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(6-OHDA) induces selective dopaminergic neurodegeneration and hemiparkinsonism in rats with contralateral predominant motor impairment. The aim was to evaluate whether the decrease in testosterone concentration by orchiectomy (ORX) would be a positive factor on the neuroprotective effect induced by estrogen (E) and progestrone (P) administration on the motor and depressive-like behavior alterations observed in the injured animals. Male Sprague-Dawley rats (280-320 g) aged 60 days ORX and non-ORX were used. At 10 days post ORX, neurodegeneration was induced by microinjection of 6-OHDA into the left striatum. The experimental groups were 1- non-ORX: control (C), E and P-treated control (CEP), hemiparkinsonian (HP), E and P-treated hemiparkinsonian (HPEP) and 2-ORX: control (CO), E and P-treated control (COEP), hemiparkinsonian (HPO), E and P-treated hemiparkinsonian (HPOEP). Signs of motor impairment and hopelessness, were assessed by a forced swim test (PNF). Data were expressed as mean+SEM and analyzed by ANOVA 2 and Student Newman-Keuls.
ORX induced a significant increase in swimming time in HP animals with respect to group C ($p<0.0001$). This significant increase was increased in the HPOEP group with respect to the COEP group ($p<0.05$). Likewise, the magnitude of the increase was greater in HPOEP animals with respect to HPO animals ($p<0.0001$). We conclude that the decrease of testosterone by ORX is a positive inducing factor on the alterations in the motor and hopelessness signs, at the same time that the administration of E+P potentiates the positive response on the evaluated variables, proposing this combination of neuroendocrine modifications as a potential neuroprotective and neuroregenerating inducing treatment on neurodegenerative noxas.

422. (500) **OXIDATIVE STRESS IN HUNTINGTON DISEASE MODELS: BDNF ANTIOXIDANT EFFECT**

Federico López Couselo, Julieta Saba, Julieta Bruno, Lila Carniglia, Daniela Durand, Mercedes Lasaga, Carla Caruso.
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Huntington disease (HD) involves oxidative stress and mitochondrial dysfunction which can be mimicked by 3-nitropropionic acid (3NP), a phenotypic model of HD. Reactive oxygen species (ROS) generate oxidative stress which is associated with neuronal death. Glutathione (GSH) is an antioxidant molecule secreted by astrocytes that can protect neurons from death by reducing ROS levels. Superoxide dismutase 2 (SOD2) is a mitochondrial antioxidant enzyme that reduces ROS levels and its overexpression provides neuroprotection. We have shown that brain-derived neurotrophic factor (BDNF) reduces ROS levels induced by 3NP in astrocytes and increases intracellular GSH while 3NP reduces extracellular GSH levels. Now, we have studied BDNF effect on ROS production in cortical astrocytes, and GSH levels and SOD2 expression in cortical and striatal astrocytes. We found that BDNF reduces ROS levels induced by 3NP in cortical astrocytes ($p<0.05$ DCFH-DA assay). Intracellular GSH levels were increased by BDNF in both astrocyte populations ($p<0.05$ NDA assay). 3NP reduced extracellular GSH levels regardless of the presence of BDNF ($p<0.05$ cortical, $p<0.01$ striatal astrocytes). SOD2 expression, although not modified by BDNF, was increased by 3NP in striatal astrocytes ($p<0.05$). We also evaluated motor performance, ROS and GSH levels in Q175 (HD mice), a knock-in model of HD which has not been tested for oxidative stress. We observed reduced motor performance in the open field test in 4-month-old ($p<0.05$) and 8-month-old ($p<0.0001$) HD mice compared to WT mice. 4-month-old HD mice cortex presented higher ROS levels ($p<0.05$) and 8-month-old HD mice striatum showed lower GSH levels ($p<0.05$) than WT mice. In brief, BDNF antioxidant effect could be a protective mechanism for neurodegeneration by reducing ROS levels and increasing intracellular GSH. Q175 mice model of HD exhibits signs of oxidative stress as early as 4 months.

423. (505) **LIPOTOXICITY- INDUCED METABOLIC INFLAMMATION: POTENTIAL ROLE OF CERAMIDES IN GLIAL CELLS INTERACTION AND INFLAMMATORY-DAMAGE PROPAGATION**

Melina Bellotto1,2, Angeles Vinuesa1,2, Melisa Bentivegna1,2, Amal Gregosa1,2, Carlos Pomilio1,2, Nicolás González Pérez1,2, Jessica Presa1,2, Juan Beauquis1,2, Flavia Saravia1,2
1 Instituto de Biología y Medicina Experimental (IBYME-CONICET). 2 Departamento de Química Biológica, FCEN, UBA.

