2021

medicina

BUENOS AIRES Vol. 81 Supl. III - 2021

MEDICINA

Volumen 81, Supl. III, Págs. 1- 250

medicina

BUENOS AIRES, VOL. 81 Supl. III - 2021

COMITÉ DE REDACCIÓN

MIEMBROS EMÉRITOS

La Tapa
Médanos
Daniela Kantor

MEDICINA (Buenos Aires) - Revista bimestral – ISSN 1669-9106 (En línea)

Registro de la Propiedad Intelectual N° 02683675
Personería Jurídica N° C-7497
Publicación de la Fundación Revista Medicina (Buenos Aires) Propietario de la publicación: Fundación Revista Medicina
Queda hecho el depósito que establece la Ley 11723

Publicada con el apoyo del Ministerio de Ciencia, Tecnología e Innovación Productiva.
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e-mail: revmedbuenosaires@gmail.com – http//: www.medicinabuenosaires.com

Vol. 81, Supl. III, Noviembre 2021

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lin resistance and reduces the anxious behavior. Additional studies are required to propose Oe as a new source of therapeutic phytocompounds and to extrapolate these effects to humans. (PIP-0243, PICT2019-623).

425. (576) **EVALUATION OF THE ANTINOCICEPTIVE EFFECT OF MORPHINE IN A MODEL OF NEUROPATHIC PAIN IN MALE AND FEMALE MICE**

Perez V., Canero E., Balerio G.
Universidad de Buenos Aires. Facultad de Farmacia y Bioquímica: Cátedra de Farmacología. Buenos Aires, Argentina. Junín 956 5° piso, Buenos Aires (C1113AAD), Argentina.
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Morphine is one of the most widely used analgesics in the treatment of moderate and severe pain. However, its clinical use in long-term chronic pain treatment is limited by the enormous addictive potential. The co-administration of morphine with other drugs that enhance the analgesic effect and reduce its reinforcing properties, could be an alternative in pain treatment with opioids.
In the present study, we propose to determine the lower effective dose of morphine to ameliorate the nociceptive threshold by using the partial sciatic nerve ligation (PSNL) in male and female Balb/C mice, a widely used model of neuropathic pain. The Von Frey test (VFT) was performed in order to evaluate mechanical allodynia by calculating the nociceptive threshold (g). First, mice were habituated to the environment of the experiment during 4 days. After the habituation period, baseline responses were measured and surgery of the right paw was performed in a group of animals with PSNL (PSNL group), and surgery without PSNL was executed in another group (Sham group). On day 9 after surgery, VFT was performed after administration of morphine (1, 3, 9 mg / kg, i.p.) or saline solution as vehicle.
Finally, three-factor ANOVA (sex, surgery, treatment) was applied with Tukey's post-hoc test, using a $p < 0.05$ as statistically significant. Our results showed that morphine (1 mg/kg and 3 mg/kg) was able to reduce neuropathic pain in male and female mice, respectively ($p < 0.05$). The sexual dimorphism observed herein, confirms the lower sensitivity of females compared to males in the antinociceptive response of morphine.
The lower effective doses of morphine determined in male and female mice by a neuropathic pain model, will allow us to continue with our research in order to evaluate potential therapeutic targets to enhance the analgesic effect of opiates, reducing or preventing the addictive properties.

426. (584) **MANGANESE-EXPOSED BV-2 MICROGLIA INDUCES DAMAGE IN N27 DOPAMINERGIC NEURONAL CELLS**

Adriana María Belén Abiuso[1], Soledad Porte Alcon[1], Angeles Vinuesa[2], Flavia Saravia[2], Mónica Lidia Kotler[1], Roxana Mayra Gorojod[1].
[1]Laboratorio de disfunción celular en enfermedades neurodegenerativas y nanomedicina. QB-FCEN-UBA. IQUIBICEN-CONICET.
[2]Laboratorio de Neurobiología, QB-FCEN-UBA. IBYME-CONICET

Manganese (Mn) intake is essential at physiological concentrations. However, prolonged exposure produces a neurodegenerative disease called manganism, whose symptoms are often confused with idiopathic Parkinson´s disease. Even though the harmful effect of Mn in different cell types has been described, much remains to be understood regarding the outcomes of glial activation on neuronal death. Objective: To evaluate the effect of soluble mediators released by microglial cells after Mn exposure on neuronal integrity. For this purpose, we first characterized the direct effect of Mn exposure on neuronal and microglial cells, and then explored the influence of microglia-conditioned medium (MCM) on neurons viability. Methodology: MCMs were generated by BV-2 cells incubation with 250-1000 μM Mn for periods of 3 or 6 h, and were used to stimulate N27 neuronal cells for 24h; cell viability was assessed using MTT reduction assay; the study of ROS production was performed using DCFDA; the change in mRNA expression was quantified by RT-qPCR. Results: In N27 neuronal cells, Mn exposure induced a concentration-dependent decrease in cell viability after 24h (100-1000 μM, $P<0.05$), which was associated with an increase in ROS production. On the other hand, BV-2 cells increased ROS production after 3 and 6 h of Mn exposure, with no change in their viability ($P<0.05$). MCM of cells exposed to Mn induced a decrease in N27 viability ($P<0.01$), consistent with an increase in ROS production and a change in N27 morphology. Finally, we observed a higher expression of IL-1β and TNF-α mRNA in Mn exposed BV-2 cells (6 and 4 fold-increase, respectively, $P<0.001$, 750 μM). Conclusion: In microglial cells, Mn exposure induces cytokines expression and ROS generation, probably responsible for decreasing neuronal viability. The advance in the knowledge of Mn toxicity mechanisms will facilitate its diagnosis and the design of effective therapeutic strategies to avoid neurodegeneration.

