaptic plasticity. Diminishing the extracellular Ca2+ concentration, restored the readily releasable pool (RRP) size and rescued β-AR-mediated potentiation and parallel fiber LTP. Interestingly, VU 0155041, a selective positive allosteric modulator of mGlu4 receptors, also restored both the RRP size and parallel fiber LTP. Moreover, VU 0155041 injected into Fmr1 KO mice improved both parallel fiber LTP and a cerebellum based motor skilled reaching test. Thus, pharmacological activation of mGlu4 receptors may offer therapeutic relief in Fragile X Syndrome.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-23

IMPACT OF BRAIN STATE ON TRANSCRANIAL DIRECT-CURRENT STIMULATION (tDCS) EFFECTS IN MICE

Mr. Guillermo Sánchez-Garrido Campos[1], Mrs. Ángela M. Zafra[1], Dr. Isabel Cordones[1], Mrs. Marta Estévez-Rodríguez[1], Dr. Javier Márquez-Ruiz[1]
[1]*Universidad Pablo De Olavide, Seville, Spain*

Transcranial direct-current stimulation (tDCS) is a non-invasive brain stimulation technique capable of inducing polarity-specific changes in neuronal excitability. Whilst cathodal tDCS has been related to long-term depression in mice primary somatosensory cortex (S1), anodal tDCS have no long-term effects. The physiological changes induced in the brain during and after tDCS must be interpreted as the result of the interaction between the imposed electrical currents and fields and the on-going, endogenous cortical activities. The aim of this study was to determine the impact of different brain states (awake vs anesthetized) on the short- and long-term effects observed during and after tDCS on mice S1 cortex.

For that, we prepare C57 mice for chronic recording of LFPs in S1, ventroposterior-medial thalamus nuclei (VPM) electrical stimulation and tDCS in head-restrained animals. Evoked potentials (EPs) induced in S1 due to electrical stimulation of VPM (every 10±2s) were recorded on awake and under anesthesia condition (isoflurane). Short-term (15s pulses, ±50µA, ±100µA, ±150µA and ±200µA) and long-term (±200µA, 20min) effects of tDCS in both conditions were compared.

Differences within EPs were found between brain states (smaller amplitudes and longer latencies appeared under anesthesia). Short-term effects of tDCS on EPs were evident for both awake and anesthetized conditions inducing an increase and decrease in the amplitude during anodal and cathodal, respectively. On the other hand, clear long-term effects were observed in anesthetized animals whilst no significant long-term effects were observed on awake mice for anodal nor cathodal tDCS. Under isoflurane condition, a decreased amplitude in EPs was induced remaining up to 1 hour after cathodal tDCS offset. Contrarily, an increase in the amplitude of EPs was observed after anodal tDCS offset.

These results demonstrate an important role of the brain state on long-term plastic changes induced by tDCS in mice S1 region.

PS1-24

Nutrient-mediated regulation of GluA1 surface levels

Ms. Rocío Rojas Martín[1], Dr. Rut Fadó Andrés[1], Dr. Alfredo Miñano Molina[2,4], Dr. José Rodríguez Álvarez[2,4,5], Dr. Núria Casals Farré[1,3]

[1]Faculty of Medicine and Health Sciences, Universitat Internacional de Catalunya, Sant Cugat del Vallès, Spain, [2]Institute of Neurosciences (INc), Universitat Autònoma de Barcelona, Barcelona, Spain, [3]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain, [4]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain, [5]Albert Einstein College of Medicine, New York, United States of America

It is widely known that brain needs a lot of energy to carry out all its functions. Neurons use most of this energy to maintain glutamatergic synapsis in which AMPA receptors play an important role. Our group has recently demonstrated that the basal transport of AMPAR subunit GluA1 to the plasma membrane is downregulated upon glucose depletion. Moreover, it has been described that specific nutrients also modulate synaptic strength, as well as some diets have an impact on learning and memory processes. The aim of this study is to elucidate the molecular mechanisms by which different nutrients can regulate synaptic function, analyzing its effects on AMPAR trafficking. In order to address this objective, primary cortical mouse neurons were treated with different fatty acids or ketone bodies at 14-15 days of culture. Then, GluA1 surface levels were analysed by immunocytochemistry. Our results indicated that, on the one hand, palmitic acid, a saturated fatty acid mostly found in palm oil, decreased the amount of GluA1 surface levels in neurons. However, oleic acid, an unsaturated fatty acid which comprises the majority of olive oil, did not show a negative impact on GluA1 synaptic level. Nevertheless, a polyunsaturated fatty acid found in fish like salmon, the ω-3 docosahexaenoic acid, increased the amount of GluA1 subunit at plasma membrane. On the other hand, the β-hydroxybutyrate, a ketone body used as a source of energy in the brain during ketogenic diet (based on low carbohydrate and high fat intake), raised GluA1 surface levels. In summary, we demonstrate that saturated fatty acids reduce GluA1 surface levels, while polyunsaturated fatty acids and ketone bodies seem to have beneficial effects in neurons. These results give insight into why certain diets are able to delay cognitive impairment in neurodegenerative diseases.

PS1-25

Running and swimming dependent fast-to-slow BDNF/TrkB signalling optimisation at the NMJ

Ms. Laia Just-Borràs[1], Mr. Víctor Cilleros-Mañé[1], Ms. Erica Hurtado[1], Ms. Aleksandra Polishchuk[1], Ms. Maria Duran-Vigara[1], Ms. Marta Balanyà-Segura[1], Mr. Olivier Biondi[2], Mr. Frédéric Charbonnier[2], Ms. Marta Tomàs[1], Ms. Neus Garcia[1], Mr. Josep Tomàs[1], Ms. Maria A. Lanuza[1]

[1]Unitat d'histologia i neurobiologia, Universitat Rovira i Virgili, Reus, Spain, [2]INSERM UMRS 1124, Université de Paris, Reus, España

Exercise is the most common physiological stimulus and has the capacity to modify tissues functionality. It improves motor control and cognitive abilities and reinforces neuroprotective mechanisms in central and peripheral nervous system. Peripheral nerves interact with skeletal muscles at the neuromuscular junction to guarantee an appropriated functionality of each other and of the neuromuscular synapse. Thus, modifications of this bidirectional communication through physical activity preserve this synapse as it increases quantal content and resistance to fatigue, acetylcholine receptors expansion and myocytes fast-to-slow functional transition.

Here, we provide the intermediate step between physical activity and functional and morphological changes by analysing the molecular adaptations of the full BDNF/TrkB downstream signalling in the skeletal muscle pathway, directly involved in acetylcholine release and synapse maintenance. After 45 days of training at different intensities, the BDNF/TrkB molecular phenotype of trained muscles from male B6SJLF1/J mice evidence a fast-to-slow transition without affecting motor neuron size. We provide further knowledge to understand how exercise induces muscle molecular adaptations towards a slower phenotype, resistant to prolonged trains of stimulation or activity that can be useful as therapeutic tools.

Funding: This research was funded by Ministerio de Ciencia, Innovación y Universidades, the Agencia Estatal de Investigación (AEI) and the European Regional Development Fund (ERDF) PID2019-106332GB-I00, the support of the Universitat Rovira i Virgili (URV) (2017PFR-URV-B2-85) and the Catalan Government (2017SGR704). L.J.-B. has been supported by the Universitat Rovira i Virgili (URV) under the framework of the "Programa Martí i Franquès d'ajuts a la investigació. Contractes de personal investigador predoctoral en formació (PMF-PIPF).

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-26

Existence of FGFR1-5-HT1AR heteroreceptor complexes in hippocampal astrocytes. Putative link to 5-HT and FGF2 modulation of hippocampal gamma oscillations

Dr. Manuel Narvaez[1,4], Dr. Yuniesky Andrade-Talavera[8], D. Ramon Fores-Pons[1,4], Dr. Ismael Valladolid-Acebes[3], Dra. Pia Siegele[4], Dr. Alejandro Hernandez-Sosa[4], Dr. André Fisahn[5], Dr. Alexander López-Salas[4], Dr. Dasiel O. Borroto-Escuela[4,6,7]

[1]Instituto De Investigación Biomédica De Málaga,Facultad de Medicina, Universidad de Málaga, Malaga, Spain, [2] Laboratorio de Neurociencia Celular y Plasticidad , Universidad Pablo Olavide, Sevilla , Spain , [3]The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Karolinska University Hospital L1, SE-171 76, Stockholm , Sweden , [4]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden , [5]Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Neuronal Oscillations Lab, Karolinska Institutet, Stockholm, Sweden , [6]Department of Biomolecular Science, Section of Physiology, University of Urbino, Urbino , Italy , [7]Grupo Bohío-Estudio, Observatorio Cubano de Neurociencias, Yaguajay, Cuba , [8]epartment of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Neuronal Oscillations Lab, Karolinska Institutet, Stockholm, Sweden

The majority of the fibroblast growth factor receptor 1-serotonin 1 A receptor (FGFR1-5-HT1AR) heterocomplexes in the hippocampus appeared to be located mainly in the neuronal networks and a relevant target for antidepressant drugs. Through a neurochemical and electrophysiological analysis it was therefore tested in the current study if astrocytic FGFR1-5-HT1AR heterocomplexes also exist in hippocampus. They may modulate the structure and function of astroglia in the hippocampus leading to possible changes in the gamma oscillations. Localization of hippocampal FGFR1-5-HT1AR heterocomplexes in astrocytes was found using in situ proximity ligation assay combined with immunohistochemistry using glial fibrillary acidic protein (GFAP) immunoreactivity as a marker for astroglia. Acute i.c.v. treatment with 8-OH-DPAT alone or together with basic fibroblast growth factor (FGF2) significantly increased FGFR1-5-HT1AR heterocomplexes in the GFAP positive cells, especially in the polymorphic layer of the dentate gyrus (PoDG) but also in the CA3 area upon combined treatment. No other hippocampal regions were studied. Also, structural plasticity changes were observed in the astrocytes, especially in the PoDG region, upon these pharmacological treatments. They may also be of relevance for enhancing the astroglial volume transmission with increased modulation of the neuronal networks in the regions studied. The effects of combined FGF2 and 5-HT agonist treatments on gamma oscillations point to a significant antagonistic interaction in astroglial FGFR1-5-HT1AR heterocomplexes that may contribute to counteraction of the 5-HT1AR-mediated decrease of gamma oscillations.

PS1-27

Activity-Dependent Reconnection of Adult-Born Dentate Granule Cells in a Mouse Model of Frontotemporal Dementia

Ms. Julia Terreros-Roncal[1,2,3], Ms. Elena P. Moreno-Jiménez[1,2,3], Mr. Miguel Flor-García[1,2,3], Dr. Jesús Ávila[1,2], Dr. María Llorens-Martín[1,2]

[1]Department of Molecular Neuropathology, Centro de Biología Molecular "Severo Ochoa", CBMSO, CSIC-UAM, Madrid, Spain, [2]Centre for Networked Biomedical Research on Neurodegenerative Diseases (CIBERNED), Madrid, Spain, [3]Department of Molecular Biology, Faculty of Sciences, Universidad Autónoma de Madrid, Madrid, Spain

Frontotemporal dementia (FTD) is characterized by remarkable neuronal loss in both the frontal and temporal lobes of the brain. FTD-Tau is a variant of this disease that belongs to the family of tauopathies. Our laboratory generated a mouse model which carries three familial mutations, namely G272V (V), P301L (L), and R406W (W), on MAPT, the gene encoding tau. This mouse model (named TauVLW) exhibits behavioural impairments as well as hippocampal anatomic alterations similar to those described in patients with FTD. The hippocampus is involved in learning, memory, and mood regulation. Moreover, it hosts the generation of new hippocampal dentate granule cells (DGCs) throughout life. This process, named adult hippocampal neurogenesis (AHN) is impaired in patients and animal models of neurodegenerative diseases.

We used a novel combination of retroviral approaches to in-depth characterize the morphological and functional maturation of adult-born DGCs in TauVLW mice. First, we used Red-Green-Blue (RGB) retroviruses to address the temporary course of the morphological alterations observed in these neurons. Retroviruses encoding either PSD95: GFP or Syn: GFP revealed dramatic impairments in the afferent and efferent connectivity of newborn DGCs in TauVLW mice. Monosynaptic retrograde rabies virus tracing showed that these cells are disconnected from distal brain regions and local sources of excitatory innervation, and subjected to increased inhibitory innervation by local interneurons. Similarly, increased levels of markers of inhibitory neurotransmission were found in the DG of FTD patients.

Finally, we used a retrovirus that encodes the excitatory Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) H3Dmq and achieved a complete reversion of the morphological alterations exhibited by newborn DGCs of TauVLW mice. Moreover, functional impairments were also partially reversed. Our results suggest that chemoactivation may be explored as a future therapeutic target for the treatment of distinct neurodegenerative diseases in which neuronal connectivity is compromised.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-28

CANNABINOID RECEPTOR TYPE 1 (CB1R) EXPRESSION IN THE BRAIN STRUCTURES OF GENETIC MODELS OF EPILEPSY

PhD Rui Milton Patrício Da Silva Júnior[1,2], PhD Willian Lazarini-Lopes[2], Dr Alejandro Fuerte-Hortigón[3], PhD Laura Zeballos[1], Prof Mª. Dolores E. López García[1], Prof Norberto Garcia-Cairasco[2]

[1]Neuroscience Institute of Castilla y León (INCyL, Faculty of Medicine. University of Salamanca (USAL), Salamanca, Spain, [2]Neuroscience and Behavioral Sciences Department, Ribeirão Preto School of Medicine, Ribeirão Preto, Brazil, [3]Department of Neurology, Virgen Macarena Hospital, Sevilla, Spain

The endocannabinoid system (ECS) is related to several physiological processes associated with the modulation of brain excitability, with impact on the expresión, susceptibility and control of epileptic seizures. The cannabinoid receptor type 1 (CB1R) is widely expressed in the brain, especially in the limbic structures of the forebrain. Changes in CB1R expression are associated with seizures in animal models and in humans. The Wistar Audiogenic Rat (WAR) strain and Genetically Audiogenic Seizure-Prone Hamster from Salamanca (GASH/Sal) are genetic models of epilepsy that present tonic-clonic and limbic seizures in response to intense sound stimulation. In this work we aim characterize the expression of CB1R by immunohistochemistry in brain structures important for the expression of limbic seizures. For this, we used an immunohistochemical protocol to evaluate the effects of acute and chronic audiogenic seizures on the expression of CB1R in different regions of the hippocampus and amygdala. WARs showed increased immunostaining for CB1R in the inner molecular layer of the hippocampus. Acute and chronic audiogenic seizures increased CB1R immunostaining in limbic structures of WARs. Furthermore, changes in CB1R expression in the amygdala, but not in the hippocampus, were associated with limbic recruitment and severity of limbic seizures in WAR. The expression of CB1R in GASH/Sal showed a wide distribution in many brain nuclei. These CB1R immunostaining patterns are practically identical between the GASH/Sal and the control animals, varying in the intensity of immunostaining in limbic regions, being slightly weaker in the GASH/Sal than in the control, mainly in brain regions associated with epileptogenic circuits. Our results suggest that endogenous alterations in CB1R immunostaining in genetic models of epilepsy could be associated with genetic susceptibility to audiogenic seizures. Also, we demonstrate neuroplastic changes of CB1R in amygdala and hippocampus is associated with acute and chronic seizures. Furthermore, the present study provides important information on CB1R and susceptibility to seizures in genetic animal models of seizures and supports the relationship between ECS and epilepsy.

PS1-29

Simultaneous encoding of fear state and threat identity in prefrontal cortex neuronal populations.

