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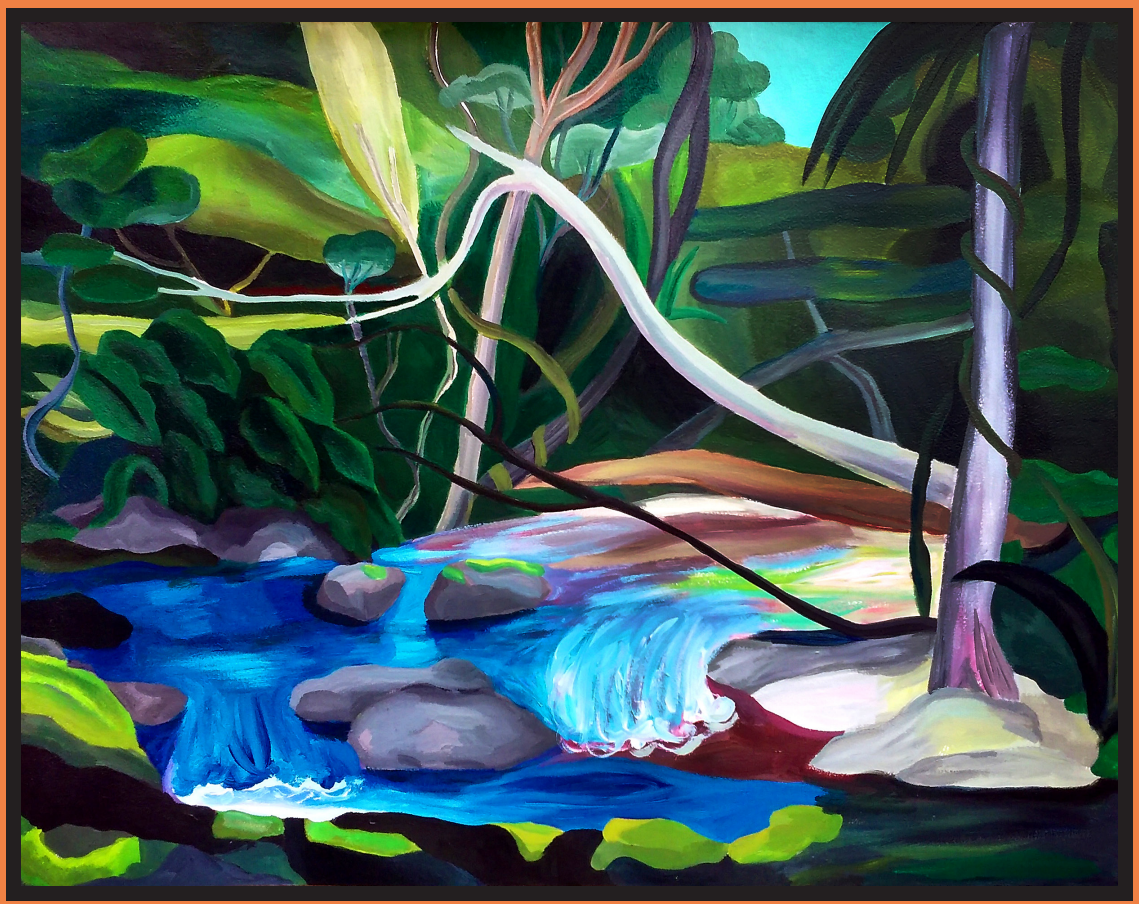

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REUNIÓN CONJUNTA SAIC SAB AAFE AACYTAL 2023

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15-17 de noviembre de 2023
Hotel 13 de Julio – Mar del Plata

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The expansion of adipose tissue plays a crucial role in the progression of obesity, a chronic disease that generates oxidative stress and an imbalance in the production of proinflammatory adipokines promoting a deleterious impact in many tissues. Bisphosphonates are drugs employed as first line therapy for bone-related diseases, such as postmenopausal osteoporosis. However, several extraosseous effects have been demonstrated in the last decades. Postmenopausal women exhibit a higher prevalence of obesity and overweight, so that, in this work we investigated the impact of the bisphosphonate alendronate (ALN) on adipose tissue in a model of hypoestrogenism and obesity. For this purpose, retroperitoneal adipose tissue was isolated from bilaterally ovariectomized Wistar rats fed with a high-fat diet (27%). For in vitro treatments, slices of adipose tissue (40 mg) were incubated with 5 µM ALN for 18 h. Control group received vehicle only (phosphate buffered saline). Hydrogen peroxide (H_2O_2), TBARS and leptin levels were measured. Firstly, we detected that serum H_2O_2, TBARS and leptin levels in obese rats were higher than those detected in normal weight rats (6, 65 and 122% above control, respectively, $P<0.05$), compatible alterations with oxidative stress and inflammatory conditions. When adipose tissue was incubated with ALN, a marked reduction in H_2O_2 levels with respect to the control group was detected (2731 ± 419 vs 1642 ± 89 nmol H_2O_2/g of tissue, control vs ALN respectively, $P<0.002$, fluorometric assay). We also observed that treatment with ALN significantly inhibited the production of TBARS (12% vs control, $P<0.0001$, colorimetric assay). The bisphosphonate significantly reduced leptin levels released to the culture medium compared to the control group (31% vs control, $P<0.0025$, ELISA kit). In conclusion, the results presented suggest a novel extraosseous effect of ALN through a direct action on adipose tissue, reducing oxidative stress and leptin production.

