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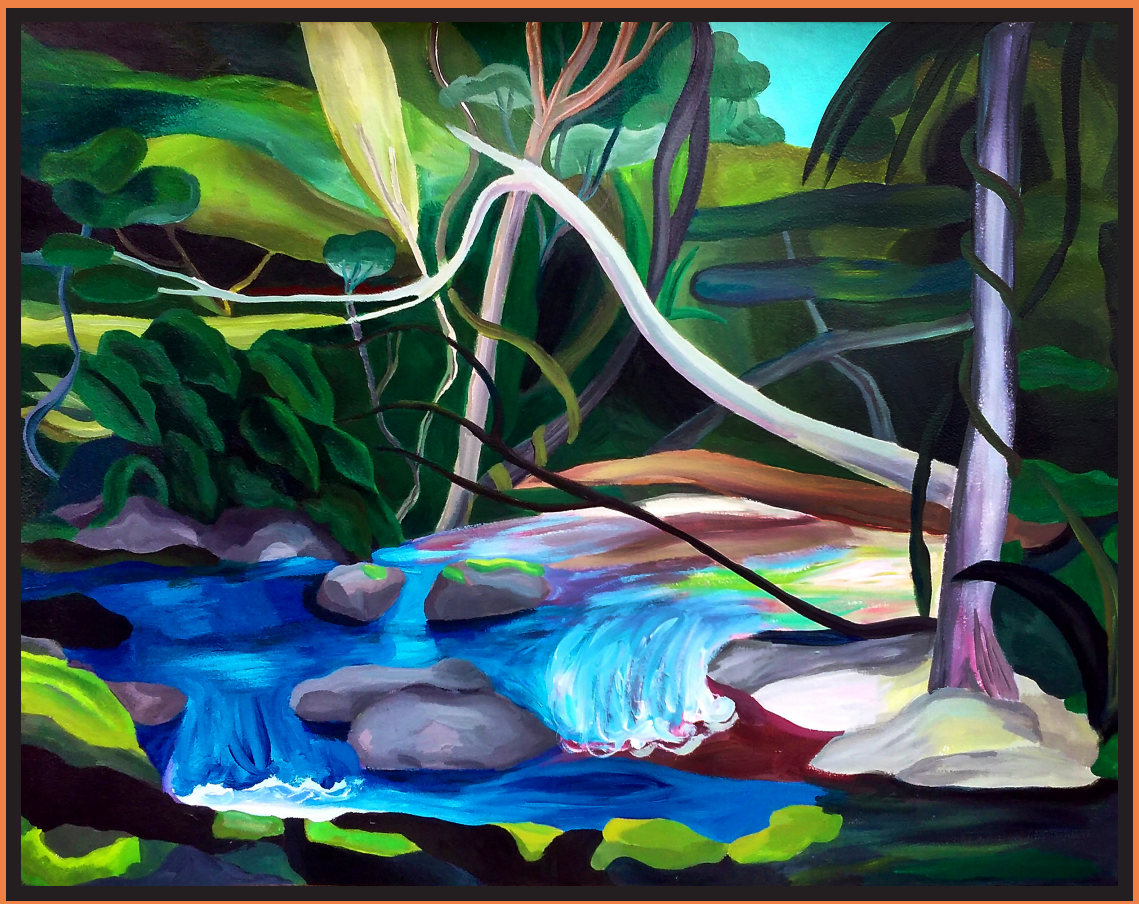

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REUNIÓN CONJUNTA SAIC SAB AAFE AACYTAL 2023

LXVIII REUNIÓN ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACIÓN CLÍNICA (SAIC)

XXV JORNADAS ANUALES DE LA SOCIEDAD ARGENTINA DE BIOLOGÍA (SAB)

LV REUNIÓN ANUAL DE LA ASOCIACIÓN ARGENTINA DE FARMACOLOGÍA EXPERIMENTAL (AAFE)

VIII REUNIÓN CIENTÍFICA REGIONAL DE LA ASOCIACIÓN ARGENTINA DE CIENCIA Y TECNOLOGÍA DE ANIMALES DE LABORATORIO (AACYTAL)

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

EDITORES RESPONSABLES
Dra. Isabel Luthy
Dra. Silvina Pérez Martínez
Dr. Ventura Simonovich
Dr. Gabriel Pinto

JOINT MEETING SAIC SAB AAFE AACYTAL 2023

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daf-18 mutants exhibit morphological defects in GABAergic neurons (abnormal branching, and incomplete commissures). In contrast, we did not find significant differences in the morphology of cholinergic neurons. DAF-18 specific rescue in GABAergic neurons partially rescued the defective phenotypes, suggesting an autonomic role of the PI3K pathway in GABAergic function. In addition, we found that the GABAergic deficit in *daf-18* mutants is entirely dependent on the inactivation of the transcription factor DAF-16/FOXO. Ketogenic Diets have been used for refractory epilepsy. The mechanisms underlying this therapeutic effect remain elusive. We found that exposure to the ketone body hydroxybutyrate (βHB) during early development ameliorated GABA defects in *daf-18* mutants. Interestingly, this ketone body does not alleviate the defects observed in daf-16/FOXO mutants, suggesting an essential role of this transcription factor in the βHB effect. Since fundamental processes are highly conserved throughout the animal kingdom, this study may contribute to the understanding of disorders associated with E/I imbalances in mammals.