Dr. Mario Martin-Fernandez[1,2], Ana Paula Mengolla[1,2], Guillem Lopez-Fernandez[1,2], Dr. Cyril Herry[1,2]
[1]Université de Bordeaux, Neurocentre Magendie, Bordeaux, France, [2]INSERM, Neurocentre Magendie, Bordeaux, France

In response to specific threats, mammals select a response among a repertoire of different defensive behaviors. The selection and the rapid execution of this response are crucial for animal survival and are determined not only by the nature of the threat but also by the contextual contingencies. Therefore, in order to survive a dangerous situation mammals have to integrate multimodal information regarding the threat, the context and its internal state to rapidly elicit the most adaptive fear response. The neuronal circuits and mechanisms allowing this rapid selection of appropriate defensive fear responses are still largely unknown. To address this question, we used a multi-level approach combining simultaneous electrophysiological recordings and optogenetic manipulations in a novel and unique behavioral paradigm allowing mice to select different defensive behaviors when facing different threats. Using this combination of techniques, we monitored the neuronal activity of dmPFC neurons of mice presented with different threats to demonstrate that at the population level, dmPFC neuronal activity encodes both a general fear state and more specific information about the identity of the threats. We further investigated the processes that allow for this simultaneous encoding of threat and fear information and the effects of manipulating the activity of the dmPFC in the selection of specific defensive responses.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-30

Using Hippocampome.org to investigate hippocampal circuit dynamics

Dr. Alberto Sanchez-Aguilera[1], Dr. Diek W Wheeler[2], Dr. Teresa Jurado-Parras[1], Dr. Elena Cid[1], Dr Nate Sutton[2], Dr Giorgio G Ascoli[2], Dr Liset Menendez de la Prida[1]

[1]Instituto Cajal - Csic, Madrid, Spain, [2]George Mason University, Fairfax, United States of America

Understanding brain operation demands linking basic behavioural traits to cell-type specific dynamics of different brain-wide subcircuits. This requires a system to classify the basic operational modes of neurons and circuits. Single-cell phenotyping of firing behaviour during ongoing oscillations in vivo has provided a large body of evidence on hippocampal function, but data are dispersed and diverse. Here, we mined literature and obtained new data to update information on oscillatory dynamics of over 100 hippocampal neuronal types defined in Hippocampome.org. We integrate all current knowledge about the morphology, biophysics, genetic identity, connectivity, and firing patterns of a wealth of GABAergic and glutamatergic neurons to provide a comprehensive single-cell map of the hippocampal region. Finally, we show how using Hippocampome.org can provide knowledge-based classification of hippocampal neurons recorded with extracellular methods as well as provide additional resources for biologically realistic computational modelling to ease applications in artificial intelligence.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-31

Pre-training RNNs on ecologically relevant tasks explains sub-optimal behavioral reset

Dr. Manuel Molano-mazón[1], Dr. Daniel Duque[1], Dr Guangyu Robert Yang[2], Dr Jaime de la Rocha[1]
[1]IDIBAPS, Barcelona, Spain, [2]Center for Theoretical Neuroscience, Columbia University, New York, USA

When faced with a new task, animals' cognitive capabilities are determined both by individual experience and by structural priors evolved to leverage the statistics of natural environments. Rats can quickly learn to capitalize on the trial sequence correlations of two-alternative forced choice (2AFC) tasks after correct trials, but consistently deviate from optimal behavior after error trials, when they waive the accumulated evidence. To understand this outcome-dependent gating, we first show that Recurrent Neural Networks (RNNs) trained in the same 2AFC task outperform animals as they can readily learn to use previous trials' information both after correct and error trials. We hypothesize that, while RNNs can optimize their behavior in the 2AFC task without a priori restrictions, rats' strategy is constrained by a structural prior adapted to a natural environment in which rewarded and non-rewarded actions provide largely asymmetric information. When pre-training RNNs in a more ecological task with more than two possible choices, networks develop a strategy by which they gate off the across-trial evidence after errors, mimicking rats' behavior. Our results suggest that the observed suboptimal behavior reflects the influence of a structural prior that, adaptive in a natural multi-choice environment, constrains performance in a 2AFC laboratory task.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-32

Using Uniform Manifold Approximation and Projection (UMAP) for unsupervised sorting of sharp-wave ripples

Mr. Enrique R. Sebastian[1], Dr. María Teresa Jurado-Parras[1], Dr. Alberto Sánchez-Aguilera[1], Dr. Liset Menendez de la Prida[1]
[1]*Instituto Cajal - Csic, Madrid, Spain*

Sharp-wave ripples (SWR) are high frequency hippocampal events, which presumably play different cognitive roles in memory consolidation and planning. Understanding how SWR waveform variability relates to the underlying microcircuits remains elusive but is essential to dissect cognitive function.
Here, we use topological data analysis to estimate the intrinsic structure of a wealth of SWRs recorded from head-fixed mice in vivo. We apply dimensionality reduction and visualization methods, such as Uniform Manifold Approximation and Projection (UMAP) to facilitate discovery of different SWR features. First, we show that a low number of intrinsic dimensions can explain waveform variability using a set of methods (Maximum Likelihood; Isomap; DanCo; Expected Simplex Skewness; PCA) tested against a ground-truth. Next, we apply UMAP to reduce dimensionality of SWR events and to visualize how different potential features (e.g. frequency, amplitude, slopes, etc…) accounted for waveform variability. Using cluster measures, we evaluate the distribution of these different features over the low dimensional manifold. We find different contribution of frequency, amplitude, slope and spectral entropy to the global variance of SWR, and confirmed some of these trends in synthetic datasets. Moreover, by projecting physiologically relevant measures over the UMAP manifold, we identify potential mechanisms associated to the expression of different features. Our study shows how topological analysis can be applied for unsupervised sorting of SWR events.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-33

Using 1D-convolutional neural networks to detect and interpret sharp-wave ripples

Ms. Andrea Navas-Olive[1], Mr. Rodrigo Amaducci[2], Dr. Maria Teresa Jurado-Parras[1], Mr. Enrique R. Sebastian[1], Dr. Liset Menendez de la Prida[1]

[1]Instituto Cajal - CSIC, Madrid, Spain, [2]Grupo de Neurocomputación Biológica (GNB). UAM, Madrid, Spain

Sharp-wave ripples (SWR) are high frequency events recorded in the local field potential (LFP) of the hippocampus of rodents and humans. During SWR, the sequential firing of ensembles of neurons act to reactivate memory traces of previously encoded experience. SWR-related interventions can influence hippocampal-dependent cognitive function, making their real-time detection crucial to understand underlying mechanisms. However, existing SWR identification tools mostly rely on using spectral methods, which remain suboptimal.

Here, we introduce a 1D convolutional neural network (CNN) operating over high-density LFP recordings to detect hippocampal SWR both offline and online. The adapted architecture included seven convolutional deep layers composed of different filters to process 8-channel LFP inputs in increasing hierarchical complexity and one output layer delivering the probability of an occurring SWR. We report offline performance on several types of recordings (e.g. high-density probes, linear arrays, ultradense Neuropixels) as well as on open databases that were not used for training. By saturating the operation of different filters, we examine and interpret their optimal behavior associated to the ground truth versus a random selection. We then use dimensionality reduction techniques to visualize how the network evolve across learning. Finally, we show how by building a plug-in for a widely used open system such Open Ephys, our method detects SWRs in real time. We conclude with discussion on how this approach can be used as a discovery tool for better understanding the dynamics of SWR.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-34

STUDY OF THE ANTIDEPRESSANT EFFECT OF NEW GENERATION DRUGS BASED ON GLUTAMATERGIC TRANSMISSION.

Mr. Esteban Merino[1], Dr. Vicent Teruel-Martí[1], Dra Ana Cervera-Ferri[1], Mrs. Anna Teruel-Sanchís[1,2], Dr. Sergio Martínez-Bellver[1], Mrs. Maria Villafranca-Faus[1], Mrs. Alicia González-Martínez[1], Mrs. Hanna Vila-Merkle[1], Mr. Manuel Esteban Vila-Martin[1,2], Dr. Enrique Lanuza[2], PhD Sharon Cabanu[3], Dr. Albert Adell[3], Dr. Joana Martínez-Ricós[1]

[1]University of Valencia, Valencia, Spain, [2]University of Valencia, Burjassot, Spain, [3]Institute of Biomedicine and Biotechnology of Cantabria, IBBTEC (CSIC University of Cantabria), Cantabria, Spain

Depression is an extended pathology, with more than 300 millions of people affected. However, the most used antidepressants, based on the monoamine theory of depression, have several limitations. Hence, new therapeutic alternatives based on glutamatergic transmission have emerged. In order to optimize the use of these new therapies, it would be useful to describe biomarkers of their antidepressant effect and of other undesired but potential outcomes.

Therefore, the main objective of this work is to characterize the electrophysiological activity generated by two of these antidepressants, Ketamine and LY 404187, to propose potential electrical biomarkers of their effects.

To do so, two doses (5 and 30mg/Kg) of Ketamine and a dose of LY 404187 (3 mg/kg) were injected to different groups of CD1 mice, and local field potentials were recorded from their infralimbic cortex (IL), dorsal hippocampus (HPCd) and basolateral amygdala (BLA). Electrophysiological recordings were also performed during several days following drug administration to describe the duration of the effects. In other groups of animals, behavioural tests to measure antidepressant effects (Forced Swimming Test and Tail Suspension Test), psychotic symptomatology (Novel Object Recognition) or anxiety traits (O-Maze and Open Field) induce by each drug and dose were carried out. This allowed to better interpret the behavioural correlation of the electrical effect induced by each treatment.

Results showed that immediately to the administration of Ketamine there was an increase of the power of low theta and gamma oscillations in all nuclei and a decrease of that of beta oscillations into HPCd and BLA. Furthermore, animals showed psychomimetic behaviours. After LY administration, low theta oscillations in HPCd and BLA during the first 30 min as well as the expression of anxiety-related behaviours rose. Both drugs produce rapid and lasting antidepressant effects, so electrophysiological changes would also be predictive of these.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-35

Functional diversity of motoneurons innervating extraocular muscle fibers

Dr. R. G. Hernández[1], Ms. P. M. Calvo[1], Ms. G. Carrero-Rojas[1,2], Prof. R. Blumer[2], Prof. R. R. de la Cruz[1], Prof. A. M. Pastor[1]

[1]Facultad de Biología, Universidad De Sevilla, Sevilla, Spain, [2]Center of Anatomy and Cell Biology, Medical University Vienna, Wien, Austria

Extraocular muscles contain singly innervated fibers (SIF), that receive one en plaque motoneuronal synapse and twitch upon electrical stimulation, and the atypical and less abundant multiply innervated fibers (MIF), which receives multiple en grappe motoneuronal contacts along its entire length and are non-twitch. Previous morphological studies have reported a distinct anatomical distribution and afferent pattern of SIF and MIF motoneurons, suggesting that SIF motoneurons would participate in the whole repertoire of eye movements, while MIF motoneurons would contribute only to slow eye movements.

We aimed to discern the function of electrophysiologically-identified abducens and medial rectus SIF or MIF motoneurons by extracellular single-unit recordings in awake cats during fixations, saccades, disjunctive and vestibularly-induced eye movements. Additionally, retrograde tracing of MIF motoneurons and the combination with ChAT immunolabeling allowed us to carry out a morphological study comparing between both types of motoneurons.

We have demonstrated that abducens and medial rectus SIF and MIF motoneurons participated in all different types of eye movement. However, MIF motoneurons exhibited lower firing rate, were recruited earlier and presented lower eye position and velocity sensitivities than SIF motoneurons. Anatomically, MIF and SIF motoneurons distributed intermingled within the abducens nucleus, and both in the dorsal and ventrolateral part of the medial rectus subdivision of the oculomotor complex, with MIF motoneurons being smaller and having a lesser somatic synaptic coverage.

In conclusion: 1) MIF and SIF motoneurons both discharge during all types of eye movements, although with different thresholds and sensitivities; 2) the smaller size of MIF motoneurons could explain their longer antidromic activation latencies and lower recruitment thresholds; 3) the larger synaptic coverage of SIF motoneurons could explain their higher firing rates and eye sensitivities; and 4) MIF motoneurons appear randomly distributed in the abducens and oculomotor nuclei.

Supported by: PGC2018-094654-B-100 (MCI/AEI/FEDER, UE).

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-36

Thyroid hormone transporters MCT8 and OATP1C1 are expressed in neurons in the human and monkey basal ganglia and motor thalamus.

Ms. Ting Wang[1,2,3], Mr. Yu Wang[1,2], Prof. Lucía Prensa[1], Prof. Ana Guadaño[2], Prof. Estrella Rausell[1]

[1]School of Medicine, The Autonomous University of Madrid., Madrid, Spain, [2]The Instituto de Investigaciones Biomédicas "Alberto Sols" (IIBM), Madrid, Spain, [3]Xi'an Lintong Shiyoucheng General Clinic, Xi'an, China, [4]PhD Program in Neuroscience, Autonoma de Madrid University, Madrid, Spain

Thyroid hormone (TH) is essential for proper brain development, function, and metabolism. Monocarboxylate transporter 8 (MCT8) and organic anion transporting polypeptide 1C1 (OATP1C1) are highly specific TH transporters that facilitate TH to cross the plasma membrane to perform its bioactivity. Mutations of MCT8 and OATP1C1 affect inevitably the motor system in human, and so far it is unknown the nature of the neural cells in which these transporters are expressed in the adult monkey and human basal ganglia and motor related structures.

We performed immunohistochemistry, immunohistochemistry combined with NADPH-diaphorase histochemistry or double immunofluorescence of 30-50µm floating frozen brain sections from three cynomolgus monkeys and four adult humans. The immunolabeling results were plotted in distribution maps by means of the Neurolucida system (MicroBrightField Biosciences).

MCT8 and OATP1C1 are expressed in neuronal subtypes with different morphologies in the neostriatum both in human and monkey. MCT8 is expressed in medium-sized aspiny non-NOS expressing GABAergic interneurons. OATP1C1 and MCT8 are expressed in neurons in the globus pallidus and the motor thalamus. OATP1C1 and MCT8 distribution is similar in the human and monkey tissues, although their protein expression is stronger in the monkey brain. MCT8 is less abundant than OATP1C1 in general. In addition, we have noticed that both transporters are strongly expressed in substantia nigra in the monkey and in nucleus basalis of Meynert in human and monkey. MCT8 is expressed extensively in the endothelial cells of the various size vessels and capillaries in the basal ganglia and thalamus, while OATP1C1 is occasionally observed.

Our study provides the first evidence for the abundance of TH transporters MCT8 and OATP1C1 in the basal ganglia and thalamic neurons in the adult human and non-human primates, which suggests their important role in the motor system functionality.

PS1-37

Cortical pyramidal cells express thyroid hormone transporters MCT8 and OATP1C1 in human and monkey brain.

Mr. Yu Wang[1,2], Ms. Ting Wang[1,2,3], Prof. Lucía Prensa[1], Prof. Ana Guadaño-Ferraz[2], Prof. Estrella Rausell[1]
[1]School Of Medicine, The Autonomous University Of Madrid, Madrid, Spain, [2]The Instituto de Investigaciones Biomédicas "Alberto Sols" (IIBM), Madrid, Spain, [3]Xi'an Lintong Shiyoucheng General Clinic, Xi'an, China, [4]PhD Program in Neuroscience, Autonoma de Madrid University, Madrid, Spain

Monocarboxylate transporter 8 (MCT8) and organic anion-transporting polypeptide 1C1 (OATP1C1) are thyroid hormone (TH) transmembrane transporters that play a crucial role in the availability of systemic THs for neural cells allowing their appropriate development and function. MCT8 mutations are the underlying reason of Allan-Herndon-Dudley syndrome which expresses a dramatic motor disfunction. This study aims to analyze the presence of these two proteins at the cellular level in the monkey and human cerebral cortex.
We analyzed the distribution of these two transporters in the cerebral cortex of 30-50 µm floating frozen cerebral cortex sections taken from three cynomolgus monkeys and four adult humans by Nissl staining, immunohistochemistry, double labeling immunofluorescent and immunohistochemistry combined with NADPH-diaphorase histochemistry.
OATP1C1 is expressed in pyramidal neurons in layers II, III, V, and VI in both monkey and human brain, as evidenced by colocalization with RC3/Neurogranin. Non-colocalization with NADPH-diaphorase implies that OATP1C1 is not expressed in multipolar, bitufted and stellate NOS-expressing GABAergic interneurons in the cortex. MCT8 distribution is similar to that of OATP1C1 in monkey and human brain, although the intensity of its signal is lower. Interestingly, Cajal-Retzius like cells expressing OATP1C1 are observed in layer I. OATP1C1 and MCT8 immunostained cells with very small soma and large processes compatible with astrocyte morphology are found in the subcortical white matter in close relation to vessels. MCT8 is also expressed in the endothelial cells of the different size vessels and capillaries throughout the monkey and human cortex, while OATP1C1 is occasionally observed in the endothelium of large and medium-sized vessels.
Our results demonstrate the abundance of MCT8 and OATP1C1 TH transporters in the long and short projection pyramidal cortical neurons and in the astrocyte-vessel complexes in adult human and non-human primates, which suggest their critical position in the efferent cortical motor system.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-38

Retrieval under different conditions: it is always easy to recover the spatial information?

Ms. Candela Zorzo[1], Jorge L. Arias[1], Marta Méndez[1]

[1]Laboratory of Neuroscience, Department of Psychology, University of Oviedo, Plaza Feijóo, s/n, E-33003. Instituto de Neurociencias del Principado de Asturias (INEUROPA)., Oviedo, Spain

Introduction. Spatial navigation is an indispensable cognitive function. It makes possible to find a path to reach a goal location. When retaking routes, the original visual stimuli that allowed us to establish cognitive mapping using an allocentric strategy during the acquisition phase may not remain physically identical at the time of retrieval, as a consequence of environmental changes. In the standard experimental paradigms to assess spatial memory, the cues are typically maintained constant, obviating the mentioned issue. Material and methods. In order to deepen into cue availability during the retrieval phase in comparison with learning, we trained rats on a reference memory protocol with five cues placed on black curtains that surrounded the pool, and seven days later, we tested memory retrieval under different conditions: maintenance of the five cues, removal of two and four of them, and the addition of three extra ones. Rats subjected both to the maintenance or the removal of some of the original visual distal cues during retrieval achieved it adequately, whereas those exposed to extra cues failed to retrieve the spatial memory. Then, we assessed brain oxidative metabolism through cytochrome c oxidase (CCO) histochemistry. Results: Under full- and partial-cue conditions, there is an enhancement of the hippocampal, prefrontal, retrosplenial, parietal, and rhinal cortex metabolism. However, rats that failed to retrieve spatial information in the extra cues condition showed similar or lower CCO activity than controls across many limbic areas. Conclusions: The presence of a partial portion of visual stimuli from learning makes it possible to reactivate the entire memory trace, but extra spatial information makes difficult to disengage the novel information from the older knowledge and establish a contextual generalization.

