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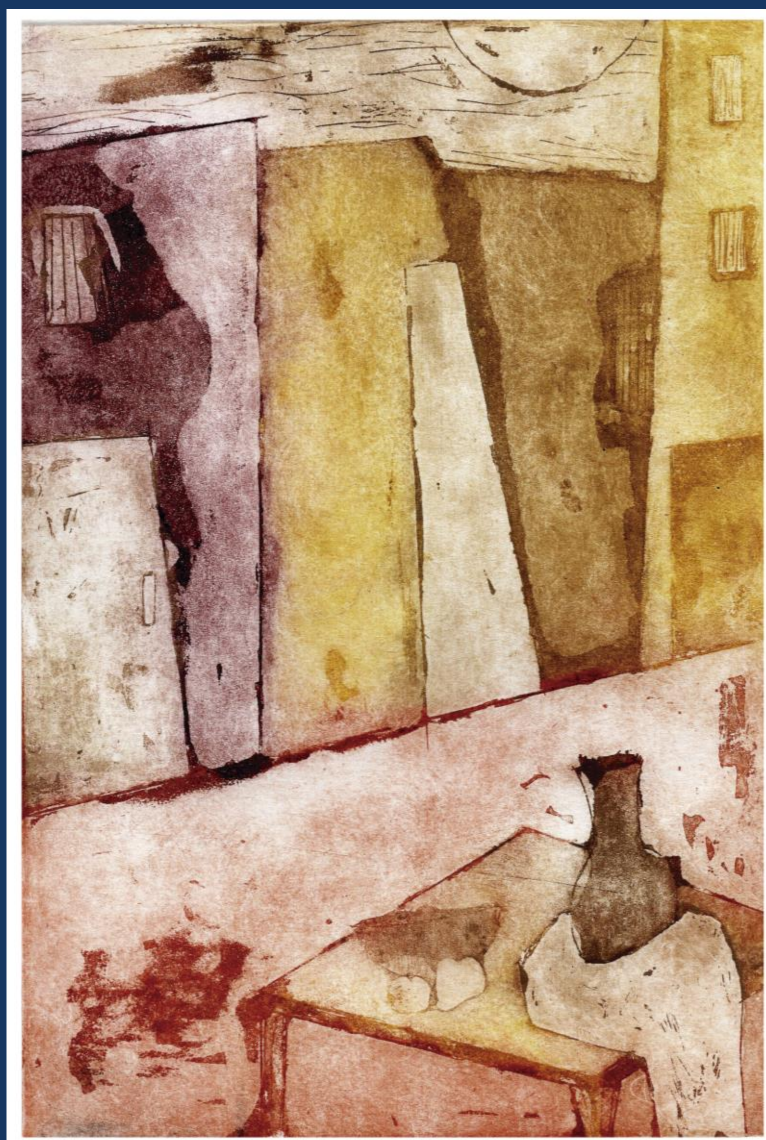

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La Tapa (Ver pág. 4)
Atardecer en la tarde
Antonella Ricagni

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LXIV Reunión Anual de la
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XXI Reunión Anual de la
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XXXI Reunión Anual de la
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IX Reunión Anual de la
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(NANOMED-ar)

VI Reunión Científica Regional de la Asociación Argentina de Ciencia y Tecnología de Animales de Laboratorio (AACyTAL)

con la participación de
The Histochemical Society

13 - 16 de noviembre de 2019
Hotel 13 de Julio - Mar del Plata

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CONICET - UNIVERSIDAD DE BUENOS AIRES, INSTITUTO DE QUÍMICA BIOLÓGICA DE LA FACULTAD DE CIENCIAS EXA

