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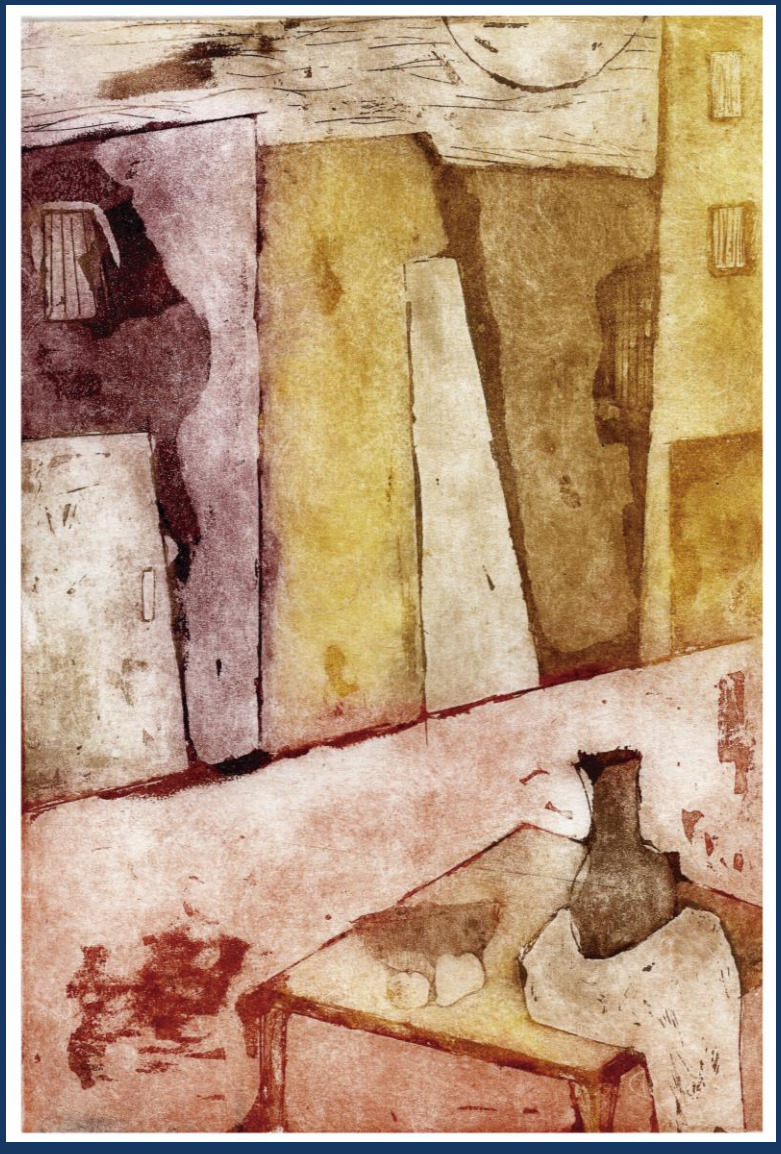

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VI Reunión Científica Regional de la Asociación Argentina
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con la participación de
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of FKBP51 promoted neuritogenesis. Similarly, the axonal damage of the cells was reversed with FK506, being accelerated when overexpressed to FKBP52 or by knock-down of FKBP51. This suggests that these immunophilins could have neuroprotective or neuroregenerative actions in adverse situations such as, for example, oxidative stress associated with neurodegenerative diseases, cerebrovascular accidents or neuronal overexcitation. In this study, it was analyzed whether treatments with FK506 can prevent and/or reverse the deleterious effects associated with oxidative stress of H_2O_2. Undifferentiated N2a (murine neuroblastoma) cells were incubated in DMEM/OptiMEM medium (without serum) with 1 µM FK506, observing the rapid generation of neurites. Two hundred fifty µm thick sections obtained from prefrontal cortex of male BALB/C mice (60 d) were incubated in special medium on 4 % agar. After 72 hours of tissue stabilization, the explants were incubated for 4 hours with 200 µM H_2O_2. The induction of Hsp90, Hsp70, FKBP52 and p23 was evidenced, which was prevented by pretreatment (1h) with 1 mM FK506. Regarding FKBP51, the controls showed three bands corresponding to their known phosphorylated isoforms, while explants treated with H_2O_2 showed only the least phosphorylated band. Pretreatment with FK506 protected phosphorylated isoforms, showing the same pattern of isoforms as the control. In turn, the samples treated with FK506 showed only the intermediate phosphorylated band, suggesting that this isoform (reactive with anti-P-Tyr antibodies) is favored in the mechanism of action of the drug.To show effects in vivo, relative hypoxia was generated by stereotactic injection of 2 ml 50 mM $CoCl_2$ in the prefrontal cortex of the right hemisphere, using the contralateral as a control. Chaperone expression was induced in tissue lysates obtained 24 h later, which was partially prevented by pretreatment (24 h) with 10 mg/kg FK506. The effects on motor balance were studied after 21 days (FK506 injected every 3 days) by Rotarod and open field (Anymaze), observing a better and faster recovery in mice treated with FK506. This is the first study that shows a neuroprotective effect of FK506 against oxidative stress.

0907 - INCREASED VASCULAR PERMEABILITY TO EVANS BLUE DYE IN THE HIPPOCAMPUS OF PDAPPJ20 MICE, MODEL OF ALZHEIMER'S DISEASE (AD). POTENTIAL IMPLICATION OF ER STRESS MECHANISMS.