Keywords: cytochrome c oxidase; brain metabolism; retrieval; cue availability; spatial memory.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-39

Synchronized eye blinks predict narrative content in videos

Dr. Celia Andreu-Sánchez[1], Dr, Miguel Ángel Martín-Pascual[1,2], Prof. José María Delgado-García[3], Prof. Agnès Gruart[3]

[1]Universitat Autònoma De Barcelona, Cerdanyola Del Vallès (Barcelona), Spain, [2]Instituto Radio Televisión Española, Sant Cugat del Vallès (Barcelona), Spain, [3]Universidad Pablo de Olavide, Sevilla, Spain

On average, humans blink 8-21 times per minute while resting, but this unconscious rate changes with activities such as talking, listening, or watching screens. Apart from the primary physiological function of wetting the cornea, blinks are linked to attention and vary according to the cognitive processing of visual activities. Previously, we found that the style of edition of videos affected viewers' eye blink rate.

We presented three videos with the exact same narrative but different styles of editing and recorded the blink rate of 40 participants (age: 43.97 ± 8.07 years). We compared the eye blinks of participants while watching the actions within the three styles of edition.

Blinks were distributed into 40 bins of 4.95 s each for visual presentation in a histogram and observed that blink evolution across bins was very similar, regardless of the style of edition presented to participants. We found a significant effect of Time [$F(39,3041) = 5.199$, $p < 0.001$] and a significant Time × Style interaction [$F(78,3041) = 2.004$, $p < 0.001$], while no main effect of Style was found. In addition, we found six actions in the narrative content when special synchronization of viewers' blink happened. Three actions corresponded with a decrease of the blinks, the rest with an increase. The moments of increased blinks corresponded to those when the actor leaves the scene and when the movie repeats the same action for a while. The moments of decreased eye blinks corresponded to actions where visual information was crucial to proper understanding of the scene presented.

According to our results, viewers' attention is more related to the narrative content presented on videos than to the edition style. We conclude that in the context of managing viewers' attention, content overrules the style.

PS1-40

Cognitive neurodynamics during audiovisual cuts in media professionals

Dr. Miguel Ángel Martín-Pascual[1,2], Dr. Celia Andreu-Sánchez[2], Prof. Agnès Gruart[3], Prof. José María Delgado-García[3]

[1]Instituto Radio Televisión Española, Sant Cugat del Vallès (Barcelona), Spain, [2]Universitat Autònoma de Barcelona, Cerdanyola del Vallès (Barcelona), Spain, [3]Universidad Pablo de Olavide, Sevilla, Spain

Professionalization requires long-time training. In the case of media professionals, they watch screens steadily over time (taking related decisions with high level of attention). Previous results from our group suggest that there is a media professionalization effect in visual perception of media contents.

We recorded electroencephalographic signals from 36 participants (18 media professionals and 18 non-media professionals) while they were watching audiovisual contents. We compared their brain activity and connectivity after the cuts. We analyzed event-related potentials (ERPs) for periods of 1.5 s (from 0.5 to 1 s). We approached brain connectivity from functional (phase-locking value, PLV) and effective (Granger causality, GC) connectivity analysis.

We identified substantial differences in the spontaneous blink rate (SBR) related to media professionalization. In media professionals, cuts have a greater impact with a decrease of SBR [$t(17) = -2.99$, $p = 0.008$, paired t-test], while cuts do not have such impact in non-media professionals [$t(17) = -1.14$, $p = 0.269$, paired t-test]. We found an effect of professionalization and scalp area in ERPs during the viewing of audiovisual cuts [$F(2,306) = 4.822$, $p = 0.009$]. Although we did not find statistical differences related to media professionalization in alpha band, we observed differences in functional connectivity (PLV) in all studied bands (theta, alpha, beta, low gamma) after the cut. We found a more dispersed GC index in non-media professionals, while media professionals' GC connectivity was much more concise since it was mostly concentrated in visual cortex, somatomotor, and frontal areas.

Cuts evoke an artificial interruption of the visual content in videos and movies. However, their impact varies depending on the media professionalization of viewers. Apparently, cuts start a similar activation of basic brain processing of the new visual information presented, but how that visual content is managed by the two groups differs afterwards.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-41

Spatial memory evaluated by low anxiogenic Barnes Maze is preserved in the 3xTg-AD mice model of Alzheimer's disease following a cannabinoid treatment

Mr. Iker Bengoetxea de Tena[1], Dr. Marta Moreno-Rodríguez[1], Dr. Jonatan Martínez-Gardeazabal[1], Mr. Gorka Pereira-Castelo[1], Dr. Iván Manuel[1,2], Dr. Lydia Giménez-Llort[3], Dr. Rafael Rodríguez-Puertas[1,2]

[1]Dept. Pharmacology, Fac. of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa, Spain, [2]Neurodegenerative Diseases, BioCruces Bizkaia Health Research Institute, Barakaldo, Spain, [3]Dept. Psychiatry and Forensic Medicine, School of Medicine & Institute of Neuroscience, Autonomous University of Barcelona (UAB), Barcelona, Spain

Alzheimer's disease (AD) is characterized by a cognitive decline associated with a selective vulnerability of basal forebrain cholinergic neurons (BFCN), under the modulation of the endocannabinoid (eCB) system.

In this work, we assessed cognitive function using low anxiogenic Barnes Maze (BM) in the triple transgenic mice model of genetic AD (3xTg-AD), following a sub-chronic five-day treatment with 0.1 mg/kg (i.p.) of WIN55,212-2 (7-month old male mice, WIN-treated group, n=9). Their performances were compared with control mice for treatment (vehicle, n=8), and genotype (WT mice, n=6). Mice performed a five-day BM protocol with 4 daily trials for learning acquisition and spatial memory test on the fifth day.

Both Vehicle and WIN-treated mice showed delayed learning compared to WT mice, as shown by their longer learning latencies throughout the first two days (Two-way Repeated Measures ANOVA; post-hoc test Bonferroni, $p<0.01$ for Vehicle vs. WT, and WIN-treated vs. WT). Vehicle and WIN-treated groups reduced their latency from day 1 to day 4 (Paired t-test; $p<0.001$ for Vehicle, day 4 vs. day 1; $p<0.01$ for WIN-treated, day 4 vs. day 1), but no differences in acquisition were observed between both 3xTg-AD groups. On the probe day for spatial memory, mice showed target quadrant preference regardless of treatment (Kruskal-Wallis test; post-hoc test Dunn's, $p<0.001$ for Vehicle, and $p<0.05$ for WIN-treated).

3xTg-AD mice showed spatial memory impairment in more anxiogenic tests, such as Morris water maze, but we did not observe that in BM. Moreover, previous results from our group showed high levels of anxiety in 3xTg-AD mice, measured as an increase in acquisition latency to an aversive stimulus, which were ameliorated following this same cannabinoid treatment. Anxiety, rather than cognitive impairment, might explain these distinct behaviors. To avoid anxiety-related bias in the evaluation of cognitive dysfunction in 3xTg-AD mice, low anxiety behavioral tests are recommended.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-42

Evaluation of the neuroprotective activity of the ethanolic extract of Myrciaria dubia HBK McVaugh "camu camu" in a murine model of Parkinson's disease.

Bach. Marco Peña[1], M.Sc. Roy Andrade[2], Eng. Richard Cisneros[3], M.Sc. Luis Baquerizo[4], Ph.D. Fernando Ramos[4], Ph.D. Ivan Best[4], Ph.D. Ana Muñoz[4], Ph.D. Luis Aguilar[4]

[1]San Marcos University, Lima, Peru, [2]Cayetano Heredia University, Lima, Peru, [3]National University of Huancavelica, Huancavelica, Peru, [4]San Ignacio de Loyola University, Lima, Peru

Myrciaria dubia "camu camu" is an amazonian plant that is known to have high levels of antioxidants. The objective of this work was to determine if pretreatment with “camu camu” ethanolic extract reduces neurodegeneration and neuroinflammation caused by 6-hydroxydopamine (6-OHDA) in the nigrostriatal pathway. To prepare the extract, “camu camu” fruit flour was macerated in 70% ethanol for 24 hours, followed by drying the supernatant in a double boiler at 37 °C. The dry extract was dissolved in saline solution (NaCl 0.9%) to be administered to Sprague Dawley rats. This dissolved extract was administered orally (daily doses of 100 mg / Kg (ESC100 group) (n = 6) and 300 mg / Kg (ESC300 group) (n = 7)) for 15 days prior to bilateral intracranial injection in the striatum of 6-OHDA. In addition, there were two control groups not treated with the extract: the sham group (rats injected with vehicle solution) (n = 9) and the park group (rats injected with 6-OHDA) (n = 7). 21 days after the injection, the analysis of the hike pattern showed statistically significant differences between the ESC300 group and the park group in three variables. Through the histological immunofluorescence trials, it was found that the ESC300 group has a greater number of dopaminergic neurons in the black substance and greater axonal irrigation in the striatum, compared to the park group. Additionally, through immunohistochemistry, less neuroinflammation was found in the striatum of this latter group. This work concludes that pretreatment with ethanolic extract of “camu camu” at a dose of 300 mg / Kg protects neurons from the nigrostriatal pathway of 6-OHDA and reduces neuroinflammation in Sprague Dawley rats, as a consequence improves motor coordination. This project was supported by FONDECYT, Government of Peru, Contract number 109-2018-FONDECYT-BM-IADT-MU.

PS1-43

Maternal separation alters working memory and brain function of male Wistar rats

Ms. Alba Gutiérrez-Menéndez[1], María Banqueri[2], Marta Méndez[1], Nélida M. Conejo[1], Jorge L. Arias[1]
[1]University Of Oviedo, Plaza Feijóo, s/n, E-33003, Oviedo, Asturias, Spain, [2]Nencki Institute of Experimental Biology, Ludwika Pasteura 3, 02-093 Warsaw, Poland

Early life stress increases the risk of anomalous development of several brain areas and it could lead to diverse cognitive impairments related to learning, mnesic and executive functions, such as working memory (WM). Maternal separation is an established animal model of early life stress that produces changes in brain development. The aim of this study was to evaluate the effect of maternal separation on the WM function and on the metabolic activity of adult Wistar rats. We employed 24 rats divided into a control group (AFR, n=12) and an experimental group (MS, n=12) subjected to maternal separation for 4h a day for 21 consecutive days. In adulthood, we tested spatial WM of both groups using the Morris water maze, and brain metabolic activity was determined using the histochemical technique of cytochrome c oxidase (CCO). Results showed that MS subjects acquired the WM task with a significant delay. MS subjects increased their WM-related CCO activity in the cingulate cortex, anterior thalamus and supra mammillary areas along with a decrease in the medial-medial mammillary nucleus. These findings could contribute to the long term effects of early stress on executive functions but further studies should be necessary to explore other behavioural and brain alterations after a period of maternal separation.

Keywords: early stress, maternal separation, working memory, cytochrome c oxidase, brain development.

19th MEETING 3-5 November 2021 Lleida
www.congresosenc.es
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-44

Role of Astrocyte-Neuron signaling in Major Depressive Disorder

Candela González Arias[1], Cristina Sánchez-Puelles[1], Julio Esparza[1], Gertrudis Perea[1]
[1]*Instituto Cajal (CSIC), Madrid, Spain*

Major depressive disorder (MDD) is a severe and debilitating mental illness with a very large socioeconomic impact worldwide (1). The neurobiology of this disease has been studied for a long time, focused on neuronal alterations; however, the underlying etiology is not yet fully understood. Astrocytes, a glial cell type, have been shown to play relevant roles in synaptic transmission and plasticity, with significant impact on behavioral responses (2). Evidence collected during the past two decades have shown that astrocytes might contribute to the pathophysiology and pathogenesis of MDD (3). Therefore, we aim to investigate the role of astrocyte-neuron signaling in this mental disease.

Here, we used a corticosterone treatment approach as depressive-like mouse model to evaluate the role of astrocyte-neuron signaling in medial prefrontal cortex (mPFC) from naïve and MDD mice. Ca2+ imaging techniques in vivo and ex vivo, and behavioral test have been performed.

Results: 1- In vivo spontaneous and behaviorally-related astrocyte calcium signaling was altered in MDD mice.
2- Serotonin-evoked astrocyte calcium dynamics were reduced in mPFC slices from MDD mice.
3- Selective chemogenetic activation of astrocytes by Gq-DREADDs in mPFC was able to restore the behavioral deficits of MDD mice.

Although additional experiments are required, these results reveal the potential impact of astrocyte signaling in the pathophysiology of MDD.

(1) Artigas F, Bortolozzi A. Therapeutic Potential of Conjugated siRNAs for the Treatment of Major Depressive Disorder. Neuropsychopharmacology. 2017;42(1):371. doi:10.1038/npp.2016.182.
(2) Mederos S, Gónzalez-Arias C, Perea G. Astrocyte-Neuron Networks: A Multilane Highway of Signaling for Homeostatic Brain Function. Frontiers in Synaptic Neuroscience. 2018; 10:45. doi: 10.3389/fnsyn.2018.00045.
(3) Cao X, et al. Astrocyte-derived ATP modulates depressive-like behaviors. Nat Med. 2013 Jun;19(6):773-7. doi: 10.1038/nm.3162.

*PhD Program in Neuroscience, Autonoma de Madrid University, Madrid, Spain 28029.
Funding: MINECO PID2019-106579RB-I00 to G.P; BES-2017-080303 to C.G-A.

19th MEETING 3-5 November 2021 Lleida
www.congresosenc.es
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-45

Learning of allocentric and egocentric strategies in an automatized maze

Mr. Juan P. Quintanilla[1,2], Dr. Jorge R. Brotons-Mas[2,3], Dr. Liset Menéndez de la Prida[1]
[1]Instituto Cajal. CSIC. , Madrid, Spain, [2]Universidad Cardenal Herrera CEU, Elche, Spain, [3]Instituto de Neurociencias, UMH-CSIC, Alicante, Spain

The hippocampus and related structures play an important role in learning behavioral responses that are best suited for particular situations. Understanding how these structures map the environment through allocentric and egocentric representations is crucial for understanding cognition, but the processes that allow the use of these representations to generate goal directed behaviors are equally important and have received much less attention. Testing for the mechanisms underlying how mice learn under different contingencies requires maze-based tasks while recording neural activity, as well as interventional tools such as optogenetics. We used an Arduino-based automatized pizza-shaped maze (P-maze) that allows clamping spatial and temporal components of different tasks while changing reward contingencies in order to force learning of different navigational strategies. The maze consists on a plus sign and a circular track platform with four potential reward chambers equipped with water ports. Multiple linear trajectories can be implemented to force navigation based on different set of rules. We ran a variety of reference and working memory tasks requiring egocentric and allocentric learning strategies. Our results show how some strategies are more demanding than others and illustrate the potential mechanisms underlying adaptive behavior.

PS1-46

Transcranial magnetic stimulation reveals the experience-dependent role of the prefrontal cortex in making decisions based on abstract rules.

Ms. Jennifer Paz Canosa[1,2,3], Dr. Jose L. Pardo-Vazquez[1,2,3], Dr. Carmen De Labra[1,2,3], Dr. Javier Cudeiro[1,2,3,4], Dr. Casto Rivadulla[1,2,3]

[1]NEUROcom, Departamento de Fisioterapia, Medicina e Ciencias Biomédicas, Facultad de Ciencias da Saúde, Universidade da Coruña (UDC), A Coruña, Spain, [2]Instituto de Investigación Biomédica de A Coruña (INIBIC), A Coruña, Spain, [3]Centro de Investigacións Científicas Avanzadas (CICA), Universidade da Coruña (UDC), A Coruña, Spain, [4]Centro de Estimulación Cerebral de Galicia, A Coruña, Spain

Recent evidence suggests that the brain substrate of executive function changes with experience, with the prefrontal cortex (PFc) assuming the control in the initial phases and more posterior areas taking over with training. To assess this experience-dependent involvement of the PFc on working memory and decision-making, we designed a complex behavioral task in which performance depends on the participants' ability to learn abstract rules and apply them to compare the visual properties of two stimuli. The task began with the simultaneous presentation of two visual stimuli (static gratins) that varied in two dimensions (frequency and orientation). After a short delay, the participant was presented with a cue that indicated what stimulus and dimension were relevant. After a second delay, one stimulus was presented in the center of the screen and the participant had to indicate, with an eye movement, whether this last stimulus was the same as the relevant stimulus regarding the relevant dimension. The participants (n=16) were tested in two sessions; half received transcranial magnetic stimulation (TMS) over the left dorsolateral prefrontal cortex (2 pulses at 7 Hz immediately after the cue, 100% resting motor threshold) during the first session and over the vertex (same stimulation protocol) in the second session, and the other half received the TMS in the inverse order. Our results show that the order in which the TMS was applied had significant effects on performance. When the participant received the TMS over the PFc in the first session, its performance was significantly worse than when the stimulation was applied in the second session. We did not find significant differences between stimulating the vertex in the first or second sessions. This suggests that the PFc is required to learn the rules of the task but, once this knowledge is acquired, this area plays a minor role in performance.