Abstract/Resumen: Manganese (Mn) is a trace metal required for human health. As a micronutrient, Mn is needed only in small quantities and can become toxic at higher concentrations. Chronic exposure to Mn, in occupational or environmental settings, causes a parkinsonian-like syndrome known as Manganism. More than a century after its discovery, Mn neurotoxicity is still considered a public health concern. Like neurons, glial cells are susceptible to Mn-induced injury. We have previously demonstrated that Mn triggers microglial cell death by regulated necrosis, involving both parthanatos and lysosomal disruption. Autophagy is a catabolic pathway in which cellular components are degraded by lysosomes in response to stress conditions. Nevertheless, autophagy activation may have both beneficial and detrimental effects, depending on the context. Evidence indicates that Mn activates autophagy in microglial cells. However, the role of autophagy on microglial cell death remains unknown. To address this question, we exposed BV-2 cells to Mn and analyzed the time-course of autophagy activation and the effect of its modulation on cellular fate. We detected a time-dependent increase in LC3-II protein levels (WB and ICC; $p<0.001$). The expression of SQTM1/p62, an autophagic substrate, followed the same kinetics as LC3-II ($p<0.001$), suggesting an impairment of autophagy. Nevertheless, both LC3-II and p62 levels significantly increased after bafilomycin A1 treatment ($p<0.001$), indicating an active autophagic flux. Induction of autophagy with both rapamycin (200 nM) and melatonin (10 µM) partially prevented Mn toxicity at 24 h (MTT; $p<0.01$ and $p<0.001$, respectively). Surprisingly, autophagy inhibition (wortmannin, 50 nM) had no effect on cell survival, at any time-point tested. Our results suggest that autophagy could play a protective role in Mn-induced cell death. Thus, evidence obtained represent a valuable contribution to the design of novel therapeutic tools for the treatment of Manganism.

0550 - NEUROPROTECTIVE EFFECTS OF 17ß-ESTRADIOL ADMINISTRATION ON DOPAMINERGIC SYNTHESIS IN AN ANIMAL MODEL OF PARKINSON DISEASE.

María Paula BONACCORSO MARINELLI | Silvina GOMEZ | Susana Ruth VALDEZ | Ricardo Jorge CABRERA

CONICET

Abstract/Resumen: We investigate estrogen neuroprotective actions in adult male rat brain tissue after neurotoxic injury. Using inmunohistochemical techniques (IHQ), we label and localize neurons that express tyrosine hydroxylase (TH) on substantia nigra (SN) and their projections to corpus striatum (CPu). TH is the first enzyme in dopamine (DA) biosynthesis and catalyses the conversion of L-tyrosine to L-DOPA. We use it to quantify neuron loss in SN and analyze striatal dopamine depletions. On postnatal day 60 (D= 0) rats were injected with 6-hydroxydopamine (6-OHDA) or vehicle (V) in the left CPu. From D 7-17 (10 days), they received a chronic treatment with 17ß- Estradiol (E= 0.1 µg/kg/day s.c.) or corn oil (O). Groups were conformed as HP (6-OHDA lesion, O treatment n= 18); HP+E (6-OHDA lesión, E treatment n= 18); E (V lesion, E treatment n= 15); C (V lesion, O treatment n= 15). On day 60 all animals were euthanized for TH IHQ. CICUAL approval 86/2016. In SN, the number of TH+ cells (NN) on both hemispheres was statistically lower in HP animals in comparison to the other groups (C= 26 ± 1.4, E= 29.8 ± 3.7, HP= 12.5 ± 1.1, HPE= 28.7 ± 2.3; $p<0.0001$). To calculate the size of the lesion (SL) we used NN mean values on both hemispheres and compared the mean difference to control group. There was a significant increase in HP group compared to C (mean diff= 13.60, $p<0.001$). This represents an expansion of the 18.2 % in the size of lesion. In the case of E (mean diff= -3.7) and HP+E (mean diff= -2.6) there was no statistical difference between means in comparison to C, but the SL was diminished in 18.4 % for E and 19.7 % for HPE group. We made a plugin to automatically count and label TH+ neurons in SN, using this approach we calculated regression analysis of NN vs. stained area (mm^2). Results indicate a linear and positive relation for all groups; goodness of fit (r^2) for C was 0.54 and perfect ($r^2= 1$) for E, HP and HP+E. Linear regression analysis shows that, NN is a good predictor for the stained area proportion. What is more, treatment with E improved CPu dopaminergic projections and neuron arborization. Staining was more intense and better distributed in HPE group compared to HP. While 6-OHDA administration diminishes NN and increases lesioned size in HP; evidence shows that E administration attenuates loss and almost reverts tissue detrimental effects in HPE group. In conclusion, E has neuroprotective effects on the nigrostriatal dopaminergic pathway which may stimulate dopamine synthesis.