481. 325. **INTRAVAGINAL ADMINISTRATION OF PHARMABIOTIC/PHYTOBIOTIC CAPSULES WITH AUTOCHTHONOUS LACTIC BACTERIA FOR THE PREVENTION OF INFECTIONS OF THE BOVINE REPRODUCTIVE TRACT**

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The postpartum bovine reproductive tract is susceptible to infections that are treated with antibiotics and hormones, or a combination of them. The growing problem of the transmission of resistance to antimicrobials requires to reduce their use and look for alternative therapies, such as probiotics and phytobiotics. The objective of this work is to advance in the design of pharmabiotics/phytobiotics formulas with bovine beneficial autochthonous lactic acid bacteria (BBALB) for the prevention of reproductive tract infections. Hard gelatin capsules containing BBALB ($3x10^{10}$ CFU), individually or combined with phytoderivatives (Malva and Lapacho) were administered intravaginally to bovine females (n=30). Two doses were applied with an interval of 15 days, before the probable date of delivery, and two postpartum doses. The modification of the autochthonous microbiota from vaginal washings and the permanence/colonization of the inoculated BBALBs were evaluated, and the safety of the designed formulas was determined through nutritional-clinical and hematological-biochemical parameters in blood and serum. All the females of the different experimental groups (EG) remained healthy before parturition (5±0.0 RS). During the postpartum period, two cows from the BBALB MG group and one from the Control group showed signs of reproductive infections. The females of the different GE maintained or slightly decreased their postpartum weight (304.5 ± 4.95 KgLW). All the animals showed normal hematocrit (36.44±1.08%), and leukocyte formula within bibliographic reference values (RV) in the BBALB Vg, BBALB Vg+VE and BBALB MG+VE groups, without significant differences between the animals EG and with Control. Glycemia was lower at RV=40-88.2 mg/dl, with no significant differences between EG and Control at the same sampling time. Metabolic parameters (glycemia, proteinemia, albuminemia and C-reactive protein) were normal in all animals throughout the trial. The normal culturable microbiota of the bovine vagina was slightly modified after the administration of the capsules. Total aerobic mesophiles increased slightly in all EGs after parturition. Culturable Enterobacteriaceae remained at 2.50±0.05 logUFC/ml during the assay in all EGs, except in BBALB Vg+VE. Cultivable lactic bacteria increased in all postpartum EGs (BBALB Vg:2.15±0.07, BBALB Vg+VE:2.00±0.02 and BBALB MG:1.91±0.05 logUFC/ml). The results indicate that the intravaginal administration of pharmabiotic/phytobiotic capsules is safe and does not produce adverse effects when administered to pre- and postpartum cows.

482. 326. **BENEFICIAL AND SAFETY CHARACTERISTICS OF AUTOCHTONOUS LACTIC BACTERIA (LB) WITH PROBIOTIC POTENTIAL FOR CANINE PUPPIES**

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Centro de Referencia para Lactobacilos.
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Probiotics are defined as "live microorganisms that, when administered in adequate amounts, produce a health benefit in the host". For the selection process of new autochtonous probiotic microorganisms, functionality, safety, and technological aspects must be taken into account. This work is aimed at evaluate different beneficial properties and safety of LB isolated from mother's milk and fecal matter of different dog breed, in order to advance in the design of an homologous probiotic formula with LB to reconstitute the intestinal microbiota and protect from infections in dogs. 100 different strains isolated from dogs: 79 LB (17 from mother's milk, 62 from puppy fecal material) together with 21 other LB (adult dogs) available in the group were evaluated in the a) production of beneficial enzymes (protease, lipase, amylase, cellulase and feruloyl esterase), b) H_2O_2 production and c) innocuity (gelatinase, hemolysin and lecithinase). Protease was determined in agarized skim milk, lipase in MRS-milk cream, showing an inhibition halo. Amylase production was evaluated in MRS-starch agar medium (revealed with Indole), feruloyl esterase in 1% in methanol (w/v) ethylferulate 1g/L added to MRS agar without glucose, cellulase in MRS-carboxymethyl cellulose agar (revealed with lugol). H_20_2 production was detected using the tetramethyl benzidine-MRS agar (TMB-MRS) plate method. Hemolysin activity was determined on blood agar (BHI agar+5% human blood), lecithinase on egg yolk agar and gelatinase on BHI agar+3% gelatin. The LB in study were 13 cocos and 87 bacilli. The survey of beneficial enzymes showed 24% strains with protease activity, 20% with cellulase activity and 19% with feruloyl esterase activity. 39% of the strains evidenced H_20_2 production (12% weak, 9% strong and 18% very strong). Hemolysis was produced in 68% as partial (alpha), 2% total (beta) and 30% gamma. No isolates expressed lecithinase and gelatinase activity. This work allowed us to select the LB strains with the best characteristics, and to correlate them in a way to define the optimal combinations, supported also with the origin and breed of the isolate. The strains sharying properties are being subjected to genotypic identification, in order to advance in the design of probiotic formulas with homologous strains for the health of canine puppies.