404. 258. **REGULATORY MODULATION OF NF-κB ACTIVITY BY HSP90-BINDING IMMUNOPHILINS AND β-CATENIN**

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β-Catenin is a ubiquitous client protein of the chaperone Hsp90 that activates the Wnt-dependent transcriptional pathway responsible of cell adhesion, cell development, and a variety of diseases, including cancer. Its aberrant activation leads to the nuclear accumulation of β-catenin promoting the induction of many oncogenes. NF-κB is a transcription factor that plays key roles in inflammation, stress response, tumour growth, and apoptosis. Previously, we reported that two highly homologous Hsp90-binding immunophilins regulate transcriptional activity of NF-κB, where FKBP52 is an activator and FKBP51 is an inhibitor. Therefore, we hypothesised that these Hsp90-binding immunophilins, β-catenin, and NF-κB may be integrated in a common functional pathway. To evaluate whether a signalling crosstalk exists between β-catenin and NF-κB pathways, HEK cells expressing an NF-κB-Luc reporter gene, NF-κB, and increasing concentrations of β-catenin were stimulated (or not) with 0.1 ug/ml phorbol-12-myristate-13-acetate for 7 h. Under both conditions, β-catenin showed a strong inhibitory effect on NF-κB activity. As expected, the overexpression of FKBP52 enhanced NF-κB biological activity, whereas β-catenin impaired the immunophilin effect. On the other hand, the overexpression of FKBP51 showed inhibitory action on the NF-κB activity, and the expression of β-catenin greatly improved that effect in a concentration-dependent manner. Confocal microscopy studies demonstrated that the mere overexpression of the p65 subunit of NF-κB showed β-catenin translocated into the nucleus in unstimulated cells. Both factors, p65 and β-catenin, exhibit nuclear colocalization. Moreover, β-catenin coimmunoprecipitated with p65, indicating the existence of complexes. Interestingly, increased levels of p65 stimulated β-catenin expression. In summary, this study evidences a novel crosstalk between β-catenin and NF-κB pathways that is regulated by the Hsp90-binding immunophilins FKBP51 and FKBP52.

405. 425. **QUINUCLIDINE ETHER DERIVATIVES AS NOVEL LIGANDS OF THE ALPHA7 NICOTINIC RECEPTOR**

Juan Facundo Chrestia[1], Franco Viscarra[2,3], Yaima Sanchez[4], Edwin G. Pérez[5], Philip C. Biggin[3], Isabel Bermudez[2], Jhon J. López[4], Cecilia Bouzat[1]
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The α7 nicotinic acetylcholine receptor is a ligand-gated cation channel expressed in the brain, mainly in cortex and hippocampus, where it contributes to cognition, attention, and working memory. Its reduced activity has been associated to schizophrenia and Alzheimer's disease. α7 is also expressed in non-neuronal cells, such as astrocytes, microglia and lymphocytes, where it plays a role in inflammation and immunity. Therefore, potentiation of α7 has emerged as a therapeutic strategy for neurological, neurodegenerative and inflammatory disorders. The quinuclidine scaffold was used for the development of nicotinic agonists, with the hydrophobic substituents at position 3 providing selectivity for α7. Here, six new ligands (4–9) containing a 3-(pyridin-3-yloxy)quinuclidine moiety were synthesized, and its pharmacological activity upon α7 was evaluated by two-electrode voltage-clamp and single-channel recordings. Only ligand 4 activated α7. Ligands 5 and 7 had no effects on α7, but ligands 6, 8, and 9 potentiated the ACh-currents. Ligand 6 was the most potent and efficacious of the potentiating ligands, with a EC_{50} of 12.6 ± 3.32 µM and a maximal potentiation of EC_{20} ACh responses of 850 ± 120%. The concentration–response curve of ACh was shifted to the left by 10 µM ligand 6 (control EC_{50} = 125 ± 25 µM; ACh + ligand 6 EC_{50} = 96 ± 30 µM; $p<0.05$). At the single-channel level, the potentiation exerted by 10 µM ligand 6 was evidenced by the appearance of prolonged bursts of channel openings (1.08 ± 0.32 ms) compared to the control (0.38 ± 0.08 ms, $p<0.001$). The burst duration is the most sensitive parameter to determine potentiation and relates to the efficacy of the modulator. Computational studies revealed the preference of ligand 6 for an intersubunit site in the transmembrane domain and highlighted some putative key interactions that explain the different profiles of the synthesized ligands. We conclude that ligand 6 is a novel positive allosteric modulator of α7.

406. 593. **THERAPEUTIC DRUG MONITORING IN EPILEPSY: LEVETIRACETAM**

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Introduction and Objective: Therapeutic Drug Monitoring (TDM) applicability in newer anticonvulsants (AED), such as Levetiracetam (LEV) is controversial. However, it is known that inter and intra individual variability exists, often related to brand changes or variable renal function. Hence, TDM in these patients would be of clinical importance. We aim to present the validation of a quantitative method using High-Performance Liquid Chromatography (HPLC) for AED in serum samples, and its potential application in pharmacokinetic analysis. Materials and Methods: A HPLC-UV reverse phase system was used, at 40°C. The isocratic mobile phase consisted of a mix-