0654 - DISTINCTIVE SYNAPTIC REMODELING PROPERTIES OF HIPPOCAMPAL NEURONS IN THE VALPROIC ACID RAT MODEL OF AUTISM

Marianela Evelyn TRAETTA | Martín CODAGNONE | Nonthue UCCELLI | Maria Jose MALLEVILLE CORPA | Einav LITVAK | Sandra ZÁRATE | Analía REINÉS

INSTITUTO DE BIOLOGÍA CELULAR Y NEUROCIENCIA "PROF. E. DE ROBERTIS", UBA-CONICET

Abstract/Resumen: Autism spectrum disorders (ASD) are characterized by impairments in social interaction and repetitive-stereotyped behaviors. These core symptoms imply alterations in brain areas of the limbic system including the hippocampus. Previously, we reported hippocampal alterations using the well-validated ASD animal model by prenatal exposure to valproic acid (VPA, 450 mg/kg ip). The hippocampus of juvenile VPA rats displayed decreased synaptic marker synaptophysin (SYN) along with an increased expression of the neural cell adhesion molecule (NCAM) and a decrease in its polysialylated form (PSA-NCAM). Also, neurons from VPA animals showed a smaller dendritic tree and fewer glutamatergic synapsis which also depicted the NCAM/PSA-NCAM imbalance in vitro. The aim of this study was to evaluate the remodeling properties of primary hippocampal neurons either from VPA or control male pups. After neuronal treatment (DIV13 or 7), cytoskeletal and synaptic markers were evaluated (DIV14) by immunocytochemistry. While in neurons from control animal glutamate (5 µM-3min, DIV13) induced an NMDA-dependent dendritic retraction and synaptophysin (SYN) puncta number reduction, neurons from VPA animals were only capable of dendritic retraction without any change in synapse number. When evaluating the response to fluoxetine (0.1 µM, DIV13), neurons from VPA animals were unable of remodeling their dendritic tree but SYN puncta number decreased. These changes were accompanied with increased PSA-NCAM expression only in VPA neurons. Similar effects were generated by a functional PSA mimetic peptide (DIV13) in the VPA group but not in the control one. A sialic acid precursor (DIV7) normalized synapse number and dendritic tree in neurons from VPA animals without affecting the control group. To sum up, our results indicate distinctive remodeling features of neurons from VPA animals and suggest that NCAM/PSA-NCAM balance modulation may play a key role in restoring synaptic and dendritic profile.

0679 - RECRUITING SPHINGOLIPIDS TO PROMOTE MIGRATION OF RETINAL PIGMENT EPITHELIUM CELLS

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INIBIBB CONICET- INSTITUTO DE INVESTIGACIONES BIOQUÍMICAS DE BAHÍA BLANCA