483. 350. **α7 NICOTINIC EXPRESSION AND FUNCTION IN HUMAN RETINAL PIGMENT EPITHELIUM CELLS**

Julieta Ailen Mader, María Florencia Fernández Delias, Juan Facundo Chrestia, Florencia Anahí Sotelo, María del Carmen Esandi, Cecilia Bouzat
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The α7 nicotinic receptor (nAChR) is one of the most abundant nAChRs in the nervous system and is also present in non-neuronal cells, including immune and epithelial cells. It is involved in cognition, memory, pain, neuroprotection and inflammation and its potentiation has emerged as a therapeutic strategy for neurological, neurodegenerative, and inflammatory disorders. Given that the increase in oxidative stress in retinal pigment epithelial cells contributes to the development of age-related macular degeneration and that α7 activation exerts cell protective effects, we explored the presence and functional relevance of α7 in D407 retinal pigment epithelium cells. By confocal microscopy using the α7 specific antagonist α-bungarotoxin labeled with Alexa 488 and real time-PCR we demonstrated the presence of α7 in these epithelial cells. To simulate the events occurring in age-related macular degeneration, we treated cells with 500 μM ferric ammonium citrate (FAC) for 48 h to induce stress damage and measured reactive oxygen species (ROS) with the fluorescent probe DCFH-DA and cell viability by the MTT assay. FAC treatment resulted in a significant 56 ± 23% increase in ROS levels with respect to the control. To determine if α7 protects against oxidative damage, we exposed cells for 4 h to a specific α7 agonist, PNU-282987, before the FAC treatment. This exposure reduced 29

± 3% basal levels of ROS. Notably, PNU-282987 exhibited protective effects against the FAC treatment, leading to a reduction of 46 ± 15% in ROS levels when compared to the treated cells. In line with these observations, exposure to the α7 agonist restored the 20% reduction in cell viability induced by FAC. Overall, we demonstrated for the first time the presence of α7 in the D407 cell line, which is a model system for studying various retinal diseases, and its protective role against oxidative damage, a key factor linked to the onset of macular degeneration.

484. 360. **DIFFERENTIATION OF N2A CELLS: COMPARISON BETWEEN HDAC INHIBITORS AND DIFFERENTIATING AGENTS**

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2. Instituto de Fisiología, Biología Molecular y Neurociencias, Universidad de Buenos Aires, CABA.

Differentiation is a crucial process upon cell development. Epigenetic mechanisms play an important role in it and HDACs, a family of enzymes whose major function is to acetylate histones and, therefore, regulate gene expression is one the main character in cell differentiation. The aim of this work was to compare differentiating agents in the N2a cells (mouse neural crest-derived cell line) where its neuronal stem cell could differentiate into neurons. Cells were treated with differentiating drugs such as: dbcAMP (cAMP analogue), resveratrol (polyphenol) and two selective HDACi (HDAC inhibitors) MS-275 (class I) and MC-1568 (class IIa). N2a were incubated with DMEM high glucose, 1% Glutamax and 0,5% SFB at 37°C and 5% CO_2. For 4 days cells were observed and counted if necessary. Finally, cells were characterized by phase-contrast or fluorescence microscopy. We first determined cell viability at day *in vitro* 4 (DIV4) and noticed that MS275 500 nM significantly reduced the total number of viable cells (p= 0,021) while other conditions did not affect viability. After that, we analyzed the number of differentiated cells in each condition: 24% Resveratrol 6.2 *μ*M vs 9% ethanol, 27% dbcAMP 0.5 mM vs 3% water and 20% MS-275 50 nM vs 14% DMSO. Finally, we observed morphological changes in N2a cells comparing presence or absence of typical neuron structures such as dendrites, axons and filopodia. Here we found that HDACi induced differential transformation in cell morphology. We saw that MS-275 increased the number of axons (p=0.037) and dendrites (p=0.013) while MC-1568 showed an increase of filopodia (p=0.08) and dendrites (p=0.02). These results show differentiating agents which can convert neuronal stem cells into mature neurons as we observed. Although further work is still needed, we can assume that class I HDACs are necessary to maintain a tumor-like conformation and, evenmore, that HDACi stop tumoral growth and lead to N2a neuron-like differentiation.