This work was supported by the Ministerio de Economía, Industria y Competitividad, BFU2017-82296-P. XUGA: Grupos de Referencia Competitiva (ED431C 2018/24)

19th MEETING 3-5 November 2021 Lleida
www.congresosenc.es
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-47

The role of Akkermansia muciniphila and environmental enrichment in reversing cognitive impairment associated with high-fat high-cholesterol consumption in rats

Dr. Natalia Arias[2,4], Dr Sara G Higarza[1,2], Dr Silvia Arboleya[3], Prof Jorge L Arias[1,2], Dr Miguel Gueimonde[3]

[1]Laboratory of Neuroscience, Department of Psychology. University of Oviedo, Oviedo, Spain, [2]Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain, [3]Department of Microbiology and Biochemistry of Dairy Products, Instituto de Productos Lácteos de Asturias (IPLA-CSIC), Villaviciosa, Spain, [4]Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, London, Spain

Non-alcoholic steatohepatitis (NASH) is one of the most prevalent diseases globally. A high-fat, high-cholesterol (HFHC) diet leads to an early NASH model. It has been suggested that gut microbiota mediates the effects of diet through the microbiota–gut–brain axis, modifying the host's brain metabolism and disrupting cognition. Here, we target NASH-induced cognitive damage by testing the impact of environmental enrichment (EE) and the administration of either Lacticaseibacillus rhamnosus GG (LGG) or Akkermansia muciniphila CIP107961 (AKK). EE and AKK, but not LGG, reverse the HFHC-induced cognitive dysfunction, including impaired spatial working memory and novel object recognition; however, whereas AKK restores brain metabolism, EE results in an overall decrease. Moreover, AKK and LGG did not induce major rearrangements in the intestinal microbiota, with only slight changes in bacterial composition and diversity, whereas EE led to an increase in Firmicutes and Verrucomicrobia members. Our findings illustrate the interplay between gut microbiota, the host's brain energy metabolism, and cognition. In addition, the findings suggest intervention strategies, such as the administration of AKK, for the management of the cognitive dysfunction related to NASH.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-48

Assessment of social behaviors in C57BL/6 mice exposed to chlorpyrifos: An association with autistic-like behaviors

Ms. Judit Biosca-Brull[1,2], Dra. Laia Guardia-Escote[1], Dra. Pia Basaure[1], Dr. Jordi Blanco[1,3], Dra. Maria Cabré[1,4], Dra. María Teresa Colomina[1,2]

[1]Universitat Rovira i Virgili, Research in Neurobehavior and Health (NEUROLAB), Tarragona, Spain, [2]Universitat Rovira i Virgili, Psychology, Research Center for Behavioral Assessment (CRAMC), Tarragona, Spain, [3]Universitat Rovira i Virgili, Basic Medical Science, Reus, Spain, [4]Universitat Rovira i Virgili, Biochemistry and Biotechnology, Reus, Spain

The balance between glutamate and GABA is essential for proper brain development and functioning. An imbalance between these two neurotransmitters is hypothesized to be associated with Autism spectrum disorder (ASD) symptoms. Moreover, a massive use of pesticides, in particular chlorpyrifos (CPF), has been shown to cause adverse effects, especially when the exposure takes place during development. In fact, recent literature has associated its exposure to neurodevelopment disorders including ASD. In this study, we aimed to assess social autistic-like behaviors and identify the association between the disorder and the time at CPF exposure in both sexes. For these reasons we assessed two developmental periods: i. Prenatal exposure experiment, where C57BL/6 pregnant mice were exposed to low doses of CPF through the diet, between gestational day (GD) 12 and 18. In this experiment, a positive control for autism (C57BL/6 mice exposed to valproic acid (VPA) on GD 12 and 13) was included; ii. Postnatal exposure experiment, where mice were exposed to the vehicle (corn oil) or low doses of CPF by oral gavage (from postnatal day (PND) 10 to 15). In both experiments, social behavior was evaluated during the adolescence by means of The Crawley three-chamber test. Then, at 45 days of age mice were sacrificed and brain samples collected to study gene expressions (related to glutamate and GABA signaling) in hippocampus samples. Results showed a preference for the social stimulus in all groups, while social recognition was altered in all treated mice, especially in males. Our findings suggest that males are more prone to CPF exposure, providing a plausible explanation for the sex bias in autism.

PS1-49

Genomic Basis of Drosophila Social Memory

Dr. Francisco A Martin[1], Beatriz Gil-Martí[1], Dr Abhijit Das[2], Celia G Barredo[1], Carmen Rodriguez-de Navas[1], Dr Enrique Turiegano[3], Prof Andrea H Brand[4]

[1]Cajal Institute (csic), Madrid, Spain, [2]b School of Bioscience, Indian Institute of Technology , Kharagpury, India, [3]Autonomous University of Madrid , Madrid, Spain, [4]The Gurdon Institute and Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

It is well known that isolation affects many different behaviors, such as sleep or aggressiveness. However, this raises the question of whether or not there is a "social memory": a memory specifically generated when individuals of the same species interact within a group. Interestingly, social behavior of Drosophila melanogaster has been demonstrated in recent years. In fact, the mushroom body (MB, functionally analogous to mammalian hippocampus) plays a role in such behavior, pointing towards the existence of a memory component.

We show that co-habitation increases the number of activated Kenyon Cells in the mushroom body (MB) when compared to isolated animals. This increase is also reflected in a differential behavior when a single fly is placed in a plate, which depends on its previous experience with other individuals. Both phenotypes rely on the MB and on cAMP levels, as expected if long-term memory formation does play a role. Surprisingly, memory-mutant animals behave closer to housed flies than to isolated ones, suggesting that the basal state of Drosophila is to be social.

In order to identify social memory-related genes we performed Targeted DamID in the MB comparing grouped, isolated and lack-of-memory mutant isolated animals. We show here how the epigenetic and transcriptional landscape of the MB changes in single flies, suggesting the existence of a loneliness-generated memory that affects to the final behavioral output. In summary, our work may shed light on a possible evolutionary-conserved genetic and epigenetic basis of social behavior.

PS1-51

Joint replay of correlated place maps in hippocampus

Dr. Emma Roscow[1], Dr Alex Roxin[1]
[1]*Centre de Recerca Matemàtica, Bellaterra, Barcelona, Spain*

Place cells in the mammalian hippocampus show tuning to location. During rest and sleep, when immobile, the hippocampus replays place cell sequences which represent recent trajectories taken through the environment. Such replay is enabled by attractor dynamics in the CA3 area of the hippocampus, where bursts of excitation push the network towards recently active states characterized by newly strengthened synapses between excitable place cells. Hippocampal replay is believed to play an important role in memory consolidation, generalizing across episodes, and more.

On constrained, linear paths, place cells also exhibit directional tuning, which means that trajectories in different directions are encoded by different activity patterns. Replayed trajectories can therefore be decoded to one direction only, or both directions; however, models and analysis of replay typically consider just one direction at a time.

To address this, we re-analyzed previously published single-unit recordings from CA1 in five rats during exploration of novel linear tracks. Place cells quickly developed directionally modulated tuning, forming two correlated place maps corresponding to runs in opposite directions. During brief rest periods between runs, we could detect offline reactivation of the place maps, whose Bayesian decoding often revealed a clear trajectory along the track. Joint replay, reflecting replayed patterns which are decodable to both place maps at once, appeared more than could be predicted by chance, suggesting that they form mixed attractors in the hippocampal network.

To test whether mixed attractors can explain the prevalence of joint replay, we extended a previous computational model of CA3 to produce spontaneous replay of correlated place maps. We found that only a small overlap between place maps is sufficient to produce attractor dynamics that reflect coherent replay in both place maps at once. This has implications for how hippocampal replay enables generalization between distinct episodes for flexible navigation.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-52

A computational model of Slow Wave Oscillation propagation across cortical and striatal networks

Dr. Javier Alegre-Cortés[1], Dr Maurizio Mattia[2], Dr Ramón Reig[1]
[1]Instituto de Neurociencias UMH-CSIC, San Juan de Alicante, Spain, [2]Instituto Superiore di Sanità, Rome, Italy

The activity of every neural circuit is limited by anatomical and functional constrains, which will restrict its repertoire of activity patterns. Therefore, the knowledge obtained from the study of the brain spontaneous activity is a valuable resource to understand how those circuits operate during behaviour.

We present a computational model of cortical and striatal populations under the Slow Wave Oscillation (SWO) regime. This spontaneous brain state is characterized by periods of high spontaneous activity (Up states) intermingled with silent periods (Down states) at the frequency of ~ 1 Hz. It originates in the cortex and from there propagates to the striatum, among other brain regions. While traditional SWO models are focused on single and isolated cortical areas. our study aims to provide a theoretical understating of the contribution of local and long range connections to the properties of the SWO in multiple connected neuronal populations. This includes the study of the neuronal and circuit substrates behind the different Up state attributes across cortical regions and the rostrocaudal preferential directionality of the SWO propagation. With this, we will provide an explanation to the differences in the SWO recorded in slices or brain slabs compared to the intact brain. In addition, we will use it to investigate the neural mechanisms that differentiate the dorsolateral and dorsomedial striatal regions, which were demonstrated to be two different functional circuits, based on their activity (Alegre-Cortés et al. Elife, 2021)

In conclusion, we have designed a model of SWO propagation along cortical and striatal populations. With this tool, we studied the neuronal and circuit substrates of the propagation of this wave along these networks, unifying the previous knowledge based on in vivo and ex vivo recordings. Together with this, we will predict and ultimately test the key components that differentiate dorsal striatal circuits.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-53

GENE EXPRESSION PATTERN OF HNS1 HUMAN NEURAL STEM CELLS IN DIFFERENTIATION TO APPLICATIONS IN NEUROSCIENCE

Ms. Rosa González[1], Ms. Raquel Coronel[2], Ms. Andreea Rosca[2], Ms. Patricia Mateos[2], Dr. Isabel Liste[2], Dr. Victoria López[1]

[1]Unidad de Biología Computacional, Unidad Funcional de Investigación de Enfermedades Crónicas (UFIEC), Instituto De Salud Carlos III, Madrid, Spain, [2]Unidad de Regeneración Neural, Unidad Funcional de Investigación de Enfermedades Crónicas (UFIEC), Madrid, Spain

hNS1 are multipotent Neural Stem cells (NSC) which differentiate to neurons and glial cells. Several molecular mechanisms and signalling pathways involved in NSC differentiation have been previously reported, however due to their complexity are still not fully understood. The aim of this study was to identify and characterize key molecular mechanisms involved in proliferation and differentiation of hNS1 as an experimental model to research applications in neuroscience.

To analyze gene expression alterations of hNS1 in differentiation versus proliferation we conducted RNA sequencing and in silico pathway analysis. We found 1900 genes up regulated in differentiation and 3341 genes up regulated in proliferation. hNS1 in differentiation has increased the expression of genes in the signaling pathways of axón guidance, Wnt, Notch, Sonic hedgehog (Shh), and Neurotrophins. Gene Ontology and Gene set enrichment analysis (GSEA) report genes involved in axonogenesis and synaptogenesis. The number of genes associated to extracellular matrix (ECM) is also important in neural differentiation of hNS1. Systematic search for regulatory targets from ChEA and ENCODE ChIP-seq found a significant number of genes in differentiation of hNS1 associated with REST and EZH2. We also compare the transcriptomic data obtained in this study with data from neural databases.

This poster discuss challenges and potential future directions using hNS1 as a model to approach in vitro research in neuroscience, for example enabling the research to elucidation of mechanisms of human neurodevelopmental processes.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-54

Lactoperoxidase might be a pathogenic factor in Parkinson´s disease

Dr. Emilio Fernández Espejo[1,3], Dr Fernando Rodriguez de Fonseca[2,3], Dr Juan Suárez[2,3]
[1]Reial Academia De Medicina De Catalunya, Barcelona, Spain, [2]Instituto de Biomedicina, Málaga, Spain, [3]Red Andaluza Neuro-RECA, Málaga, Spain

Introduction. Hemeperoxidases have been proposed to play a pathogenic role in neurodegenerative diseases. Lactoperoxidase (LPO), an antimicrobial hemeperoxidase, has been reported by our group to be enhanced in the cerebrospinal fluid (CSF) in patients with Parkinson disease (PD). The objective was to look at the relationship of LPO in the CSF and serum with clinical features of idiopathic PD. Material and methods. LPO concentration was analyzed through ELISA techniques. Correlation of CSF or serum LPO and MDS-UPDRS, dopaminergic medication, and other clinical parameters and scales was examined. Results. The findings revealed that LPO concentration in the CSF, not serum, was found to be elevated in patients with PD relative to controls ($p<0.001$). CSF LPO concentration negatively correlated with MDS-UPDRS part-IV score ($p<.0001$), a rating scale that allows evaluating motor complications; and with the dose intensity of the dopaminergic medication regimen, as evaluated with levodopa equivalent dose or LED (mg/day; $p<.0001$). Conclusions. CSF LPO is found to be elevated in the CSF of PD patients, and CSF LPO holds promise as potential biomarker for diagnosis of PD. Increasing the dose intensity of dopaminergic medication regimen attenuates the elevation in LPO levels in the CSF. The pathophysiological mechanisms that seem to be responsible for LPO increase would include dopamine deficiency, oxidative stress, and less likely, microbial infection.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-55

Native and nitrated α-synuclein, and patterns of nitro-α-synuclein-positive inclusions in saliva and submandibulary gland in idiopathic Parkinson's disease

Dr. Emilio Fernández Espejo[1,6], Dr. Fernando Rodríguez de Fonseca[2,6], Dr. Juan Suárez[2,6], Dr. Eduardo Tolosa[3,5], Dr. Dolores Vilas[4], Dr. Iban Aldecoa[3], Dr. Joan Berenguer[3]

[1]Reial Academia De Medicina De Catalunya, Barcelona, Spain, [2]Instituto de Biomedicina de Málaga, Málaga, Spain, [3]Hospital Clinic, Barcelona, Spain, [4]Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [5]CIBERNED, Madrid, Spain, [6]Red Andaluza Neuro-RECA, Málaga, Spain

Background. Salivary α-synuclein (aSyn) and its nitrated form or 3-nitrotyrosine-α-synuclein (3-NT-αSyn) hold promise as biomarkers for idiopathic Parkinson's disease (IPD). The objectives are to study the levels and clinical correlations of native and nitrated αSyn in saliva and submandibulary glands in patients with IPD and controls. Material and methods. Salivary and serum αSyn, and 3-NT-αSyn level is evaluated with ELISA and immunoblots. Correlations of native αSyn and 3-NT-αSyn, and clinical features of the disease are examined. Submandibulary gland sections are analyzed. Results. A) Salivary concentration and saliva/serum ratios of native and nitrated αSyn are found to be similar in patients and controls; b) salivary αSyn and 3-NT-αSyn do not correlate with any clinical feature; c) three patterns of 3-NT-αSyn-positive inclusions are observed in histological sections: rounded "Lewy-type" aggregates of 10-25 µm in diameter, and coarse aggregates with varied morphology that are all located within the interlobular connective tissue of the gland, and spheroid bodies of 3-5 µm in diameter in the cytoplasm of duct cells. Lewy-type inclusions are only observed in IPD patients, and the remainder aggregates are observed in the patients and controls. Conclusions. The patients´ saliva presents similar concentration of native αSyn and nitrated αSyn than controls, and no clinical correlations with clinical features are found. These findings preclude the utility of native and nitrated αSyn as biomarkers. "Lewy-type" inclusions expressing 3-NT-αSyn are observed only in patients, a novel finding which suggests that biopsy of submandibulary glands, if proven safe, could be a useful technique for diagnosing IPD. Finally, to our knowledge, this is the first description of 3-NT-αSyn-immunoreactive spheroid bodies within the cytoplasm of duct cells. These bodies are present in the submandibulary gland sections from all subjects regardless their pathology, and they could be related to aging.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-56

Functional epi-genomics unveils new risk genes and treatments for Alzheimer´s disease

Dr. Jose Vicente Sanchez Mut[1]
[1]*Instituto De Neurociencias De Alicante, San Juan De Alicante, Spain*

Alzheimer's disease (AD) is a complex disorder caused by a combination of genetic and non-genetic factors, which are investigated by genome- (GWAS) and epigenome- (EWAS) wide association studies, respectively. Combining the strengths of both type of studies, we have recently identified a new genetic-epigenetic interaction on Peptidase M20 Domain Containing 1 (PM20D1) associated with AD. We showed that PM20D1 expression depends on a haplotype-dependent chromatin loop between PM20D1 enhancer and promoter regions, that PM20D1 expression is increased by AD-like stressors, upregulated in AD mice and non-risk human haplotype carriers, and that its overexpression improves cognitive performance and reduces AD pathologies.