Western diet is associated with the elevated rates of obesity and related metabolic disorders, also considered important risk factors for brain dysfunction. Chronic inflammation and insulin resistance comprise the most relevant shared pathways, promoting alterations in the plasticity of limbic structures such as the hippocampus. With the aim to study the impact of metabolic disturbances on the brain we focused on the role of glial cells in two different approaches: *in vivo*, in the hippocampus of C57BL/6 mice exposed to a high fat diet (HFD) and *in vitro*, emulating the lipotoxic context with the saturated fatty acid palmitate (PA) as an insult to microglia and astrocyte cell lines and the role of ceramide pathway.
We have previously found that HFD mice exhibited decreased neurogenesis and structural synaptic alterations, together with spatial memory impairment and neuroinflammation, with increased expression of hippocampal TNFα and IL1β cytokines and enlarged microglia. Here, we show that astrocytes also respond to the inflammatory status with a trend to increased S100b staining and a higher cell complexity (assessed by GFAP labeling and Sholl analysis RM-ANOVA $p<0.05$). Microglial cells exposed to PA showed induced phagocytic ability and the expression of IL1β, but this effect was prevented if ceramide synthesis was inhibited by Cambinol ($p<0.05$).
Regarding the interaction between glial cells, while PA failed to induce IL1β expression in astrocytes, conditioned media (CM) from PA-exposed microglia did ($p<0.001$) and this effect was absent when microglia was pretreated with Cambinol. Interestingly, preliminary data showed that exosomes derived from PA-microglia exerted the same effect as the complete PA-derived CM, suggesting a relevant function .
Our results suggest a role of ceramide pathway in the induction and propagation of the inflammatory context induced by PA in glial cells.

424. (532) ***OXALIS ERYTHRORHIZA* MODIFIES THE ANXIOUS TYPE BEHAVIOR LEVELS IN RATS SUBJECTED TO A CHRONIC SUCROSE BEVERAGE**

Héctor Coirini[1], María Sol Kruse[1], Clara Belén Requena D'Alessio[1], Alejandro Tapia[2], Gabriela Egly Feresin[2], Mariana Rey[1]
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In the Cuyo region (Argentine), *Oxalis erythrorhiza Gillies* ex Hooker et Arnott *(*Oxalidaceae*;* Oe) is popularly consumed as a "medicinal plant" to regulate the level of glucose and cholesterol. The recent chemical characterization of Oe revealed the presence of an antidiabetogenic compound. We have previously reported that Oe produces beneficial properties on rats with experimental induced diabetes. The sustained sucrose consumption during the early developmental stage may cause insulin resistance. Also, we have recently reported that this consumption increases the anxious type behavior in adulthood. Here we studied the preventive effects of Oe on insulin resistance development and anxiety of rats subjected to sucrose consumption during the juvenile stage (childhood-adolescence). Male rats (SD) received as drinking solution sucrose (10% W/V; group SUC) or sucrose + Oe decoction (5% W/V; group SUC+Oe) from PND 21 to PND 61. A glucose tolerance test was performed on PND 62 and the values of the area under curve (AUC) were obtained. An open field test was realized on PND 63 and the recorded sessions were analyzed using the ANY-maze© software. This program determines the entrance number (EN), the distance traveled (DT) and the permanence time (PT) in three zones of the device (central: zone 1; intermediate: zone 2; peripheric: zone 3). The AUC levels of SUC+Oe were 25% lower than those of SUC ($p<0.001$). The EN and PT the zones 1 and 2 from SUC+Oe animals were higher than those of SUC ($p<0.05$). Also, the PT in zone 3 of SUC+Oe was lower than that of SUC ($p<0.05$). These results revealed that rats drinking SUC+Oe had lower levels of anxiety than those drinking only SUC. Thus, the Oe administration may prevent the development of insu-

lin resistance and reduces the anxious behavior. Additional studies are required to propose Oe as a new source of therapeutic phytocompounds and to extrapolate these effects to humans. (PIP-0243, PICT2019-623).

425. (576) **EVALUATION OF THE ANTINOCICEPTIVE EFFECT OF MORPHINE IN A MODEL OF NEUROPATHIC PAIN IN MALE AND FEMALE MICE**

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Morphine is one of the most widely used analgesics in the treatment of moderate and severe pain. However, its clinical use in long-term chronic pain treatment is limited by the enormous addictive potential. The co-administration of morphine with other drugs that enhance the analgesic effect and reduce its reinforcing properties, could be an alternative in pain treatment with opioids.
In the present study, we propose to determine the lower effective dose of morphine to ameliorate the nociceptive threshold by using the partial sciatic nerve ligation (PSNL) in male and female Balb/C mice, a widely used model of neuropathic pain. The Von Frey test (VFT) was performed in order to evaluate mechanical allodynia by calculating the nociceptive threshold (g). First, mice were habituated to the environment of the experiment during 4 days. After the habituation period, baseline responses were measured and surgery of the right paw was performed in a group of animals with PSNL (PSNL group), and surgery without PSNL was executed in another group (Sham group). On day 9 after surgery, VFT was performed after administration of morphine (1, 3, 9 mg / kg, i.p.) or saline solution as vehicle.
Finally, three-factor ANOVA (sex, surgery, treatment) was applied with Tukey's post-hoc test, using a $p < 0.05$ as statistically significant. Our results showed that morphine (1 mg/kg and 3 mg/kg) was able to reduce neuropathic pain in male and female mice, respectively ($p < 0.05$). The sexual dimorphism observed herein, confirms the lower sensitivity of females compared to males in the antinociceptive response of morphine.
The lower effective doses of morphine determined in male and female mice by a neuropathic pain model, will allow us to continue with our research in order to evaluate potential therapeutic targets to enhance the analgesic effect of opiates, reducing or preventing the addictive properties.