485. 670. **INVOLVEMENT OF $GABA_B$ RECEPTORS IN THE CONTROL OF THE ANALGESIC RESPONSE OF MORPHINE USING A MODEL OF NEUROPATHIC PAIN IN MALE AND FEMALE BALB/C MICE**

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Neuropathic pain (NP) is a type of chronic pain that affects between 7-10% of the world population and continues without effective treatments. It has been suggested that the efficacy of combining pharmacological treatments lies in using analgesics that have different mechanisms of action. In previous studies of our laboratory, a GABAergic-opioid interaction was evidenced in a pain model. In this line, baclofen (BAC, $GABA_B$ agonist) was able to increase the antinociceptive effect of morphine (MOR) in the hot plate. On the other hand, it has been reported that the nerve injury that causes NP induces changes in the expression of brain derived neurotrophic factor (BDNF) in different brain areas related to pain. BDNF is a potential biomarker for NP because it promotes neuronal growth, maintenance, survival, and neurogenesis. The aims of the present study was to evaluate the participation of $GABA_B$ receptors in a model of neuropathic pain in mice of both sexes from a pharmacological approach. In addition, we analysed the expression of BDNF in areas related with pain. The behavioral results showed that MOR was able to reduce the NP in males and females ($p < 0.05$,0.001, respectively), while BAC increased this effect only in males ($p < 0.05$). In contrast, 2-OH-saclofen ($GABA_B$ antagonist) blocked the antinociceptive effect of MOR in males ($p<0.001$) and this effect was only attenuated in females ($p<0.05$). These results confirm the involvement of $GABA_B$ receptors in the analgesic effect of MOR in a NP model. $GABA_B$ receptors could be considered as a potential therapeutic target for the NP pain treatment.

P1-REGENERATIVE MEDICINE AND NANOMEDICINE

WEDNESDAY 15TH NOVEMBER 9:00 - 10:30
CHAIRS: JULIETA MAYMÓ
ESTEBAN FIORE
ANA TORBIDONI

486. 166. **CHEMICAL MATURATION OF HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES**

Smucler J. [1], Halek J.M. [2], Miriuka S.G., Luzzani C.D., Waisman A.
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[2] IMETTYB, Universidad Favaloro, CONICET

Cardiovascular diseases are the main cause of death wordwide. Efforts to model these pathologies are continously made in order to improve therapy and drug treatment. In the last years, human induced pluripotent stem cells (hIPSCs) models have yield a variety of tools in order to design new clinical approaches. hIPSCs derived cardiomyocytes (CMs) are an advanced model that had brought the opportunity to study cardiac cells. Nevertheless, hIPSC-CMs lack crucial characteristics present in the adult human heart since they are differentated in short term protocols and thus resemble embryonic CMs. In this work we differentiated hIPSCs into pure immature CMs (day 21) and then applied a maturation cocktail consisting of the hormone T3, dexamethasone, a PPARa small molecule agonist and palmitic acid in low-glucose DMEM medium until day 38. As a control, we cultured immature CMs in RPMI $B27^-$ base medium. We evaluated the expression of cardiac maturation markers by RT-qPCR. These included structural components, metabolic genes and specific ion channels. We found that the maturation medium significantly upregulated the expression of metabolism (COX6A2, CPT1B) and ion transport (RYR2, ATP2A2, CX43), and enhanced the structural proteins isoform switch from immature to mature (MYL7 to MYL2 and TNNI1 to TNNI3). Using quantitative bioinformatic analysis, we evaluated a key property of mature CMs, which is polynucleation/poliploidy. By DAPI staining of CMs in maturation vs control media, we confirmed that CMs in the mature media have a greater population of 4n nuclei. Finally, we evaluated the proliferative capacity of both conditions, with the control population yielding a near 1.5 fold in the amount of cells at the end of the protocol. In conclusion, we show that this protocol robustly generated pure mature like hIPSCs-CMs in 40 days with well-defined sarcomere structures and key maturative traits, generating a unique model to target key questions about cardiac regeneration.

487. 179. **DIFFERENTIAL EXPRESSION OF HIPPO PATHWAY MEADIATORS IN FETAL AND ADULT OVINE HEARTS.**