However, the precise mechanism by which PM20D1 exerts its protective role in AD remains largely unknown. PM20D1 facilitates the condensation of fatty acids and amino acids generating a series of compounds named N-acyl amino acids (NAAs). NAAs are present in all tissues, including brain, notwithstanding, little is yet known about their function and regulation. To investigate their role in AD, we NAA treated AD primary cultures, worms and mouse models, and measured AD-related pathologies and cognitive performance, and to unveil the underlying mechanisms, we applied scRNA-seq approaches and cell-type specific manipulations. Following this approach, we demonstrated that NAAs are effective in multiple cell-types and AD models, improving cognitive performance and amyloid pathologies, and activating neuronal pro-survival and microglia amyloid-clearance mechanisms.

Our approach and results not only supports the use of NAAs as a therapeutic approach for AD, but also broaden current experimental and therapeutic strategies, which is sorely needed to alleviate the burden of this devastating disease.

PS1-57

CERKL, a retinitis pigmentosa gene, is involved in the regulation of mitochondrial dynamics in retinal and hippocampal neurons

Ms. Rocío García-Arroyo[1,2], Dr. Gemma Marfany[1,2,3], Dr. Serena Mirra[1,2]
[1]Universitat De Barcelona, Barcelona, Spain, [2]CIBERER- ISCIII, Barcelona, Spain, [3]IBUB-IRSJD, Barcelona, Spain

The retina is the specialized region of the central nervous system that transduces light into neural signals. It is endowed with an active metabolism and displays a particular vulnerability to genetic and environmental alterations causing mitochondrial dysfunction. Mitochondrial alterations make photoreceptors and retinal ganglion cells (RGCs) more susceptible to cell death.

CERKL mutations cause Retinitis Pigmentosa in humans, a visual disorder characterized by photoreceptors and retinal neurons degeneration and progressive vision loss. Preliminary evidences indicate that CERKL is a sensor of photoreceptor stress by contributing to the formation of RNA stress granules. Both in human and mouse, CERKL produces a wide range of mRNA isoforms that translate into proteins displaying different domains. Depending on the domains of each protein isoform, CERKL subcellular localization and functional role may be different.

Although CERKL function has been mostly related to the retina, we have detected CERKL expression in hippocampus, where its intracellular behaviour in control and stress conditions is similar to that in RGCs. Hence, we use hippocampal cells as an additional suitable tool to study mitochondrial dynamics through live imaging.

Here we describe a pool of CERKL isoforms that localize at mitochondria in RGC and hippocampal cell primary cultures. Using Cerkl KD/KO mouse models, we studied the impact of CERKL downregulation on the mitochondrial network organization and dynamics. Our results show that the depletion of Cerkl causes alterations in mitochondrial size, distribution, and trafficking. In addition, we analysed the expression of proteins regulating mitochondrial dynamics (Mitofusin2, Opa1 and Drp1), and observed specific changes.

Overall, our studies indicate that Cerkl is a neural gene involved in the regulation of mitochondrial dynamics, thus becoming a new player in the multiple pathways that control mitochondrial health in the mammalian retina.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-58

Rifaximin prevents motor incoordination in rats with mild liver damage by preventing immune cell infiltration and neuroinflammation in the cerebellum

Ms. Gergana Ivaylova[1], Dr. Paola Leone[1], Dr. Tiziano Balzano[2], Dr. Michele Malaguarnera[3,4], Dr. Vicente Felipo[1], Dr. Marta Llansola[1]

[1]Centro de Ivestigación Príncipe Felipe, Valencia, Spain, [2]HM Hospital Universitario Puerta del Sur, Móstoles, Spain, [3]Universitat de Valencia, Valencia, Spain, [4]Universidad Nacional de Educación a Distancia, Valencia, Spain

Patients with liver cirrhosis may show minimal hepatic encephalopathy (MHE), with mild cognitive impairment, psychomotor slowing and motor incoordination, which reduce life quality and span. MHE onset is associated with a shift in peripheral inflammation that would promote infiltration of lymphocytes into the brain. Cerebellum of patients with steatohepatitis show T-lymphocytes infiltration and neuroinflammation suggesting that the changes triggering MHE may already occur at early stages of liver disease. Moreover, patients with steatohepatitis may show cognitive and motor impairment. The mechanisms leading to MHE and how to prevent or reverse it remain unclear. Rifaximin improves neurological function in MHE but the underlying mechanisms remain unclear. The aims of this work were to study the mechanisms triggering immune cells infiltration into the cerebellum, neuroinflammation and motor incoordination at early stages of liver disease in rats and advance in the understanding of the mechanisms of action of rifaximin by analyzing its effects on the above alterations.

Mild liver damage was induced in rats by CCl_4 injection during 4 weeks. Rifaximin was administered daily orally starting at 2 weeks of CCl_4. Motor coordination was assessed in the Rotarod. Immune cells infiltration, chemokines, TNFα expression and neuroinflammation in cerebellum were analyzed by immunohistochemistry. The content of extracellular GABA and glutamate and membrane expression of their transporters were analyzed.

TNFα, CCL20, CCL2 and CX3CL1 increased in cerebellum promoting T-lymphocytes and macrophages infiltration which induce neuroinflammation. Mild liver damage altered neurotransmission in cerebellum inducing motor incoordination. Rifaximin prevents immune cells infiltration and neuroinflammation and restores neurotransmission in cerebellum, improving motor incoordination.

This report shows that the induction of motor incoordination occurs at early stages of liver damage, provides clues on the mechanisms of the beneficial effects of rifaximin and suggests that early treatment with rifaximin could improve cerebellar neuroinflammation and motor alterations in patients with steatohepatitis.

PS1-59

Sphingomyelin 16:0 is a specific target for brain pathology in the acid sphingomyelinase deficiency

Dr. Angel Gaudioso[1], Dr. Josefina Casas[2], Dr. Edward Schuchman[3], Dr. Maria Dolores Ledesma[1]
[1]Centro De Biología Molecular Severo Ochoa, Madrid, Spain, [2]Catalan Institute of Advanced Chemistry (IQAC/CSIC), CIBEREHD, Barcelona, Spain, [3]Icahn School of Medicine at Mount Sinai, New York, USA

Acid Sphingomyelinase Deficiency (ASMD) is a fatal lysosomal storage disorder caused by mutations in the acid sphingomyelinase (ASM) gene leading to neurodegeneration. ASM loss of function in neurons increases total levels of sphingomyelin (SM) resulting in lysosomal alterations, oxidative stress and cell death. Lipidomic analysis have indicated that certain SM species, which differ in the fatty acid chain length and unsaturation degree, increase much more than others in brain extracts from mice lacking ASM (ASMko) that mimic ASMD.

To test the pathological effects of different SM species we added them individually to cultured cortical neurons from wild type (WT) and ASMko mice. SM 16:0, which shows the highest relative increase in the ASMko mouse brain, is also the SM species accumulating the most in neuronal cultures leading to lysosomal permeabilization and exocytosis, oxidative stress and cell death. In contrast SM 24:1 had no deleterious effects.

Gene expression analysis by qPCR in brain extracts of ASMko mice indicated the upregulation of Ceramide Synthase 5 (CerS5), which is involved in SM16:0 synthesis. We therefore proposed CerS5 inhibition as a suitable strategy to prevent SM16:0 associated toxicity. Infection of cultured ASMko neurons with adenovirus encoding shRNA-CerS5 reduced lysosomal alterations, oxidative stress and death. Moreover, intracerebellar injection of AAV9-shRNA-CerS5 improved motor abilities and Purkinje cell survival in the ASMko mice.

These results demonstrate the different toxicity of SM species in neurons and unveil SM16:0 accumulation as a specific target to address brain pathology in ASMD.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-60

STIMULATION OF MICROVESICLE/EXOSOME SECRETION BY POLYPHENOLS FOR THE TREATMENT OF NIEMANN PICK DISEASES

Ms. Beatriz Soto Huelin[1], PhD. Rebeca Busto[2], PhD. Mª Dolores Ledesma[1]

[1]Centro de Biología Molecular Severo Ochoa, Madrid, España, [2]Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, España

Niemann Pick diseases types A (NPDA) and C (NPDC) lead to cognitive impairment, neurodegeneration and early death. NPDA and NPDC have different genetic origin being caused by mutations in the acid sphingomyelinase or the cholesterol transport protein NPC1, respectively. However, they share as pathological hallmark the accumulation in the endolysosomal compartment of lipids such as sphingomyelin and cholesterol. Recently, secretion of microvesicles/exosomes (ECV) has been described as a mechanism to eliminate toxic material from cells. Polyphenols, which are organic molecules present in fruits and vegetables, have been shown to stimulate ECV secretion preventing endolysosomal lipid accumulation in different cellular models. The objective of this work was to analyze the efficacy and safety of different polyphenols to stimulate ECV release and reduce lipid overload in NPD cells, both in vitro and in vivo. To this aim we have used mice deficient in the acid sphingomyelinase (ASMko) or mutant for NPC1 (NPC nmf164), which mimic NPDA and NPDC respectively. We have found that, among the different polyphenols tested, urolithins, are the safest and most efficient in increasing ECV secretion, reducing sphingomyelin and cholesterol levels and lysosomal size in cultured bone marrow derived macrophages and neurons derived from ASMko and NPC nmf164 mice. Moreover, oral treatment with ellagic acid, the precursor of urolithins, reduced lipid levels, improved neuronal survival and diminished inflammation in the brain of the NPD mouse models. These results support the therapeutic value of ECV secretion and polyphenols opening treatment perspectives not only for NPD patients but also for other storage disorders in which intracellular lipid overload occurs.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-61

ROLE OF mGLUR5 IN THE PSYCHIATRIC ALTERATIONS OF NIEMANN PICK DISEASE TYPE C.

Ms. Ana Toledano-Zaragoza[1], Mr. Miguel Parra[1], Dr. Víctor Briz[1], Ms. Rocío Alfaro[2], Dr. Rafael Luján[2], Dr. José Antonio Esteban[1], Dr. María Dolores Ledesma[1]

[1]Centro De Biología Molecular "Severo Ochoa", Madrid, Spain, [2]Instituto de Investigación en Discapacidades Neurológicas (IDINE), Albacete, Spain

Niemann Pick Disease type C (NPC) is a lysosomal storage disorder with severe neurological implications. Although early-onset forms of the disease are associated with more severe visceral symptoms, patients most commonly develop a progressive neurological disorder resulting in ataxia, seizures, cognitive impairment and psychiatric alterations in later onset forms. Mutations in the gene encoding NPC1, an endolysosomal protein that mediates intracellular cholesterol trafficking, lead to the accumulation of cholesterol and other lipids in the endolysosomal compartments and cause NPC. Preliminary evidence obtained in our laboratory has unveiled mood and synaptic anomalies in NPC1nmf164 mice, which bear mutant NPC1 and mimic NPC. Here we propose that these anomalies can be partly explained by alterations in the metabotropic glutamate receptor 5 (mGluR5). mGluR5 is a G-protein coupled receptor involved in the fine tuning of synaptic activity, mediating synaptic plasticity events such as Long Term Depression (LTD). Alterations of this receptor have been associated with different psychiatric conditions.

Western blot, immunofluorescence and electron microscopy analysis in the brain of NPC1nmf164 mice showed an increment of intracellular mGluR5 levels in neurons. This increment can be reproduced in cultured neurons from wild type mice by blocking cholesterol trafficking and rescued in NPC neurons by cholesterol extraction with (2-Hydroxypropyl)-β-cyclodextrin. Electrophysiological analysis showed increased mGluR-LTD in NPC1nmf164 mice, which is accompanied by enhanced downstream signaling pathway. These anomalies can be ameliorated by pharmacological inhibition of mGluR5 through oral treatment with its allosteric modulator CTEP. This drug also prevents psychiatric alterations in the NPC1nmf164 mice. Our results hence involve mGluR5 alterations in the synaptic plasticity and mood anomalies typical of NPC and provide a new therapeutic strategy that might help patients suffering from this fatal disease.

PS1-62

Nrg1 haploinsufficiency alters inhibitory cortical circuits

Dr Carmen Navarro-Gonzalez[1], Yaiza Domínguez Canterla[1], Dr Ángela Rodríguez-Prieto[1], Ana González-Manteiga[1], PhD Marta Navarrete-Llinás[2], PhD Marina Benito Vicente[3], Dr. Pietro Fazzari[1]

[1]Cipf, Centro De Investigacion Principe Felipe, Valencia, Spain, [2]CSIC, Madrid, Spain, [3]Hospital Nacional de Parapléjicos, Toledo, Spain

Neuregulin 1 (NRG1) and its receptor ERBB4 are schizophrenia (SZ) risk genes that control the development of both excitatory and inhibitory cortical circuits. Most studies focused on the characterization ErbB4 deficient mice. However, ErbB4 deletion concurrently perturbs the signaling of Nrg1 and Neuregulin 3 (Nrg3), another ligand expressed in the cortex. In addition, NRG1 polymorphisms linked to SZ locate mainly in non-coding regions and they may partially reduce Nrg1 expression.

Here, to study the relevance of Nrg1 partial loss-of-function in cortical circuits we characterized a recently developed haploinsufficient mouse model of Nrg1 (Nrg1tm1Lex). These mice display SZ-like behavioral deficits. The cellular and molecular underpinnings of the behavioral deficits in Nrg1tm1Lex mice remain to be established.

With multiple approaches including Magnetic Resonance Spectroscopy (MRS), electrophysiology, quantitative imaging and molecular analysis we found that Nrg1 haploinsufficiency impairs the inhibitory cortical circuits. We observed changes in the expression of molecules involved in GABAergic neurotransmission, decreased density of Vglut1 excitatory buttons onto Parvalbumin interneurons and decreased frequency of spontaneous inhibitory postsynaptic currents. Moreover, we found a decreased number of Parvalbumin positive interneurons in the cortex and altered expression of Calretinin. Interestingly, we failed to detect other alterations in excitatory neurons that were previously reported in ErbbB4 null mice suggesting that the Nrg1 haploinsufficiency does not entirely phenocopies ErbB4 deletions.

Altogether, this study suggests that Nrg1 haploinsufficiency primarily affects the cortical inhibitory circuits in the cortex and provides new insights into the structural and molecular synaptic impairment caused by NRG1 hypofunction in a preclinical model of SZ.

PS1-63

Aluminum Profiles in the Cerebrospinal Fluid during Alzheimer's Disease development. Relation to Pathological Biomarkers

Prof. Raquel Marin[1], Dr. Fátima Mesa-Herrera[2], Dr. Eduardo Torrealba[3], Prof. Mario Diaz[1]
[1]Universidad De La Laguna, Santa Cruz De Tenerife, Spain, [2]Centro Atlántico del Medicamento, La Laguna, Spain, [3]Hospital Universitario de Gran Canaria Dr. Negrín, , Spain

Alzheimer´s disease (AD) is a complex neurodegenerative disease characterized by progressive destruction of mainly brain cortical areas related to cognitive and memory performances. Most identified forms of AD are idiopathic and the precise pathogenic mechanisms remain yet unknown.
Aluminum is considered a neurotoxic metal for humans. Some previous studies have revealed the accumulation of aluminum in the cerebral parenchyma of postmortem brains of patients suffering AD. In this study, we show that aluminum is present in significant amounts in the cerebrospinal fluid (CSF) of control healthy individuals and that its concentration increases in individuals with AD. Aluminum in CSF is also elevated in patients with mild cognitive impairment (MCI), considered to be a prodromal stage of AD. Aluminum contents correlate with classical biomarkers of AD (particularly with phosphorylated tau and amyloid β) following complex association patterns which vary depending on the stage of the AD spectrum, and dismiss a direct relationship. Associated with increased aluminum in AD patients, indicators of oxidative stress, namely Iso-PG2 and MDA, are also increased in the CSF of AD and MCI individuals, which also correlate with aluminum concentration. We hypothesize that aluminum content in CSF is a significant factor which, in synergy with other variables, may favors the initiation and progression of AD.
Acknowledgements: Grants SAF2017-84454-R (MINECO) and ProID2020010075 (Agencia Canaria de Investigación, Innovación y Sociedad de la Información)

PS1-64

FUSΔ14 mutation causes changes in lipid metabolism in mice with motor and cognitive alterations

Mr. Juan Miguel Godoy Corchuelo[1], Ms Zeinab Ali[2], Mr Luis C. Fernández-Beltrán[1], Mr Jordi Matias-Guiu Antem[1], Mr Thomas Cunningham[2], Ms Silvia Corrochano[1]

[1]Fundación Para La Investigación Sanitaria Del Hospital Clínico San Carlos, Madrid, Spain, [2]MRC Harwell Institute , Oxfordshire, United Kingdom

Amyotrophic Lateral Sclerosis (ALS) is a lethal neurodegenerative disease characterised primarily by the progressive loss of motor neurons in the spinal cord and cerebral cortex. There are alterations in the regulation of lipid metabolism in ALS but the origin of those remains unknown. Mutations in FUS (Fused in sarcoma) are causative of ALS and forms of cognitive impairment and dementia. The FUSDelta14 mutation causes aggressive juvenile cases of ALS. The mouse model of physiological expression of mutant FUSDelta14 in heterozygosity causes very mild and late onset motor neuron degeneration with no other major phenotypes. The homozygous mice die at birth. We aim to generate homozygous mice and evaluate the effect of the mutation in the regulation of lipid metabolism and its impact in motor and cognitive phenotypes.