Abstract/Resumen: Retinal proliferative diseases, frequent causes of vision loss, involve excessive migration and proliferation of Müller glial cells (MGC) and retinal pigmented epithelium (RPE) cells. Bioactive sphingolipids, as sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P), are established mediators of inflammation and fibrosis and we have shown that S1P stimulates MGC migration (Simon et al; 2015). We now analyzed if they promote RPE migration. We supplemented ARPE19 cells, a human RPE cell line, with 5 μM S1P or 10 μM C1P. We pretreated them with SphkI2 or NVP, inhibitors of sphingosine kinase-1 (SphK1) and ceramide kinase (CerK), respectively to analyze if endogenous S1P or C1P stimulate cell migration, and with W146 and BML241, S1P1 and S1P3 antagonists, respectively to investigate if S1P activated these receptors. Migration was analyzed by the scratch wound assay. Exogenous S1P or C1P significantly promoted RPE cell migration, but their combined addition had no additive effect. Inhibiting S1P synthesis significantly reduced cell migration, and exogenous S1P and C1P partially restored it. In contrast, NVP treatment had no effect on RPE migration. Pretreatment with W146 reduced RPE migration both in control and S1P-supplemented cultures, while BML241 only reduced it in S1P-treated cultures. Our results suggest that endogenous synthesis of S1P activates S1P1 to induce RPE cell migration whereas exogenous S1P stimulates migration by activating both S1P1 and S1P3. Notably, exogenous C1P enhances RPE cell migration but its endogenous synthesis does not. Noteworthy, when added together, S1P and C1P had the same effect on migration as when added separately, implying they may share common signaling pathways. Hence, sphingolipids appear as central regulators of cell migration, and targeting their metabolism might provide tools for treating proliferative retinopathies.

0695 - MECHANISMS OF NEURONAL DEGENERATION INDUCED BY THE CYANOTOXIN ß-N-METHYLAMINO-L-ALANINE (BMAA)

Tamara SOTO (1) | Beatriz DE LOS SANTOS(2) | Edgardo BUZZI(1) | Nora ROTSTEIN(1) | Lorena GERMAN(1) | Luis Enrique POLITI(2)

INIBIBB-CONICET, DEPTO. BIOLOGÍA, BIOQUÍMICA Y FARMACIA-UNS (1); INIBIBB CONICET- INSTITUTO DE INVESTIGACIONES BIOQUÍMICAS DE BAHÍA BLANCA (2)

Abstract/Resumen: The non-proteic aminoacid BMAA is a cyanotoxin released by many cyanobacteria occurring in most dams and water resources around the world. Its chronic intake has been linked with neurodegenerative diseases, like amyotrophic lateral sclerosis (ALS), Parkinson and Alzheimer diseases. We showed that BMAA affects retinal neurons and Muller glial cell viability in vitro. Here we investigated the signaling pathway involved in BMAA deleterious effects on cultured photoreceptors and amacrine neurons, its effects on axonal architecture and whether it affects other non-retinal neuronal types. Pure rat retinal neuronal cultures and the neuronal-like, PC12 cell line, cultured in chemically defined media to promote differentiation, were treated with 400 nM and 1 μM BMAA, respectively, for three days. Neuronal cultures were pretreated with MK-801, an N-methyl-D-aspartate (NMDA) receptor antagonist. Cell death was evaluated by DAPI staining and axonal outgrowth by immunocytochemical methods. Pretreatment with MK-801 significantly prevented the increase in the percentage of pyknotic or fragmented nuclei induced by BMAA in amacrine neurons. BMAA enhanced axonal outgrowth in neurons. We then analyzed BMAA effects on PC12 cells at two different stages of differentiation, evaluated morphologically and by anti-ß III tubulin expression. PC12 cell differentiation increased with time in culture, reaching 52 and 77 % at 7 and 12 days, respectively. BMAA increased similarly the percentage of cell death at both differentiation stages, from 33 in controls to 58 % in BMAA-treated cultures. Noteworthy, BMAA also promoted axonal outgrowth in PC12 cells, while simultaneously reducing ß III tubulin levels. These results suggest that BMAA provokes degeneration and axonal changes in different neuronal types, activating NMDA receptors to promote amacrine cell death, and identify BMAA as a potential inducer of neurodegenerative damages, with its consequent deleterious effects on human health.

