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that depend on gender. Exposure to an EE during adolescence and adulthood reversed the observed changes. However, the combination of PS + CS presents a synergistic effect which prevents EE from reversing the changes. It would be necessary to study the existence of new treatments for cases in which both types of stress are present

387. (056) **MODULATION OF INFLAMMATORY MEDIATORS OF MATERNAL IMMUNE ACTIVATION BY RESVERATROL**

Julia Ticchi, Fernando Correa
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Maternal immune activation (MIA) produces structural, metabolic and epigenetic changes in the fetus associated with increased risk for various neurodevelopmental and neurodegenerative disorders. The hallmark of brain neuroinflammation is the activation of microglia, one of the main effectors of the innate immune response in the CNS. Excessive microglial activation leads to CNS damage due to excessive production of pro-inflammatory mediators, like interleukins, MMP, PGE2, NO and ROS.
It has been demonstrated that resveratrol has anti-inflammatory, antioxidant and epigenetics properties that translate into neuroprotective effects in adults.
Objectives: To study the possible neuroprotective effects of resveratrol in the fetal CNS in a model of MIA induced by bacterial lipopolysaccharide (LPS) and to determine the pro-inflammatory mediators involved in the modulation of the response.
Resveratrol was administered to Balb/c females on gestational day 15, which were then exposed or not to LPS. After LPS administration, amniotic liquid was collected to evaluate activity of MMP2 and MMP9. Additionally the brain of the offspring were collected to evaluate the expression of two inducible enzymatic pathways (COX-2 and iNOS) that produce mediators (prostaglandins and nitric oxide) known to cause inflammation and to evaluate the acetylation of H3 and H4 since DNA acetylation is associated with the regulation of inflammatory gene expression.
Results:
Preliminary results show that the LPS-triggered MIA induces COX2 expression in the fetal brains ($p < 0.05$ respectively) while resveratrol prevents this effect. Regardless to the activation of iNOS and the acetylation of H3 and H4 we couldn't see any significant variation between the different treatments.
On the other hand, LPS we observed that LPS decreases MMP2 while Resveratrol induces MMP9 in the amniotic fluid.
Conclusion: Maternal immune activation increases COX2 expression in fetal brains.

388. (082) **GENISTEIN AMELIORATES NEUROINFLAMMATION IN THE HIPPOCAMPUS OF MALE SPONTANEOUSLY HYPERTENSIVE RAT (SHR)**

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Hippocampal neuropathology is a recognized feature of the spontaneously hypertensive rat (SHR). Previous studies have found abnormalities in the hippocampus of SHR consisting of decreased neurogenesis and increased astroglial and microglial reactivity. These abnormalities are reversed by exogenous administration of estradiol, an active neuroprotective and hypotensive factor. Also, these hippocampal alterations are associated with cognitive impairment. Genistein (GEN) is a phytoestrogen which binds to ERβ and GPER and it is known to have neuroprotective actions. We have recently demonstrated that GEN exerts neuroprotective actions, increases neurogenesis, decreases astrogliosis and also improves hippocampal dependent memory.
To further investigate if this phytoestrogen exerts neuroprotective effects in hypertensive encephalopathy, we focused on neuroinflammation. We treated 5 month old SHR (BP>180 mm Hg) during 2 weeks with 10mg/kg daily s.c injections of GEN. We measured the expression of IBA1+ microglia in the CA1 region and hilus of the hippocampus by immunocytochemistry and classified microglia according to its morphology. Furthermore, we evaluated the expression of pro-inflammatory (COX-2) and anti-inflammatory (TGFβ) factors by real-time PCR. We found that while ramified microglia predominated in normotensive rats, SHR presented an increased proportion of the hypertrophied phenotype. GEN produced a shift in microglial phenotypes towards a ramified type. Furthermore, GEN treatment decreased expression of the pro-inflammatory factor COX-2 and increased the expression of the anti-inflammatory factor TGFβ
Our results indicate that GEN was able to exert direct neuroprotective actions ameliorating neuroinflammation in the hippocampus of SHR. These data, along with previous data of GEN improvements on neurogenesis, astrogliosis and memory deficits, opens an interesting possibility for proposing this phytoestrogen as an alternative therapy in hypertensive encephalopathy.