We generated FUSDelta14 homozygous mice in a defined F1 hybrid background of C57Bl/6JxDBA/2J. We use both males and females for this study and conduct a comprehensive set of metabolic, motor and cognitive tests at early age. We also performed RNA-sequencing of frontal brain, spinal cord, white and brown fat, muscle and liver from wild type and homozygous FUSDelta14 mice.

Homozygous FUSDelta14 mice are smaller than the heterozygous and wildtype littermates. These mice show systemic metabolic dysregulation with altered glucose tolerance, increased fat depots, higher blood cholesterol levels and lower resting energy expenditure. Their brains are also thinner and have reduced marble burying capacity and indifference in the recognition of noble objects. Homozygous mice develop mild motor alterations evidenced by altered electromyogram. A systemic transcriptomic analysis of several tissues confirmed the lipid metabolic alterations phenotype observed.

We show that FUSDelta14 mutation causes early central lipid metabolic alterations that affect cognitive and motor phenotypes, placing lipid metabolism dysregulation as one of the main pathological mechanisms in the ALS-FTD spectrum of disorders.

PS1-65

E2F4DN-based gene therapy recovers long-term potentiation and hippocampal-dependent memory in homozygous 5xFAD mice.

Dr. Cristina Sánchez-Puelles[1,2], Dr. Gertrudis Perea[2], Dr. José María Frade[2]
[1]Tetraneuron, Valencia, Spain, [2]Cajal Institute (CSIC), Madrid, Spain

Compelling evidence demonstrates that neurons upregulate the expression of cell-cycle markers when subjected to stress. This is the case in Alzheimer's disease (AD), in which cell-cycle reentry, followed by DNA duplication (neuronal tetraploidization), precedes and recapitulates its neuropathological hallmarks, suggesting that this process participates in the etiology of AD. E2F4, a transcription factor involved in maintenance of quiescence, becomes phosphorylated in APP/PS1 mice and in Alzheimer's patients. We have demonstrated that the phosphorylation of two conserved Thr residues of E2F4 is necessary to induce neuronal tetraploidization and cognitive loss in AD. Therefore, it was developed a novel therapy consisting in neuronal expression of a dominant negative form of E2F4 (E2F4DN), not phosphorylatable. This therapy has been patented (US9567384B2, EP2783696B1, JP6100276B2), and is licensed by Tetraneuron, a Spanish spin-off biotech company.

Initial stages of AD are proposed to be linked to alterations in synapse function, responsible for cognitive deficits associated to the disease. Thus, we hypothesized that viral expression of E2F4DN could correct this synaptic dysfunction. First of all, basal membrane properties and spontaneous synaptic activity (sEPSC) was analyzed through whole-cell recordings in hippocampal primary cultures transduced with a viral vector containing E2F4DN. We demonstrated that it does not alter basal properties of hippocampal neurons. Afterwards we expressed E2F4DN through intravenous administration of AAV-E2F4DN in six-weeks old control and homozygous 5xFAD mice. Synaptic function was measured by electrophysiological recordings of field excitatory postsynaptic potential (fEPSPs) in hippocampal CA3-CA1 synapses. We found that E2F4DN reverts LTP inhibition. Furthermore, this LTP recovery leads to cognitive improvement. 5xFAD mice treated with our therapy present a notably improvement in two hippocampal-dependent memory tasks (novel-object location and contextual fear conditioning). Thus, we report here that E2F4DN-based gene therapy represents a promising approach for AD treatment with capacity to prevent cognitive decline associated to the disease.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-66

The matricellular protein hevin´s expression in nucleus accumbens is altered by alcohol chronic treatment and administration after withdrawal

Ms. Amaia Nuñez-delMoral[1], Dr. Bianchi P.C.[2], Augusto Anesio[2], Paola Palombo[2], Dr. Cruz F.C.[2], Dr. Vincent Vialou[3], Dr. Callado L.F.[1], Dr. Erdozain A.M.[1]

[1]University of the Basque Country (UPV/EHU) and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Leioa, Spain, [2]Universidade Federal de São Paulo - UNIFESP, São Paulo, Brazil, [3]Neurosciences Paris Seine - Institut de Biologie Paris Seine (NPS – IBPS), Sorbonne Université, INSERM U1130, CNRS UMR8246, Paris, France

The matricellular protein hevin is highly expressed in adults, in both neurons and astrocytes, and enhances functional synapses formation. In a previous study, we showed a higher expression of hevin in postmortem human brain of alcoholic subjects compared to controls, which raised the question whether this alteration was the result of acute and/or chronic alcohol exposure or it was a consequence of alcohol withdrawal. Therefore, our aim was to determine the possible alterations in hevin expression due to acute or chronic alcohol intraperitoneal administration and alcohol relapse in C57BL/6J mice. We performed four different treatments: 12 days of chronic treatment with saline or ethanol (1.75 g ethanol/kg) followed by 3 days of withdrawal, and finished with a challenge dose of saline or ethanol. Groups: 1) saline – saline, 2) saline – ethanol, 3) ethanol-saline and 4) ethanol-ethanol. We used western blot technique to measure the expression levels of hevin in bilateral punches of five brain areas: frontal cortex (FC), amygdala (AMY), hippocampus (HIP), dorsal striatum (CPu) and nucleus accumbens (NAcc). In AMY, acute treatment showed decrease in the hevin´s expression in comparison to saline treatment. Interestingly, chronic ethanol treatment followed by a single dose challenge after withdrawal increased hevin expression levels in NAcc, compared to both saline treatment and acute ethanol treatment. At the same time, in NAcc lower levels of hevin expression were detected after ethanol withdrawal in comparison to the challenge after chronic administration of ethanol. We did not detect significant differences in hevin expression in FC, HIP or CPu. Thus, these results together with the alterations observed in humans suggest that alcohol intake could alter hevin´s expression, suggesting a role for hevin in the neurobiology of alcoholism.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-67

Lipid metabolism dysregulation is an early and progressive pathological mechanism in the spinal cord of transgenic SOD1 mice.

Mr. Luis Carlos Fernandez-Beltran[1], Mr. Juan Miguel Godoy Corchuelo[1], Ms. Maria Losa-Fontangordo[1], Dr. Jorge Matias-Guiu Guia[1], Dr. Silvia Corrochano Sánchez[1]
[1]*Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain*

Amyotrophic lateral sclerosis (ALS) is a multifactorial and multistep fatal degenerative disorder. There are several pathological mechanisms leading to motor neuron death, although there are many unknowns in the disease aetiology of ALS. Alterations in lipid metabolism are well documented in the progression of ALS. Both patients and animal models have significant metabolic dysregulation such as hypermetabolism, dyslipidemia and progressive weight loss. In the spinal cord of mouse models and ALS patients there are alterations of lipid metabolites, including oxysterols, ceramides and sphingolipids. The origin of these lipid metabolic alterations remains unclear. We aim to identify early lipid metabolic pathways altered before disease symptoms in the spinal cord of mouse model of ALS. We performed a transcriptomic analysis of the spinal cord of SOD1-G93A and wild type littermate mice at pre-symptomatic disease stage and identified several altered genes involved in the regulation of lipid metabolism. We expanded our study conducting a transcriptomic meta-analysis combining RNA-seq studies from the spinal cord of SOD1 mice at different stages of disease: three pre-symptomatic at 90 days, and three symptomatic at 120-150 days. The meta-analysis identified several lipid metabolic pathways dysregulated from pre-symptomatic that were progressively worsening at symptomatic disease stage. The cholesterol biosynthesis and transport, ceramide catabolism, and eicosanoid synthesis were the main lipid metabolic pathways altered from early stages. Here, we present an insight into the pathological mechanisms in ALS, supporting that lipid metabolic alterations are central to ALS aetiology, which opens new options for the treatment of these devastating conditions.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-68

Understanding the role of pre-conditioning inflammation on the onset of Alzheimer's Disease

Ms. Monica Guerrero Carrasco[1], Ms. Imogen Targett[1], Mr. Adrian Olmos-Alonso[1], Dr. Mariana Vargas-Caballero[1], Dr. Diego Gomez-Nicola[1]
[1]*University Of Southampton, Southampton, United Kingdom*

Microglial cells are self-renewing macrophages of the brain with a highly regulated system of turnover (1) and are the first line of defence in the CNS. In the onset of Alzheimer's disease, microglial cells become activated and proliferate (2) and we recently identified that the prolonged engagement of microglia in proliferation induces replicative senescence, accelerating the disease (3). We now hypothesise that early life insults could promote an accelerated proliferation of microglial cells, pre-conditioning them to become senescent. Senescent microglia may show a phenotypic change characterised by cell cycle arrest and primed inflammatory response, which later in life could have a negative impact on the onset of AD. We investigated the effect of repeated sub-threshold inflammatory challenges in early life, similar to those seen in the human life course such as bacterial infection. We model this by injecting low-doses of LPS to young mice and then studying the effect that has on the severity of AD-like pathology later in life, using an inducible APP model (line 102) (4). Our results indicate that sub-threshold inflammation promotes the proliferation of microglial cells driven by the CSF1R pathway, which might be pre-conditioning them to become senescent. The outcome of this research could support future preventative approaches to delay the onset of clinical symptoms.

(1) Askew, K., et al. (2017) Coupled Proliferation and Apoptosis Maintain the Rapid Turnover of Microglia in the Adult Brain. Cell Reports.
(2) Olmos-Alonso, A., et al. (2016) Pharmacological targeting of CSF1R inhibits microglial proliferation and prevents the progression of Alzheimer's-like pathology. Brain.
(3) Hu Y., et al. (2021) Replicative senescence dictates the emergence of disease-associated microglia and contributes to Aβ pathology. Cell Reports. In press.
(4) Sri S., et al. (2019) Emergence of synaptic and cognitive impairment in a mature-onset APP mouse model of Alzheimer's disease. Acta Neuropathological Communications.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-69

Morphological and stereological study of neurons and interneurons in the non-human primate striatum

Ms. Natalia López-González del Rey[1,2], Dr. Carmen Cavada[3], Dr. José Ángel Obeso[1,4], Dr Javier Blesa[1,4]

[1]HM CINAC (Centro Integral de Neurociencias Abarca Campal), Hospital Universitario HM Puerta del Sur, HM Hospitales, Móstoles, Spain, [2]PhD Program in Neuroscience, Autonoma de Madrid University, , Spain, [3]School of Medicine, Universidad Autónoma de Madrid, , Spain, [4]CIBERNED (Center for Networked Biomedical Research on Neurodegenerative Diseases), Instituto Carlos III, , Spain

The striatum is composed of projection neurons, the medium spiny neurons (MSN), and of a small population of interneurons which modulate and control the striatal output. Most interneurons are GABAergic; they are divided into several subtypes based on their immunostaining for various proteins such as parvalbumin (PV), calretinin (CR), neuropeptide Y, somatostatin, nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH) and tyrosine hydroxylase (TH). There is an additional non-GABAergic interneuron subtype, the cholinergic interneurons which expressed choline acetyltransferase (ChAT). Most information on the striatal neuronal populations has been gathered in rodents (3-5%), whereas the evidence in the primate striatum is scarce and fragmented (6-26%). Thus, up to date there is no accurate stereological data on the absolute number of each neuronal subtypes in primates. This raises a question: is this figure accurate for the primate brain?

Performing histological staining for each molecular marker, we provide the morphological description and the distribution pattern in the control non-human primate for each striatal neuronal population caudate, putamen and ventral striatum. We also have used unbiased stereological methods on consecutive sections where densities of projection neurons and subpopulations of interneurons were calculated to obtain a general landscape of the proportion of striatal neurons and interneurons.

We report a gradient of striatal neuronal subtypes, being the most abundant the MSN projection neurons, followed by CR+, PV+, NADPH+ and ChAT+ and TH+ interneurons. We have estimated the percentage of interneurons in the whole macaque striatum as a 14%, resembling the relative proportion of striatal interneurons in humans reported previously and significantly higher than in the rodent striatum. The presented data is important for the understanding of striatal circuits and reinforce the importance of considering the relative presence of the different neuronal populations to draw functional conclusions.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-70

Proteomic and stereological study of human amygdala in Parkinson's disease

Ms. Sandra Villar-conde[1], Ms. Melania Gonzalez-Rodriguez[1], Ms. Veronica Astillero-Lopez[1], Ms. Patricia Villanueva-Anguita[1], Dr. Daniel Saiz-Sanchez[1], Dr. Isabel Ubeda-Banon[1], Prof. Alino Martinez-Marcos[1], Dr. Alicia Flores-Cuadrado[1]

[1]*Ciudad Real Medical School/CRIB, University of Castilla-La Mancha., Ciudad Real, Spain*

Emotional impairments such as anhedonia are common non-motor symptom in Parkinson's disease (PD). Amygdala involvement by α-synuclein (Braak stage 3) could constitute neural substrates underlaying this emotional deterioration.

Differential α-synucleinopathy among amygdaloid nuclei has been described. MRI and VBM studies have revealed volumetric changes in the amygdala with conflicting results. To our knowledge, only one stereological study has studied the neuronal population in the amygdala, indicating neurodegeneration in the cortical and basolateral nucleus. However, glial populations have been neglected. Likewise, proteomic analysis focused on the amygdala in PD are lacking. This work, therefore, aims at analyzing volumetric and glial changes as well as to reveal the profile of proteomic changes of the amygdala in PD.

Brains from PD (Braak 5-6) and non-PD age-matched subjects were obtained from Spanish Biobank network. All procedures were approved by the Ethical Committee for Clinical Research at the University Hospital of Ciudad Real (SAF2016-75768-R and PID2019-108659RB-I00). Volume changes were estimated by Cavalieri's method. Optical Fractionator method was used to analyze microglia (Iba-1) and astroglia (GFAP). SWATH-MS and MALDI on tissue approaches were used for the proteomic study.

Results reveal differential glial involvement among amygdaloid nuclei as well as identify important proteomic alterations that could constitute potential biomarkers.

This work is sponsored by the UCLM/ERDF (2020-GRIN-29145 to NPND), the Spanish Ministries of Economy and Competitiveness/ERDF (SAF2016-75768-R) and Science and Innovation (PID2019-108659RB-I00 to AMM) and the Autonomous Government of Castilla-La Mancha/ERDF (SBPLY/17/180501/000430 to AMM and DSS). SVC and MGR held a predoctoral fellowship granted by UCLM/ESF and VAL held an assistant professorship granted by UCLM/ERDF. Authors thank Dr. Pilar Alberdi (technical specialist UCLM/ERDF supported) her proteomic expertise.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-71

The genetic load determines behavioural phenotype and gut microbiota composition in the 5xFAD mouse model of Alzheimer's Disease

Ms. Dina Medina-Vera[1,2,3,4], Dr. Cristina Rosell-Valle[1], Dr. Emma N. Zambrana-Infantes[5], Antonio J. López-Gambero[1,2], Mr. Andrés Gonzalez-Jimenez[6], Mr. Juan A. Navarro[1,3], Dr. Francisco J. Pavon[1,4], Dr. Luis J. Santín[5], Dr. Juan Suarez[1,3], Dr. Fernando Rodríguez de Fonseca[1]

[1]Instituto de Investigación Biomédica de Málaga-IBIMA, Unidad de Gestión Clínica de Salud Mental, Hospital Regional Universitario de Málaga, Malaga, Spain, [2]Facultad de Ciencias, Universidad de Málaga, Malaga, Spain, [3]Facultad de Medicina, Universidad de Málaga, Malaga, Spain, [4]Instituto de Investigación Biomédica de Málaga-IBIMA, Unidad de Gestión Clínica del Corazón, Hospital Universitario Virgen de la Victoria, Malaga, Spain, [5]Facultad de Psicología, Universidad de Málaga, Malaga, Spain, [6]Bioinfirmatic ECAI, Instituto de Investigación Biomédica de Málaga-IBIMA, Malaga, Spain

There are many hypotheses about the neuropathological origin of Alzheimer's disease (AD). The amyloid cascade hypothesis remains the most widely accepted by the scientific community, although the role of beta-amyloid as the sole cause of neuropathological hallmarks of the non-inherited form of AD (accounts for 95% of all cases) is questionable. The 5xFAD mice are commonly used as AD animal models that co-overexpress human APP and PSEN1 transgenes with a total of five AD-linked mutations, thus accelerating amyloid plaques formation. Many reports have described that 5xFAD mice presented cognitive alteration. However, no attention is paid to the effect of genetic load, heterozygous versus homozygous condition, on the histology, physiology, and gut microbiota composition. Hence, in this study, heterozygous and homozygous 5xFAD mice were used to test whether additional factors beyond hippocampal amyloid burden contributes to cognition impairment at 11 months old. Our results suggest that accumulation of Aβ1-40 and Aβ1-42 is present in both heterozygous and homozygous hippocampus of 5xFAD mice. However, only homozygous mice had cognitive impairment flexibility in the Morris water maze and impairment of working spatial memory in the Y-maze test. This strikes differences between behavioral and immunopathological phenotypes extend to microbiota, where the bacterial population is different in the three studied genotypes. In homozygous 5xFAD mice, a lower bacterial diversity is observed compared to the wild-type and heterozygous 5xFAD genotypes, decreasing the abundance of bacteria of the Firmicutes phylum and increasing bacteria of the Bacteroidetes phylum. Therefore, we suggest that the accumulation of beta-amyloid may not be the only cause of the worsening of cognitive impairment, but additional factors including the microbiota-brain axis might be altering the function of the immune system, favouring inflammation, and nervous system through bacterial product influencing the development of AD.