0812 - REGULATION AND ROLE OF ACYL-COA SYNTHETASE 4 IN NEUROSTEROIDOGENIC CELLS

Melina Andrea DATTILO (1) | Lucía Manuela HERRERA(1) | Yanina BENZO(1) | Jesica Giselle PRADA(1) | Juan Manuel COHEN SABBAN(1) | Corina Ileana GARCÍA(2) | Cristina PAZ(1) | Paula Mariana MALOBERTI(1)

INBIOMED- INSTITUTO DE INVESTIGACIONES BIOMÉDICAS. UBA-CONICET (1); FUNDACIÓN INSTITUTO LELOIR - IIBBA (2)

Abstract/Resumen: The brain is a neurosteroidogenic organ in which neurons, astrocytes and microglia express enzymes related to neurosteroidogenesis. Acyl-CoA synthetase 4 (ACSL4) enzyme expression in the brain has been described. Although the role of ACSL4 in neurons and in the development of the nervous system has been studied, nothing had been described about its role in neurosteroidogenesis and its regulation in glia cells. Here we show that in primary astrocyte cultures incubated with 1mM 8Br-cAMP for 12 h, ACSL4 mRNA levels are increased compared to untreated cells ($p<0.001$). This treatment also significantly stimulated P4 production ($p<0.001$) measured by radioimmunoassay. P4 synthesis was significantly inhibited when astrocytes were previously treated with Triacsin C, an ACSL4 inhibitor ($p<0.05$). In turn, cAMP increased StAR mRNA levels ($p<0.001$) and Triacsin C inhibited this increment ($p<0.05$). Also, we showed that ACSL4 is involved in migration, proliferation and process elongation of astrocytes. Triacsin C significantly inhibited cell proliferation ($p<0.01$) and cell migration ($p<0.001$) measured by wound healing assay. Astrocytes process elongation induced by AMPc was inhibited by Triacsin C ($p<0.001$). Results were confirmed in a rat glioma model by stable silencing of ACSL4 in C6 cells with a specific siRNA (C6-ACSL4 siRNA). P4 production ($p<0.001$) and StAR mRNA levels were decreased in C6-ACSL4 siRNA ($p<0.001$) compared to control cells. Moreover, cell migration, cell proliferation and colony formation ($p<0.001$) were also affected by ACSL4 knockdown. In conclusion, as in classical steroidogenic systems, we demonstrate that ACSL4 is involved in the regulation of StAR expression and in the production of steroid hormones. Moreover, we show that ACSL4 could also participate in the migration, proliferation and process elongation of neurosteroidogenic cells.

0825 - PURINERGIC REGULATION OF THE SYNAPTIC ACTIVITY BY NON-VESICULAR ENDOGENOUS ATP AT THE MOUSE NEUROMUSCULAR JUNCTION

Maximiliano HURTADO PASO | Tamara Vanesa FRONTERA | Juan GUARRACINO | Luciano GALIZIA | Adriana LOSAVIO

INSTITUTO DE INVESTIGACIONES MEDICAS A LANARI (UBA - CONICET)

Abstract/Resumen: At mammalian neuromuscular junction, ATP and its metabolite adenosine modulate ACh release via presynaptic inhibitory P2Y13, A1 and A3 receptors and facilitatory A2A receptors. It is accepted that the major source of purines in the synaptic cleft is vesicular ATP released together with ACh. However, it was recently proposed that ATP can be secreted from skeletal muscle fibers through pannexins. Considering that high K^+ concentration increases the activity of pannexins, the aim of this work was to evaluate whether the ATP released from muscle fibers contribute to the purinergic modulation upon neurotransmitter secretion when membranes are depolarized by increasing K^+ concentrations. So, in phrenic-diaphragm preparations (CF1 mice) incubated in solutions containing 10-30 mM K^+, we studied the miniature end-plate potential (MEPP) frequency when pannexins were blocked by probenecid (100 μM). At 10 and 20 mM K^+, probenecid increased MEPP frequency (K+ 10: control 2.1 ± 0.1/s, probenecid 3.4 ±