427. (586) **DEVELOPMENT OF A CELLULAR MODEL TO EXPLORE NEURONAL PATHOLOGY IN SANFILIPPO DISEASE BY CRISPR/CAS9 GENOME EDITING**

Marcos Gabriel Francia[1], Soledad Porte Alcon[2], Adriana María Belén Abiuso[2], Alejandra Sonia Guberman[1], Mónica Lidia Kotler[2], Roxana Mayra Gorojod[2].
[1]Laboratorio de regulación de la expresión génica en células madre. [2]Laboratorio de disfunción celular en enfermedades neurodegenerativas y nanomedicina. QB-FCEN-UBA. IQUIBICEN- CONICET.

Sanfilippo syndrome type IIIA (Mucopolysaccharidosis IIIA; MPSIIIA) is a rare intractable disease characterized by an early-onset, severe, progressive neurodegeneration. It is caused by mutations in the gene encoding for the lysosomal hydrolase N-Sulfoglucosamine Sulfohydrolase (SGSH), which is crucial in the stepwise degradation of the sulfated glycosaminoglycan (GAG) heparan sulfate (HS). Nowadays, there is a lack of cellular models to explore the mechanisms of disease in the central nervous system (CNS). In this work, we aimed to develop a novel neuronal model by employing CRISPR/Cas9 technology. We designed two sgRNAs targeting exon 1 of the mouse *sgsh* gene and cloned these sequences in the pX330 vector. Insert-containing plasmids were amplified and checked by PCR and sequencing. HT-22 hippocampal neurons were transfected with PEI, and transfected cells were selected with puromycin. Subsequently, clones were isolated and amplified. We determined the lack of enzyme activity by employing the fluorogenic substrate 4-MU-GlcNS and obtained five putative knock-out cell lines where we tested lysosomal and mitochondrial integrity. Once confirmed the successful knockout by sequencing, these cell lines will constitute reliable reporters of the cellular context of disease and great models to study cell-type-specific damage. The strategy used is versatile and will be employed in other cell lineages to study cell-cell interactions of different cell types within the CNS. Further research may lead to the identification of relevant signaling pathways to investigate candidate drugs for novel therapies.

428. (596) **EXTRACELLULAR MATRIX ALTERATIONS IN MÜLLER GLIAL CELLS IN A RETINAL DEGENERATION MOUSE MODEL**

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Müller glial cells (MGC) are retinal stem cells, although their regenerative capacity is very low in mammals. We recently demonstrated that these cells in the *rd1* retinal degeneration mouse have decreased regenerative potential, an excessive number of neurons interacting with MGC, and a notable reduction in their lamellipodia, respective to their wild type (*wt*) counterparts. This suggests that extracellular matrix (ECM) protein synthesis and/or secretion could be altered in *rd1*, interfering with the substrate adhesion and lamellipodia extension, and thus affecting *rd1* MGC morphology and function-

ality. The aim of this work was to study *rd1* ECM protein expression and localization, and determine whether ECM pretreatment could restore the *rd1* MGC morphology and functionality. Using mixed neuron-glial cultures obtained from postnatal day two *rd1* and *wt* mice retinas, we analyzed by immunocytochemistry, osteonectin and fibronectin (FN) expression at 6 days in vitro, and we quantified focal adhesions with paxillin. On the other hand, *rd1* mixed cultures were seeded on culture dishes previously treated or not with ECM enriched conditioned medium (CM). We analyzed *rd1* MGC morphology, proliferation and photoreceptor survival (using BrdU and DAPI respectively). Our preliminary results showed a decrease in osteonectin expression, an alteration in FN expression, and a decrease in number and length of focal adhesions in *rd1* MGC when compared to the *wt* condition. Instead, the pretreatment with CM promoted *rd1* MGC cytoplasmatic extension, increased glial cell proliferation, decreased the number of neurons with pyknotic and fragmented nuclei, and decreased the Neuron/MGC ratio by 26.9%. These results indicate that *rd1* MGC display alterations in EMC protein synthesis and/or secretion, and that EMC supplementation improves MGC morphology and functionality.