Keywords: 5xFAD, hippocampus, cognition impairment, neuroinflammation, microbiota
Acknowledgments: EULAC-HEALTH FATZHEIMER

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-72

Neuronal expression of E2F4DN attenuates the immune response observed in the cerebral cortex and hippocampus of 5xFAD mice

Ms. Morgan Ramón-Landreau[1,2], Dr. Noelia López-Sánchez[1,2], Dr. José María Frade[1]
[1]Cajal Institute (CSIC), Madrid, Spain, [2]Tetraneuron S.L., Valencia, Spain

Alzheimer's disease (AD) is a neurodegenerative disorder in which altered immune response is an important etiological factor. The transcription factor E2F4 participates in tissue homeostasis and regulates gene networks affected in AD, thus constituting a potential target for intervention. We have studied whether neuronal expression of a dominant negative form of E2F4 (E2F4DN), unable to become phosphorylated in a Thr motif that controls its activity, can modulate the immune response observed in AD. To this aim, we generated Mapt:E2F4DN knock-in mice (E2F4DN mice) that, together with control Mapt:EGFP knock-in mice (EGFP mice), were crossed with 5xFAD mice, a known murine model of AD. Neuronal expression of E2F4DN in 5xFAD mice led to reduced astrogliosis (i.e. area occupied by GFAP) at 3 months of age, both in cortex and hippocampus. In addition, Iba1-positive cells exhibited reduced size in the cortex and hippocampus of 5xFAD/E2F4DN mice at 3 and 6 months, suggesting that microglia activation is attenuated by the presence of neuronal E2F4DN. To analyze the crosstalk between E2F4DN expressing neurons and microglia, we cultured microglial cells with conditioned media from E2F4DN- or EGFP-expressing neurons. The differences in morphology observed suggest that neuron-microglia communication occurs via soluble factor. In vivo, most Iba1-positive cells of 5xFAD/E2F4DN mice were associated to amyloid beta (Aβ) deposits, which were increased in size, but not in number at 3 months of age. Moreover, neuronal expression of E2F4DN slowed down the accumulation of Aβ at 6 months of age. We speculate that the crosstalk between E2F4DN-expressing neurons and microglia favors the aggregation of oligomeric Aβ at early stages of AD, thus reducing its toxicity, and attenuates Aβ deposition at later stages. Altogether, our data are consistent with a beneficial immune response in 5xFAD mice expressing neuronal E2F4DN, which we propose as a therapeutic agent against AD.

PS1-73

The role of brain synaptic dysfunction in the progression of C9orf72-ALS/FTD

Dr. Natalia Arias[1,2], Mrs Dhruv Sigh[1], Ms Aleksandra Kaliszewska[1], Mrs Joseph Allison[1], Ms Barbora Vidimova[1], Ms Sara Ketola[1], Ms Megan Tomlin[1], Prof Christopher Shaw[1]

[1]UK Dementia Research Institute at King´s College London, Institute of Psychiatry, Psychology and Neuroscience, Department of Basic & Clinical Neuroscience, London, United Kingdom, [2]INEUROPA, Instituto de Neurociencias del Principado de Asturias, Oviedo, Spain

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are fatal neurodegenerative diseases seen in comorbidity in up to 50% of cases. The clinical overlap between the two diseases is also reflected in their genetics and neuropathology, with ALS and FTD sharing a number of key pathological characteristics. One of which is protein aggregation. Accumulation of protein aggregates leads to synapse loss and dysfunction, which has been associated with the development of cognitive deficits. Given that a hexanucleotide repeat expansion in the C9orf72 gene is the most common genetic cause of ALS and FTD, we used a transgenic mouse model C9orf72-BAC with up to 450 repeats, to study C9-ALS/FTD-related synaptic dysfunction. Using Golgi and immunofluorescent staining, we investigate how dendritic spines rearrange and neuronal and dendritic morphology change from 1 to 24 months in the cingulate cortex, hippocampus, cerebellum, and spinal cord of C9orf72-BAC mice. We used two groups: C9orf72-BAC transgenic (n=6) and non-transgenic (n=6) animals. Sholl analysis was used for quantification of morphological features in Golgi staining. Our results showed an increase in immature spines such as thin and stubby types, in the transgenic mice from 3 to 6 months of age, accompanied by an increase in soma size. Ageing effects were shown from 18 months in both groups. Those changes were accompanied by neuronal loss in hippocampus, cerebellum at early stages. Additionally, the dipeptide repeat protein (DPR) PR was found to stain axonal projections in the hippocampus and formed greater numbers of plaques in the hippocampus and cerebellum of transgenic mice. The results of our study indicate that early changes related to neuronal degeneration and DPR accumulation can be detected at the pre-onset stages of the disease.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-74

Trophic dependence of abducens motoneurons on muscle VEGF

Ms. P. M. Calvo[1], Dr. R. G. Hernández[1], Prof. R. R. de la Cruz[1], Prof. A. M. Pastor[1]
[1]*Facultad de Biología, Universidad de Sevilla, Sevilla, Spain*

Although initially discovered by its angiogenic properties, vascular endothelial growth factor (VEGF) has recently been shown to act as a neuroprotective molecule after different types of lesion, particularly in motoneurons. In the present work, we applied VEGF to axotomized abducens motoneurons to unravel whether this factor could recover the synaptic loss and firing alterations induced by axotomy. In addition, we applied VEGF neutralizing antibody in the muscle to study the role of this factor in the physiology of uninjured motoneurons.

Adult cats were prepared for the chronic recording of abducens motoneuron discharge activity simultaneously with eye movements. For the study of the effects of axotomy, the VIth nerve was cut in the orbit and its proximal stump inserted in a home-made chamber for the administration of PBS+0.1% BSA. VEGF administration was performed through either the nerve or the fourth ventricle, and the application of the neutralizing antibody was made directly on the muscle. We also carried out an immunocytochemical study of motoneuronal synaptic boutons at the confocal level, by using antibodies against synaptophysin, VGAT and GFAP, and against GLUT-1 for the study of the vasculature.

Axotomy led to an overall low firing rate and a decrease in motoneuronal sensitivities to eye movement parameters. These physiological changes were accompanied by the withdrawal of afferent synaptic boutons and an intense astrocytic reactivity. VEGF treatment recovered both the firing alterations and the synaptic stripping in axotomized motoneurons, and reverted the astrocytic reaction to control values without an increase of blood vessels. Moreover, the administration of VEGF neutralizing antibody rendered uninjured motoneurons into an axotomy-like state.

This is the first work demonstrating that VEGF acts as a powerful synaptotrophic molecule for injured motoneurons, restoring firing and synaptic inputs to the control situation. The present data reinforce the therapeutical potential of VEGF for motoneuronal disorders.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-75

The increase in doublecortin-immunoreactive immature neurons in the olfactory cortex is linked to symptom onset in a mouse model of Rett syndrome

Ms Paloma Sevilla-Ferrer[1], Mr Josep Pardo-García[1], Ms Elena Martínez-Rodríguez[1], Dr María Abellán-Álvaro[1], Dr Mónica Santos[2], Dr Enrique Lanuza[1], Dr. Carmen Agustín-Pavón[1]

[1]Universitat De València, València, Spain, [2]Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal

Rett syndrome (RTT) is a rare neurodevelopmental disorder that affects mainly females, predominantly caused by mutations in the X-linked gene coding for methyl CpG-binding protein 2 (MeCP2). This protein is involved in the epigenetic regulation of gene expression, and is broadly expressed in mature neurons. Patients with RTT suffer from intellectual disability, loss of speech and motor abilities, and seizures. We have previously shown that lack of MeCP2 leads to a region-specific increase in immature neurons, expressing doublecortin (DCX), in the olfactory cortex of young adult, symptomatic, Mecp2-null male mice, but not in age-matched, asymptomatic, Mecp2-heterozygous females. Here, we sought to investigate whether the impairment in neuronal maturation would be overt in Mecp2-heterozygous symptomatic females. To do so, we performed an immunohistochemical detection of DCX in 2 and 6 months old Mecp2-heterozygous female mice and their wild-type littermates. We found that DCX-immunoreactivity was increased in the piriform cortex, but not the olfactory bulbs or the hippocampus, of 6 months old mutant females, as compared to their wild-type controls. This increase was mainly due to an excess of DCX-tangled cells, the most immature ones, in the piriform cortex of Mecp2-heterozygous females. A slight increase in the proportion of DCX-tangled cells was already apparent in 2 months old Mecp2-heterozygous females, but became significant in older mice. These results confirm and extend our previous data, supporting that MeCP2 is involved in neuronal maturation in a region-dependent manner, and showing that this effect is linked to the onset of overt pathology. Funded by Ministerio de Ciencia e Innovación (PID2019-107322GB-C22).

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-76

FAMILIAL ALZHEIMER'S DISEASE GENE MUTATIONS REGULATE MITOCHONDRIAL DNA REPLICATION, TRANSCRIPTION AND RELEASE.

Margalida Puigròs[1,3], Verónica Pablo-Fontecha[1,3], Andrea Reparaz[1,3], Petar Podlesniy[1,3], Dr. Ramon Trullas[1,2,3]
[1]Neurobiology Unit, IIBB/CSIC, Barcelona, Spain, [2]IDIBAPS, Barcelona, Spain, [3]CIBERNED, Barcelona, Spain

Mitochondrial DNA (mtDNA) encodes proteins that are necessary for the production of cellular energy by the mitochondria. In neurons, shortage of this energy due to mitochondrial dysfunction triggers neurodegeneration. In our previous studies, we reported that subjects with pathogenic mutations that cause familial Alzheimer's disease exhibit low content of cell-free mtDNA (cf-mtDNA) in cerebrospinal fluid (CSF) before the appearance of clinical signs, suggesting that a decrease in the CSF content of cf-mtDNA precedes the clinical signs of dementia. However, the source and the mechanisms of cf-mtDNA release are unclear. Moreover, the molecular mechanisms involved in regulation of mtDNA copy number and release by different genes that cause familiar Alzheimer's disease are unknown. To explore these questions, we have now investigated the effect of APP-Swe/Ind and PSEN1dE9 mutations on mtDNA replication, transcription and release in SH-SY5Y cell clones that permanently express these mutations. We found that either APP-Swe/Ind or PSEN1d9 gene mutations both reduce mtDNA copy number, the amount of L-strand and H-strand mtDNA transcripts per cell, and the release of cf-mtDNA. In addition, we found that pharmacological inhibition of mitophagy enhances the release of cf-mtDNA in control cells, but not in cell clones expressing APP-Swe/Ind and PSEN1dE9 mutations. These results indicate the presence of an mtDNA quality control system independent of mitophagy that is impaired by APP-Swe/Ind and PSEN1dE9 mutations. Moreover, the present results show that alteration of mtDNA dynamics is a common factor of different pathogenic mutations that cause Alzheimer's disease. Supported by SAF2017-89791-R, CIBERNED PI2020/09-04 and CIBERNED CB06/05/0050 grants.

PS1-77

Cellular plasticity of neuropeptidergic systems in the mouse hypothalamus.

Dr. Pilar Madrigal[1], Dr. Sandra Jurado[1]
[1]*CSIC, San Juan de Alicante, Spain*

The neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) play critical roles in regulating complex animal behaviors and homeostatic functions. Both neuropeptides are mainly synthetized at specific hypothalamic nuclei, such as the paraventricular and suprachiasmatic nucleus (PVN and SON). Our previous work (Madrigal & Jurado, 2021) revealed a significant number of neurons co-expressing OXT and AVP during early postnatal stages (PN7) coinciding with a critical period for social interaction. This mixed population drastically decline in the adult brain suggesting that a switch in neuropeptide expression is required for the maturation of the system. Here, we have analyzed the plastic properties of OXT and AVP circuits in the adult brain using brain clearing techniques (iDISCO+) and 3D imaging. Our study has revealed region-dependent cellular plasticity in the SON and the retrochiasmatic area (RCH) in response to sexual experience and motherhood. Our observations indicate a prevalence of AVP neurons in the SON of virgin females that turns into an increase of OXT neurons after giving birth. We explored the hypothalamic neuronal subtypes more susceptible to undergo changes in neuropeptide expression by expanding our analysis to additional markers associated to OXT and AVP neurons. To this aim, we combined interneuron marker GAD67 and monoamine indicator tyrosine hydroxylase (TH) with OXT and AVP. Our results indicate the presence of GAD67 positive neurons in the hypothalamus but minimal co-localization with neither OXT nor AVP cells, suggesting that oxytocinergic and vasopressinergic interneurons may express different markers like GAD65. On the other hand, we found that sexual experience induces TH expression in a subpopulation of AVP and OXT neurons in the RCH. Our findings provide new information to understand the specification of neuropeptidergic systems during development and their plastic properties upon critical life events in the adult animal.

PS1-78

FUNCTIONAL PROPERTIES AND MOLECULAR MACHINERY UNDERLYING OXYTOCIN RELEASE

Ms. Beatriz Aznar-Escolano[1], Dr. M. P. Madrigal[1], Dr. Sandra Jurado[1]
[1]*Instituto De Neurociencias De Alicante, San Juan de Alicante, España*

The oxytocinergic system regulates key brain functions and its dysregulation leads to neurological disorders. However, it is still unknown how oxytocin (OXT) exocytosis is regulated in the Central Nervous System (CNS). Oxytocinergic neurons in the hypothalamus are responsible for modulating OXT levels in the CNS mostly through release events occurring at their soma and dendrites. Immunostaining experiments revealed the expression of two SNAP isoforms: SNAP-47 and SNAP-23 in the somatodendritic compartment of oxytocinergic neurons, suggesting a role in OXT exocytosis. Interestingly, the expression of SNAP-23 becomes apparent during the first postnatal week suggesting a tight developmental regulation. We generated specific viral-based knockdowns (shARNs) to eliminate endogenous SNAP-47 and SNAP-23 to determine their role in OXT-vesicle secretion and dynamics. To this aim, we implemented staining protocols and imaging techniques to unambiguously identify OXT-vesicle trafficking. We observed KCl stimulation significantly increased the probability of OXT release. However, this effect is only observable during short stimulation protocols since long stimulation times seem to deplete the OXT releasable pool during the first seconds of KCl application. Visualization of somatodendritic OXT-vesicles revealed heterogeneous dynamics in response to neuronal stimulation. Four main vesicle pools were identified: i) dynamic vesicles mobilized during the first 10 s of stimulation, ii) stable vesicles, iii) uncoupled vesicles and iv) delayed vesicles, the most abundant type, with observable movement after 20-40 s of stimulation. We performed electrophysiological recordings to determine how OXT-vesicles kinetics relates to the excitability of oxytocinergic neurons. Our observations indicate oxytocinergic neurons exhibit slow depolarization that might underlie the delayed dynamics of OXT-vesicles and their partial dependence on calcium. These results suggest the existence of different pools of OXT-vesicles which are distinctly mobilized in response to the same stimulus, a feature that may be relevant for orchestrating complex behavioral responses.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-79

Mitochondrial fission factor (MFF) regulates mitochondrial dynamics and excitability of Agouti related peptide (AgRP)-expressing neurons

Ms. Almudena-Rosa Del Río Martín[1,2,3], Ms. Marie H. Solheim[1,2,3], Mr. Gagik Yeghiazaryan[2,4], Mr. Alain J. de Solis[1,2,3], Mr. Paul Mirabella[1,2,3], Mr. Henning Fenselau[1,2,3], Mr. Peter Kloppenburg[2,4], Mr. Jens C. Brüning[1,2,3]
[1]Max Planck Institute For Metabolism Research, Cologne, Germany, [2]Excellence Cluster on Cellular Stress Responses in Aging Associated Diseases (CECAD), Cologne, Germany, [3]Center of Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany, [4]Institute for Zoology, Biocenter, University of Cologne, Cologne, Germany

Tight regulation of whole-body metabolism is essential in maintaining energy homeostasis and for preventing several diseases such as obesity. AgRP neurons in the arcuate nucleus of the hypothalamus (ARC) promote food intake and control systemic insulin sensitivity. Mitochondria are highly energetic dynamic organelles, which can undergo fission and fusion events also in adaptation to the energy state. Mitochondrial fission factor (MFF) has a key role during the initiation of mitochondrial fragmentation, where it serves as an adaptor for the dynamin related GTPase (DRP)-1. Recently, mitochondrial dynamics was identified as a critical regulator of synaptic transmission. Thus, we aimed to define the role of MFF in AgRP neurons and its possible role in the regulation of whole-body metabolism.
To this end, we generated mice with AgRP-neuron specific MFF inactivation. When crossed to a mouse line, which express YFP at the outer mitochondrial membrane, this allowed us to monitor mitochondrial morphology and dynamics in control mice and those lacking MFF in AgRP neurons (AgRPΔMFF-mice). While control exhibited a more fragmented mitochondrial network during fasting, this effect was attenuated in AgRPΔMFF-mice. Interestingly, electrophysiological recordings performed in AgRP neurons of AgRPΔMFF mice indicated an increase in the neuronal excitability due to differences in the spike frequency adaptation. Nevertheless, these animals retain an unaltered ability to respond to orexigenic hormones such as ghrelin. Moreover, despite altered AgRP neuron excitability, AgRPΔMFF animals showed no overall changes in body weight and glucose homeostasis.
Collectively, partially impairing mitochondrial fragmentation in AgRP neurons increases their neuronal excitability without major differences in metabolism.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-82

SELF-ASSEMBLED HYBRID HYDROGELS BASED ON GRAPHENE DERIVATES AND CERIUM OXIDE NANOPARTICLES AS THREE-DIMENSIONAL SUBSTRATES FOR NEURAL STEM CELLS.