Jessica Lorena PRESA (1) | Carlos POMILIO(1) | Agustina ALAIMO(2) | Melisa BENTIVEGNA(1) | M. Ángeles VINUESA(1) | Amal GREGOSA(1) | Rossana RAMHORST(2) | Oscar PEREZ(2) | Juan BEAUQUIS(1) | Flavia E. SARAVIA(1)

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The blood-brain barrier (BBB) limits flux from and into the brain compartment that is essential for normal neuronal functioning and information processing. Post-mortem tissue analysis indicates BBB damage in AD. However, timing and mechanisms underlaying BBB breakdown remain elusive. Endoplasmic reticulum (ER) stress is caused by disruption of homeostatic mechanisms that cause unfolded proteins to accumulate. The ER adapts to stress by activating the unfolded protein response (UPR). Chronic ER stress is increasingly being associated to neurodegeneration. We found augmented vascular permeability in the hippocampus of 12-month-old PDAPPJ20 transgenic mice, compared to the group, assessed by Evans Blue i.v. injections and analysis of coronal brain sections (D.O.= 5,666 ± 387 vs. 12,373 ± 3,082, n= 5-6, $p<0.04$) and a higher number of microhemorrhages per μm^2 in the hilium (four fold more in transgenic mice vs. non-transgenic mice, $p<0.0001$) Human brain microvascular endothelial cells (hBMEC) proved to be a very suitable human cellline for an in vitro BBB model. We treated hBMEC with 1 µg/ul of Thapsigargin (Tg), a known inductor of ER stress. Treated cells showed increased mRNA expression of Ire1$\alpha$and PERK by RT-qPCR (two and three fold increase, n= 3, p= 0.01, respectively), evidencing UPR activation. We also employed a sealed monolayer of hBMEC on a transwell membrane, monitored by TEER. Tg exposure provoked loss of resistance and augmented permeability to Evans Blue and NaFl. In addition, Aβ1-40 peptide was able to induce changes in GRP78/BiP-a central central regulator for ER stress-in endothelial cells: we found not only increased intensity in the cytoplasmic BiP area ($p<0.05$) but a different pattern distribution, with predominance of bright dots, suggesting the implication of ER in the brain vasculature exposed to amyloid peptides. Further experiments are in progress to elucidate the role of ER stress in endothelial cells and BBB integrity in vivo and in vitro models of AD.

0935 - STX2 FROM ENTEROHEMORRHAGIC E. COLI INDUCES NF-KAPPAB ACTIVATION IN REACTIVE ASTROCYTES

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Shiga toxin 2 (Stx2) from enterohemorrhagic E. coli causes hemolytic uremic syndrome (HUS) and acute encephalopathy, which may lead to fatal outcomes in patients. When neurological symptoms are evidenced mortality rate may rise up to 40 %. The mechanism by which the encephalopathy emerges in patients with HUS is still unknown. Reactive astrogliosis is a widespread glial response to brain injury and NF-kappa B activation was related to the proinflammatory-neurodegenerative astroglial polarization. The aim of this study was to determine whether Stx2, LPS or a combination of both produce astrocyte reactivity in vitro, and whether this reactivity involves the activation of NF-kappaB pathway. Primary cortical astrocytes were obtained from P3-P5 C57 mice. Confluent astroglial cultures were incubated either with control (saline solution), LPS (50 ng/ml), Stx2 (50 or 200 ng/ml), or a combination of both toxins. GFAP expression and astroglial cell morphology was evaluated by immunocytochemistry. Reactive astrogliosis was observed following the treatment with 200 ng of Stx2 plus 50 ng of LPS in comparison to the control (0.058 ± 0.006 control vs. 0.088 ± 0.006 Stx2+LPS, measured as the number of filamentous astrocytes per total number of astrocytes). Nuclear translocation of p65 NF-kappaB subunit was measured as an index of NF-kappaB activation. The 3h treatment with 50 ng/ml LPS, 200 ng/ml Stx2, and 200 ng/ml Stx2 plus LPS showed a significantive NF-kappa B activation in primary astrocytes when compared with controls (63.19 ± 4.51, 23.77 ± 1.97, 55.30 ± 4.20, 1.33 ± 0.51 respectively; expressed as a ratio of nuclear p65 vs. total number of astrocytes). We conclude that Stx2 causes reactive gliosis in vitro and NF-kappaB activation which it may be involved in the proinflammatory astroglial polarization known to produce neurodegenerative effects.

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0942 - DIFFERENTIAL SUSCEPTIBILITY TO INFLAMMATION AND NEURODEGENERATION IN TWO MODELS OF AGED RATS

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LELOIR INSTITUTE FOUNDATION - IIBBA CONICET

Parkinson's Disease (PD) is a neurodegenerative disorder whose main feature is the neuronal loss in the substantia nigra (SN). Our group and others have demonstrated that inflammation can cause or exacerbate neuronal demise in the SN, suggesting that the modulation of inflammation could be a possible site of therapeutic intervention. Several factors can influence the development of PD. Age is the most relevant risk factor for this disease. Also, a mutation (G2019S) in the LRRK-2 gene is the most prevalent mutation in PD patients. Interestingly, aged animals and animals carrying a LRRK-2 (G2019S) mutated gene produce an increased response to