426. (584) **MANGANESE-EXPOSED BV-2 MICROGLIA INDUCES DAMAGE IN N27 DOPAMINERGIC NEURONAL CELLS**

Adriana María Belén Abiuso[1], Soledad Porte Alcon[1], Angeles Vinuesa[2], Flavia Saravia[2], Mónica Lidia Kotler[1], Roxana Mayra Gorojod[1].
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Manganese (Mn) intake is essential at physiological concentrations. However, prolonged exposure produces a neurodegenerative disease called manganism, whose symptoms are often confused with idiopathic Parkinson´s disease. Even though the harmful effect of Mn in different cell types has been described, much remains to be understood regarding the outcomes of glial activation on neuronal death. Objective: To evaluate the effect of soluble mediators released by microglial cells after Mn exposure on neuronal integrity. For this purpose, we first characterized the direct effect of Mn exposure on neuronal and microglial cells, and then explored the influence of microglia-conditioned medium (MCM) on neurons viability. Methodology: MCMs were generated by BV-2 cells incubation with 250-1000 μM Mn for periods of 3 or 6 h, and were used to stimulate N27 neuronal cells for 24h; cell viability was assessed using MTT reduction assay; the study of ROS production was performed using DCFDA; the change in mRNA expression was quantified by RT-qPCR. Results: In N27 neuronal cells, Mn exposure induced a concentration-dependent decrease in cell viability after 24h (100-1000 μM, $P<0.05$), which was associated with an increase in ROS production. On the other hand, BV-2 cells increased ROS production after 3 and 6 h of Mn exposure, with no change in their viability ($P<0.05$). MCM of cells exposed to Mn induced a decrease in N27 viability ($P<0.01$), consistent with an increase in ROS production and a change in N27 morphology. Finally, we observed a higher expression of IL-1β and TNF-α mRNA in Mn exposed BV-2 cells (6 and 4 fold-increase, respectively, $P<0.001$, 750 μM). Conclusion: In microglial cells, Mn exposure induces cytokines expression and ROS generation, probably responsible for decreasing neuronal viability. The advance in the knowledge of Mn toxicity mechanisms will facilitate its diagnosis and the design of effective therapeutic strategies to avoid neurodegeneration.

427. (586) **DEVELOPMENT OF A CELLULAR MODEL TO EXPLORE NEURONAL PATHOLOGY IN SANFILIPPO DISEASE BY CRISPR/CAS9 GENOME EDITING**

Marcos Gabriel Francia[1], Soledad Porte Alcon[2], Adriana María Belén Abiuso[2], Alejandra Sonia Guberman[1], Mónica Lidia Kotler[2], Roxana Mayra Gorojod[2].
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Sanfilippo syndrome type IIIA (Mucopolysaccharidosis IIIA; MPSIIIA) is a rare intractable disease characterized by an early-onset, severe, progressive neurodegeneration. It is caused by mutations in the gene encoding for the lysosomal hydrolase N-Sulfoglucosamine Sulfohydrolase (SGSH), which is crucial in the stepwise degradation of the sulfated glycosaminoglycan (GAG) heparan sulfate (HS). Nowadays, there is a lack of cellular models to explore the mechanisms of disease in the central nervous system (CNS). In this work, we aimed to develop a novel neuronal model by employing CRISPR/Cas9 technology. We designed two sgRNAs targeting exon 1 of the mouse *sgsh* gene and cloned these sequences in the pX330 vector. Insert-containing plasmids were amplified and checked by PCR and sequencing. HT-22 hippocampal neurons were transfected with PEI, and transfected cells were selected with puromycin. Subsequently, clones were isolated and amplified. We determined the lack of enzyme activity by employing the fluorogenic substrate 4-MU-GlcNS and obtained five putative knock-out cell lines where we tested lysosomal and mitochondrial integrity. Once confirmed the successful knockout by sequencing, these cell lines will constitute reliable reporters of the cellular context of disease and great models to study cell-type-specific damage. The strategy used is versatile and will be employed in other cell lineages to study cell-cell interactions of different cell types within the CNS. Further research may lead to the identification of relevant signaling pathways to investigate candidate drugs for novel therapies.

428. (596) **EXTRACELLULAR MATRIX ALTERATIONS IN MÜLLER GLIAL CELLS IN A RETINAL DEGENERATION MOUSE MODEL**

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Müller glial cells (MGC) are retinal stem cells, although their regenerative capacity is very low in mammals. We recently demonstrated that these cells in the *rd1* retinal degeneration mouse have decreased regenerative potential, an excessive number of neurons interacting with MGC, and a notable reduction in their lamellipodia, respective to their wild type (*wt*) counterparts. This suggests that extracellular matrix (ECM) protein synthesis and/or secretion could be altered in *rd1*, interfering with the substrate adhesion and lamellipodia extension, and thus affecting *rd1* MGC morphology and function-