Yurena Polo[1,3], Jon Luzuriaga[1], Sergio Gonzalez de Langarica[1], Beatriz Pardo Rodriguez[1], Edurne Marin[1], Daniel E. Martínez-Tong[4], Gaskon Ibarretxe[1], Fernando Unda[1], JR Sarasua[1,3], Aitor Larrañaga[1,3], JR Pineda[1,2]

[1]University of the Basque Country (UPV/EHU), Leioa, Spain, [2]Achucarro Basque Center for Neuroscience Fundazioa, Leioa, Spain, [3]Polimerbio S.L., Donostia-San Sebastian, Spain, [4]University of the Basque Country (UPV/EHU), Donostia, San Sebastián, Spain

A major challenge in utilizing stem cells for regenerative therapies is the poor control over the survival, differentiation and functional integration of the transplanted cells. The combination of stem cells with scaffolds has been proposed to overcome this problem. In the present work, graphene-based hydrogels were developed as a substrate for neural stem cells (NSCs). These hydrogels were further functionalized with cerium oxide nanoparticles, thus providing a multifunctional platform for cells that combines the intrinsic physico-chemical, electrical and mechanical cues provided by graphene derivatives with the antioxidant and cytoprotective properties from cerium oxide.

The graphene/cerium oxide hydrogels were fabricated via the self-assembly of graphene oxide (GO) in the presence of ascorbic acid (AsA) at 1:1, 1:4 or 1:10 proportion. Mechanical properties (rheology), electrical conductivity, antioxidant capacity, morphology (scanning electron microscopy-SEM) and physico-chemical properties (Raman spectroscopy and X-ray diffraction) were characterized. NSCs were seeded on the hydrogels and fixed for immunostaining at different time-points (1, 3, 7 and 14 days). Several markers (Nestin, MAP2, NeuN, DCX, S100B, GFAP, Olig2) were used to distinguish between the undifferentiated and the differentiated cells found in the CNS.

NSCs were able to attach and integrate into hydrogels without need of coating. Furthermore, the presence of AsA or cerium oxide was permissive with the differentiation of NSCs towards neuronal, astroglial and oligodendroglial lineages. The increasing the amount of AsA, which acted as a reducing agent, resulted in a more collapsed structure with smaller pore size and higher shear modulus and electrical conductivity. The incorporation of cerium oxide nanoparticles endow the hydrogels with antioxidant properties reducing both their shear modulus and electrical conductivity.

In this study, we present a simple and versatile method for the fabrication of graphene-based hydrogels with tunable mechanical, electrical, physico-chemical and morphological properties, supporting the adhesion and neurodifferentiation of NSCs, thus constituting a promising tool for future cellular therapies including nerve tissue regeneration.

Funding: UPV/EHU (COLAB19/03;GIU20/050;GIU16/66;UFI11/44;IKERTU-2020.0155) GV/EJ (GV-GIC15/52; IT-927-16;IT831-13;Hazitek ZE-2019/00012-IMABI & ELKARTEK KK-2019/00093), MICINN (PID2019-104766RB-C21), MINECO (RYC-2013-13450).

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-83

Modulating corticostriatal activity with transcranial static-magnetic-field stimulation

Mr. Jaime Caballero-Insaurriaga[1,2], Dr. José Ángel Pineda-Pardo[1], Dr. Guglielmo Foffani[3]
[1]Centre for Integrative Neuroscience AC (HM CINAC), Madrid, Spain, [2]Polytechnical University of Madrid (UPM), Madrid, Spain, [3]Hospital Nacional de Parapléjicos, Toledo, Spain

Modulating corticostriatal activity with non-invasive brain stimulation (NIBS) is appealing for treating neurological diseases. Corticostriatal activity would be studied with fMRI as functional connectivity (FC) estimated as correlation, but NIBS-induced local perturbations are confounders to this metric: FC changes between two regions can be observed without interaction changes, or unnoticed in their presence. We combined transcranial static-magnetic-field stimulation (tSMS) with resting-state fMRI and developed an analysis framework to disambiguate between-region FC and assess corticostriatal modulations.

We disambiguate FC by integrating several descriptive metrics of within-region (Hom: homogeneity; Var: variance) and between-region (DCorr: distant correlation) activity, as well as with an inferential metric that uniquely represents between-region interactions (SVar: shared variance). SVar is extracted from a model-based variance decomposition, Monte-Carlo validated ($y \approx x$; $R^2>0.94$). Classical FC (correlation of mean activity) was also assessed. We first studied corticostriatal connectivity on a sample from the Human Connectome Project (N=100) and then corticostriatal effects of tSMS with data from a study stimulating the supplementary motor area (Pineda-Pardo et al, Commun. Biol. 2018) (N=20). Significance was assessed by 2-way repeated-measures ANOVA (time x treatment).

Regions in the putamen (motor and ventral attention regions) are strongly connected to the SMA, and so is the paracentral lobule (PCL) to the motor region of the striatum. In the cortex tSMS increased Var in the right SMA proper ($F_{1,19}=9.6$; PFDR<0.01), and Var ($F_{1,19}=10.2$; PFDR<0.01) and Hom ($F_{1,19}=8.2$; PFDR<0.05) in the right PCL. In the striatum only the left motor region was modulated, increasing Hom ($F_{1,19}=11.6$; PFDR<0.05). Neither classical FC nor DCorr were affected by tSMS, but the modulation of corticostriatal activity was detected as an increased SVar between the left motor striatum and the right PCL ($F_{1,19}=18.0$; PFDR<0.001).

In conclusion, we provide direct evidence of non-invasive modulation of corticostriatal activity by tSMS.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-84

Situation of university biotheriums and research centers using murine systems in Peru

Eng. Richard Cisneros[1], M.Sc. Roy Andrade[2], Ph.D. Elmer Chávez[1], Ph.D Luis Aguilar[3]

[1]National University of Huancavelica, Huancavelica, Peru, [2]Cayetano Heredia University, Lima, Peru, [3]San Ignacio de Loyola University, Lima, Peru

The use of animals for scientific purposes represents a historical practice in human civilization. In Peru, laboratory animal science has reached a higher level of development in recent years. However, the legal and regulatory framework for laboratory animal science is still embryonic. The "Guide for the care and use of laboratory animals" in its eighth edition is not adequately disseminated, as were the previous versions. There are 143 public and private universities in Peru. To date, public and private universities do not have accreditation of institutions that promote the use of animals without unnecessary suffering in scientific activities. On the other hand, a high percentage of universities do not have an "Institutional Ethics Committee for the Use of Animals in Research" (equivalent to the Institutional Committee for the Care and Use of Laboratory Animals - CICUAL), restricting the existence of these committees to the main universities in the country. In Peru, there are also around 173 research centers, most of them in the field of basic and applied sciences. Furthermore, animal production centers for research purposes are scarce in the country, with this responsibility - for the murine model - falling on four public and two private institutions.

PS1-85

Acetylcholinesterase in cortical neurons derived from patient-derived iPS.

Ms. María-Ángeles Cortés-Gómez[1,2,3], Dr. Lotta Agholme[4], Prof. Henrik Zetterberg[4], Dr Javier Sáez-Valero[1,3], Dr. María-Salud García-Ayllón[1,2,3]

[1]Instituto de Neurociencias de Alicante - UMH - CSIC, San Juan de Alicante, Spain, [2]Hospital General Universitario de Elche - FISABIO, Elche, España, [3]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, España, [4]University of Gothemburg, Gothenburg, Sweden

Acetylcholinesterase is the enzyme in charge of the hydrolysis of acetylcholine in the cholinergic synapses. It is also one of the multiple proteins affected in Alzheimer's Disease (AD), finding maintained levels of protein whereas the enzymatic activity is reduced in the brain cortex of AD patients. In addition, AChE has non-cholinergic roles like favouring neurite outgrowth or amyloid beta deposition. iPS-derived cortical neurons provide a good model for studying this disease since it can reflect specific changes from patients suffering AD. In this context, the aim of this study is to characterise AChE in patient-derived iPS and neurons when neurons are cultivated alone, co-cultured with astrocytes or/and microglia. Preliminary results indicate that there is an increase of AChE activity when neurons are co-culture with microglia or alone but in BrainPhys, a media that favours neuronal maturation. Further studies are being carried out to test whether this changes are common to control and AD patient-derived cortical neurons or specific to either and if amyloid beta treatment influences AChE similarly to what has been describe in the literature.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
www.congresosenc.es
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA

PS1-86

Genomic imprinting of Dlk1 is altered during adult neural stem cells (NSCs) reprogramming into pluripotent stem cells (iPSCs)

Dr. Anna Lozano-Ureña[1], Esteban Jiménez-Villalba[1], Dr. Mitsuroto Ito[2], Dr. Sacri R. Ferrón[1]
[1]Universitat De València, Valencia, Spain, [2]University of Cambridge, Cambridge, United Kingdom

Genomic imprinting is an epigenetic process leading to parental-origin-specific expression of certain genes – imprinted genes – resulting their monoallelic expression. This specific mechanism is essential for normal mammalian embryonic development, metabolism and adult behaviour (1). Alteration of the expression of imprinted genes has been commonly associated with perturbation of their imprinting state, leading to a loss of imprinting (LOI) (2). LOI implies the disruption of the monoallelic expression pattern of imprinted genes and has been involved in several disorders including malignant transformation (2). To understand the dynamics of genomic imprinting during acquisition of a pluripotent state, we have used neural stem cells (NSCs) from reprogrammable mice carrying a doxycycline-inducible polycistronic cassette encoding the transcriptional factors Oct4, Sox2, Klf4 and c-Myc (3), to generate induced pluripotent stem cells (iPSCs). Our results show alterations in the expression levels of most of the imprinted genes analyzed, which are partially reverted after iPSCs-differentiation into neuroprogenitors (NPs), suggesting that the plasticity in this epigenetic process might be an important mechanism during neural differentiation. These alterations in gene expression were accompanied with changes in the methylation levels at the imprinting control regions (ICRs), which control the imprinted status of imprinted genes. However, only the imprinting state of the paternally expressed gene Dlk1 varies during the acquisition of a pluripotency state and during neural differentiation.

(1) Li Y and Sasaki H. Genomic imprinting in mammals: its life cycle, molecular mechanisms and reprogramming. Cell Research 21:466-473 (2011).
(2) Bar S, Schachter M, Eldar-Geva T, Benvenisty N. Large-scale analysis of loss of imprinting in human pluripotent stem cells. Cell Reports 19:957-968 (2017).
(3) Abad M, Mosteiro L, Pantoja C, Cañamero M, Rayon T, Ors I, Graña O, Megías D, Domínguez O, Martínez D, Manzanares M, Ortega S, Serrano M. Reprogramming in vivo produces teratomas and iPS cells with totipotency features. Nature 502: 340-345 (2013).

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-87

ANALYSIS OF HIPPOCAMPAL PARTICIPATION IN SOCIAL INTERACTIONS IN A GENETIC MODEL OF AUTISTIC SPECTRUM DISORDER

Pilar Rodríguez-Martín[1], Almudena Sanz[1], Eva Monserrat[1], Inés Colmena[1], Cristina Medina-Menéndez[1], Véronique Lefebvre[2], José Luis Trejo[1], Elisa Cintado[1], Aixa V. Morales[1]
[1]Instituto Cajal (C.S.I.C.), Madrid, Spain, [2]Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

A large number of neurodevelopmental disorders associated with deficiencies in social interaction, language difficulties and repetitive behaviours are grouped under the name of autism spectrum disorders (ASD). Although the genetic causes of ASD are complex, one of the genes that have been associated with ASD is SOX5 (# 616803, LAMB-SHAFFER SYNDROME). Sox5 encodes a transcription factor with important functions in the control of neurogenesis (work in our laboratory) and in the correct specification of projection neurons of the cerebral cortex. However, alterations in regions of the brain other than the cortex such as the hippocampus have not been analysed yet.

Children with ASD present hippocampal morphology alterations associated with deficits in neuropsychological tests. Moreover, it has been described that the CA2 region of the hippocampus is fundamental in social behaviour in mice, a region where we have previously shown that Sox5 is expressed. Using conditional Sox5 mutant mice specific for the CA2 region (Amigo2-cre/Sox5fl/fl; Sox5Amigo2), we have determined that robust lack of Sox5 expression causes PCP4 level decrease in more than half of the pyramidal neurons in CA2. Using an extensive battery of mouse behavioural assays we have determined that Sox5Amigo2 mutant mice: i) exhibit normal basic reflexes, weight, and locomotion abilities; ii) males present a lower level of marbles burying activity and slight anxiety in open field test but not in elevated plus maze test; iii) exhibit a good performance in Morris water maze test; iv) present normal social preference and v) both males and females show an abnormal preference for a familiar animal over a stranger in social memory tests. Thus, we propose that Sox5Amigo2 mice could provide a new model of ASD, based on cellular and functional alterations of the CA2 region of the hippocampus that serves to understand the hippocampal component in the pathophysiology of ASD and for the testing of new therapeutic strategies.

19th MEETING 3-5 November 2021 Lleida
SPANISH SOCIETY OF NEUROSCIENCE
SOCIEDAD ESPAÑOLA DE NEUROCIENCIA
www.congresosenc.es

PS1-88

Effect of the transplant type on RGC neuroprotection and axonal regeneration after optic nerve crush

Ms. María Norte Muñoz[1], Dr. Fernando Lucas Ruíz[1], Mr. Alejandro Gallego Ortega[1], Dr. David García Bernal[1], Prof. Manuel Vidal Sanz[1], Dr. Marta Agudo Barriuso[1]
[1]*Universidad De Murcia, Murcia, Spain*

Bone marrow mesenchymal stem cell (BM-MSC) transplantation is widely studied in pre-clinical models because of their potential neuroprotective properties in central nervous system (CNS). However, microenvironmental differences between three transplants (Syn: syngeneic pigmented mouse in pigmented mouse, Allo: allogeneic pigmented mouse in albino mouse, Xeno: xenotransplant, human in pigmented mouse) are unclear and could determinate graft survival and action. Optic nerve crush (ONC) in mice is a well-studied model of neuronal degeneration in the retina, part of CNS, upon which retinal ganglion cells (RGC) die in a progressive way, so at 5 days, 50% of their population has died, and from a 1 month onwards <10% of them remain. We purposed to assess functional and histological differences between syngeneic, allogeneic, and xenotransplant of BM-MSCs after ONC.

Intravitreal injections of 20,000 cells of each transplant were performed after ONC in C57BL/6J and BALB/c mice. As controls matched groups of ONC+vehicle was done. Animals were perfused and flat mounted retinas analyzed at 3, 5 and 90 days after injury. In vivo functional retinal activity and anatomy were measured at 90 days by electroretinogram (ERG) and optic coherence tomography (OCT), respectively. To study axonal regeneration, choleric toxin tracer (CTB) assay was intravitreally injected at 85 days. Brn3a+RGCs were automated quantified and spatial distribution analyzed with isodensity maps.

Only syngeneic transplantation has significant neuroprotective properties from 5 days ($p<0.05$) to 90 days ($p<0.05$). In addition, compared ONC alone, axonal regeneration is significant in the syngeneic model, in contrast to allo- and xeno- transplantation. Finally, xenotransplant of human BMSC is the only that has negative effect in retinal function, decreasing most of ERG waves.

To evaluate graft outcome is not enough to clarify cellular properties but rather to study the microenvironment created after transplantation.