429. (600) **EVALUATION OF THE ANTINOCICEPTIVE EFFECT OF MORPHINE IN A MODEL OF NEUROPATHIC PAIN IN MALE AND FEMALE MICE**

Perez V., Canero E., Balerio G.
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Morphine is one of the most widely used analgesics in the treatment of moderate and severe pain. However, its clinical use in long-term chronic pain treatment is limited by the enormous addictive potential. The co-administration of morphine with other drugs that enhance the analgesic effect and reduce its reinforcing properties, could be an alternative in pain treatment with opioids.
In the present study, we propose to determine the lower effective dose of morphine to ameliorate the nociceptive threshold by using the partial sciatic nerve ligation (PSNL) in male and female Balb/C mice, a widely used model of neuropathic pain. The Von Frey test (VFT) was performed in order to evaluate mechanical allodynia by calculating the nociceptive threshold (g). First, mice were habituated to the environment of the experiment during 4 days. After the habituation period, baseline responses were measured and surgery of the right paw was performed in a group of animals with PSNL (PSNL group), and surgery without PSNL was executed in another group (Sham group). On day 9 after surgery, VFT was performed after administration of morphine (1, 3, 9 mg / kg, i.p.) or saline solution as vehicle.
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The lower effective doses of morphine determined in male and female mice by a neuropathic pain model, will allow us to continue with our research in order to evaluate potential therapeutic targets to enhance the analgesic effect of opiates, reducing or preventing the addictive properties.

430. (605) **THE PRESENCE OF CO SPECIFICS DURING NICOTINE EXPOSURE ALTERS DRUG PREFERENCE IN A DOSE DEPENDENT MANNER IN ZEBRAFISH (DANIO RERIO)**

Leandro Rocco, Ramón Bernabeu.
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Reinforcing drugs such as nicotine have been proven to alter the way group behaviour takes place. Interestingly, there have not been studies that show whether group dynamics alter the way individuals react to a drug. These dynamics may be highly influential on the possibility of an individual becoming addicted to a certain substance. Nicotine rewarding properties have been assessed in zebrafish using a biased conditioned place preference (CPP) protocol. In the present study, we aimed to evaluate whether individuals exposed to nicotine as a group developed different responses to those of individuals exposed to the substance in isolation ("classic" CPP) and whether these responses varied in accordance to the concentration of nicotine to which they were exposed.
By exposing fish to either a grouped or an isolated CPP Protocol our preliminary results seem to show that Nicotine elicits a stronger, more robust CPP when being exposed to the drug as a group (Nicotine 15mg/L). When Nicotine concentration is raised to 50mg/L, however, the animals exposed as a group show negative CPP scores in comparison to their isolated exposure counterparts. These results may indicate that grouped exposure enhanced the effects of nicotine to a point that higher concentrations resulted in an exacerbation of its negative, anxiogenic effects, outweighing it's rewarding, anxiolytic properties. When nicotine exposure was coupled with Phenylbutirate, an HDAC inhibitor that has been proven to arrest the development of CPP in isolated animals, blocking the unfolding of CPP in a group-enhanced CPP protocol resulted in a positive CPP score at higher concentrations (50mg/L) whereas the isolated CPP protocol still showed negative results regardless of concentration.
In conclusion, our results seem to elucidate a novel approach to alter nicotine rewarding properties that is neither invasive nor pharmacological but solely through social stimuli.

ONCOLOGÍA

431. (030) **SMYD2 INHIBITION AS A NEW THERAPEUTIC STRATEGY FOR HEPATOCELLULAR CARCINOMA**

Barbara Bueloni[1], Maria Jose Cantero[1], Luciana Dominguez[1], Catalina Atorrasagasti[1], Mariana Garcia[1], Esteban Fiore[1], Juan Bayo[1], Guillermo Mazzolini[1]
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Introduction: The development of therapies for hepatocellular carcinoma (HCC) remains a topic of interest since the impact of available therapies on patient survival is still poor. The methyltransferase SMYD2 is an epigenetic modifier frequently upregulated in tumors that has been pointed out as a potential therapeutic target. Our aim was to explore the therapeutic potential of SMYD2 pharmacological inhibition in HCC.
Methods: SMYD2 expression, its correlation with clinical prognosis and transcriptional programs relevant to the disease were explored in HCC using TCGA, ICGC and GSE1542 databases. The effect of LLY507, an SMYD2 inhibitor, on HCC cells survival, cell cycle and apoptosis were assessed by standard MTT assay and flow cytometry. RNA-Seq analysis of HuH7 cells treated with LLY507 and their correlation with HCC datasets were used to characterize the underlying mechanism upon SMYD2 inhibition.
Results: We observed that SMYD2 is upregulated in the tumoral vs non-tumoral tissue and correlates with a poor prognosis when highly expressed in HCC. Additionally, we found that SMYD2 expression negatively correlates with a set of genes linked to immune-related processes, apoptosis, and MAPK pathway, and that are downregulated in HCC. The pharmacological inhibition of SMYD2 by LLY507 showed a potent *in vitro* antitumoral effect, induced cell cycle arrest and apoptosis. Finally, RNA-seq of LLY507-treated HCC cells revealed the downregulation of aggressive, cell cycle-related genes, as well as the upregulation of immune genes that correlate negatively with SMYD2.
Conclusions: The bioinformatic analysis of public HCC datasets showed that SMYD2 can be considered a new therapeutic target for HCC. The targeted inhibition of SMYD2 by LLY507 has a potent antiproliferative effect on HCC cells and reverts an oncogenic transcriptional program. These data suggest that inhibition of SMYD2