389. (088) **NEUROGENESIS IS REGULATED THROUGH THE CLASSICAL PROGESTERONE RECEPTOR DURING AGEING.**

Julián Del Core[1], Ignacio Jure[1], Alejandro F De Nicola[1,2] and Florencia Labombarda[1,2]
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A new role has emerged for progesterone after discovering its potent actions away from reproduction in both the central and the peripheral nervous system. Progesterone effects beyond reproduction include myelin formation, neuroprotection, anti-inflammatory actions and neurogenesis regulation. Despite the fact that the precise mechanism of Progesterone actions is controversial, most studies support a role of the progesterone classical receptor (PR) in those actions. Given that during ageing hippocampal neurogenesis decreases, oligondendrocytes die and neuroinflammation is enhanced due to reactive gliosis, we decided to study whether progesterone can regulate these parameters in the aged PR knock out mouse (PRKO). This strain is depleted of both PR isoforms (PRA and PRB), as shown by postnatal genotyping. Five month, one and two year old PRKO and wild type mice (WT) were analysed by immunohistochemistry. Neurogenesis was assayed by identifying doublecortin (DCX) positive immature neurons in the subgranular zone of the dentate gyrus of the hippocampus using stereologic methods. In the course of the time analysed, neurogenesis decreased as expected therefore, the lowest number of DCX + cells were found in the 2 year old mouse ($p<0.0001$, 2 year vs 1 year and 5 month old mice). Regarding the PR receptor, there was a decrease in the production of new neurons in the PRKO mouse at all ages analysed ($p<0.05$ PRKO vs WT for 5 month, $p<0.001$ PRKO vs WT for 1 and 2 year old mice). Our results suggest that Progesterone is required during adulthood and ageing to support an age-dependent level of neurogenesis. Furthermore, Progesterone effects on this parameter is acting through its classic nuclear receptor.

390. (095) **REGULATION OF SYNAPTOSOMAL 2-ARACHIDONOYLGLYCEROL HYDROLYSIS BY CANNABIS EXTRACTS DURING AGING**

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The availability of the main neuroprotective endocannabinoid, 2-arachidonoylglycerol (2-AG), was found to decrease in rat cerebral cortex (CC) synaptosomes (syn) during aging. It was also demonstrated that 2-AG metabolism can be modulated by its own receptors. Moreover, phytocannabinoids (PC) present in Cannabis extracts (CE), have been proposed as neuroprotective agents and are being used in several studies to treat neurodegenerative processes. The aim of this study was to evaluate if THC present in CE could modulate 2-AG hydrolysis by monoacylglycerol lipase (MAGL). To this end, delta-9-tetrahydrolcannabinol (THC) enriched CE were obtained from Cannabis Y Griega female flowers, previously grinded

and heated 115°C for 40 min. Extractions were performed by adding 5% (w/v) ethanol, vortexed, sonicated and agitated. The mixture was centrifuged and the supernatant was evaporated under stream of N_2. THC, cannabidiol (CBD) and cannabinol (CBN) were quantified by HPLC. CC syn from adult (4-6 months) and aged (24-26 months) rats were isolated by differential centrifugation and purified in ficoll gradients. MAGL activity was assessed by incubating syn with either THC enriched CE (10^{-3}-50 µM THC) or 1 µM pure THC, and [^{3}H]-MAG, simultaneously. It was observed that CE containing 1 µM THC decreased MAGL activity in aged (p=0.0166) but not in adult syn (p>0.05). However, 1 µM pure THC failed to modulate 2-AG hydrolysis (p>0.05). This findings, could suggest that THC enriched CE could attenuate the deregulation of 2-AG metabolism observed in aging, and that this effect could only be generated when syn are exposed to the PC in the presence of the entire CE.

391. (122) **MOLECULAR ALTERATIONS CAUSED BY CHRONIC COCHLEAR DEPOLARIZATION IN A MOUSE MODEL OF HEARING LOSS**

Leonardo Dionisio1,2, Ezequiel Rías1,2, Camila Carignano1,2, Sofía Stupniki1,2, Marcela Vera1,2, Guillermo Spitzmaul1,2.
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The voltage-gated potassium (K+) channel KCNQ4 is the main responsible for the extrusion of the K+ that enters the cochlear sensory cells upon sound stimulation. Besides, outer hair cells (OHC) excitability is under control of the efferent neurons of the Medial Olivocochlear (MOC) system. In response to overstimulation, MOC cholinergic neurons activate the calcium-induced K+ channels BK and SK2, which extrude K+ out of the cell repolarizing the membrane. Intracellular accumulation of K+ leads to a chronic depolarization that may damage hair cells causing hearing loss (HL). KCNQ4 activity impairment is the main cause of DFNA2, a non-syndromic progressive HL. Using a mouse model lacking Kcnq4 (*Kcnq4-/-*), we reported that OHC death begins at the basal turn progressing to the apex in 3-6-week-old (W) animals. We hypothesized that the KCNQ4 absence causes MOC chronic overstimulation leading to activation of death pathways. Using immunofluorescence (IF), we evaluated the MOC terminals and observed a lower synaptic density and mislocalization of the efferent terminals contacting OHC in 4W *Kcnq4-/-* mice. In addition, we analyzed by qPCR the gene expression of the efferent components located in the MOC terminals. We detected a ~3.5-fold decrease in the mRNA expression of the nicotinic receptor α10 subunit with no changes in the α9 subunit, and a ~8-fold decrease in the mRNA expression of BK and SK2 in 4W *Kcnq4-/-* animals. Finally, we studied the possible pathways involved in OHC death. By IF, we found an increase of cleaved-caspase 3 expression in the OHC at the basal turn and gene expression analysis by qPCR revealed that the pro-apoptotic *Bax* transcript was upregulated while anti-apoptotic *Bcl2* was downregulated in *Kcnq4-/-* mice. These results demonstrate an alteration of the efferent transmission in OHC that could contribute to the activation of the apoptotic pathway driving to OHC death.

392. (123) **EPIGENETIC MECHANISMS UNDERLYING ASTROGLIAL HETEROGENEITY IN REACTIVE ASTROGLIOSIS: TARGETING CHROMATIN REMODELERS AS A POSSIBLE THERAPY TO REDUCE DAMAGE AFTER BRAIN INJURY**

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Astrocytes respond to brain injury through a phenomenon called reactive astrogliosis in which a pro-inflammatory and pathological subpopulation of astrocyte has been described, capable of promoting neuroinflammation and neuronal death. Astrocyte pathological conversion with a pro-inflammatory gain of function involves dramatic and stable transcriptomic changes, probably following activation of transcription factor NF-kB. NF-kB interacts with chromatin remodelling enzymes and recruits them to regulatory regions of target genes promoting epigenetic changes in other cell types.
We aim to address the epigenetic mechanisms that are associated with NF-kB activation in reactive astrocytes that might lead to the establishment of an astrocyte pathological identity.
Using immunofluorescence microscopy and PCR analysis in primary cultures of mouse cortical astrocytes with different microglia abundance and exposed to pro-inflammatory stimulus LPS (Lipopolysaccharide), we observed that LPS significantly promoted: 1) Sequential NF-kB activation in microglia>>astrocytes together with morphological and transcriptional changes, 2) A variable intensity of initial NF-kB activation in astrocytes depending on microglial abundance and the release of microglial soluble factors and 3) A microglial-dependent increase in gene activating histone marks H3K9K14ac and H3K27ac and a decrease in the repressive mark H3K9me3. *In vivo* brain ischemia recapitulated the increase in H3K27ac specifically in reactive astrocytes from ischemic penumbra and inhibition of histone deacetylases exacerbated astrogliosis and brain damage.
Our results showing changes in histone mark abundance are highly indicative of chromatin remodeling events in a subpopulation of pro-inflammatory reactive astrocytes. Such epigenetic mechanisms may represent plausible therapeutic targets to reduce astrocyte pro-inflammatory phenotype, neuroinflammation and neuronal loss after brain injury.
Grants: UBACYT, FONCYT, ISN-CAEN, APBIOTECH

393. (125) **SPLENECTOMY: SHEDDING LIGHT ON THE SPLEEN-BRAIN INFLAMMATORY COUPLING IN A MODEL OF TEMPORAL LOBE EPILEPSY**

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A high percentage of patients with temporal lobe epilepsy (TLE), one of the most frequent neurological diseases, refer an initial precipitating event (IPE), such as complex febrile seizures during childhood, followed by a silent latency period (LP), until the onset of the chronic seizures phase. Using the lithium-pilocarpine rat model of TLE we previously showed that neurodegeneration, reactive gliosis and macrophages brain infiltration occur during the LP and that early interventions limiting immune activation during the LP increase epileptic threshold during the chronic phase (Rossi et al., 2013; 2017). The model consists of the administration of lithium-pilocarpine (127 mg/kg /30 mg/kg, 20h apart) to male Wistar rats. Animals develop Status Epilepticus (SE) that mimics human IPE and SE is limited to 20 min by 20 mg/kg i.p. diazepam. In this work, we have found morphological evidence of early spleen white pulp activation 1 day post SE (DPSE), while increased CD3+ and CD4+ lymphocytes in the choroid plexus, without changes in the gut-associated lymphoid tissue (GALT), followed by a decreased abundance of naïve lymphocytes in blood and spleen smears were found at 2-3DPSE.
In order to evaluate the relevance of the spleen-brain inflammatory coupling in the LP that follows pilocarpine-induced SE, we performed splenectomy (n=6) to 210-220 g male Wistar rats anesthetized with ketamine-xylazine (90 mg/kg/10 mg/kg) 1 week before the lithium-pilocarpine treatment. Sham animals were used as controls. Our loss of function studies showed that splenectomy decreased astrogliosis, neuroinflammation and deep cervical lymph nodes size at 7DPSE. We conclude that peripheral immune system is responding to specific brain-derived clues triggered by the SE and the spleen is involved in the modulation of neuroinflammation that follows SE.
Supported by PICT 2017-2203; UBACYT; and FONCYT fellowship (PS).

394. (152) **UNDERSTANDING THE SPATIO-TEMPORAL DISTRIBUTION OF REACTIVE ASTROCYTES AFTER FOCAL BRAIN INJURY AND THE ROLE OF TOLL-LIKE RECEPTOR SIGNALING**

María Belén Cieri, Ingrid Mailing, Alejandro Villarreal, Alberto Javier Ramos.
Instituto de Biología Celular y Neurociencias, Prof. E. De Ro-