2022

medicina

BUENOS AIRES Vol. 82 Supl. V - 2022

MEDICINA

Volumen 82, Supl. V, Págs. 1- 338

medicina

BUENOS AIRES, VOL. 82 Supl. V - 2022

La Tapa
Maternidad Transgénica, 2007
Chino Benítez

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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Aparece en *MEDLINE (PubMed), ISI-THOMSON REUTERS (Journal Citation Report, Current Contents, Biological Abstracts, Biosis, Life Sciences), CABI (Global Health), ELSEVIER (Scopus, Embase, Excerpta Medica), SciELO, LATINDEX, BVS* (Biblioteca Virtual en Salud), *DOAJ, Google Scholar y Google Books*.
Incluida en el Núcleo Básico de Revistas Científicas Argentinas del CONICET.

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Tel. 5287-3827 Int. 73919 y 4523-6619
e-mail: revmedbuenosaires@gmail.com – http//: www.medicinabuenosaires.com

Vol. 82, Supl. V, Noviembre 2022

Diagramación y Diseño: Andrés Esteban Zapata - aez.sgi@gmail.com

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measuring the initial transport rate (ITR) of its fluorescent metabolite, GSH-S-methylfluorescein (GS-MF), a Mrp2 substrate. ITR, expressed as percent of C, was reduced by TLC (-25%), and this effect was prevented by MG132 (+6%). We conclude that sustained endocytosis of Mrp2 in cholestasis leads to its exacerbated proteosomal degradation. This finding could be relevant to understand the impairment of hepatocanalicular transporters in chronic cholestasis.

137. (524) **ESTRADIOL 17β-D-GLUCURONIDE-INDUCED NADPH OXIDASE IMPAIRS Mrp2 ACTIVITY BY CONTRIBUTING TO ITS CELLULAR INTERNALIZATION IN SANDWICH CULTURED RAT HEPATOCYTES**

Gimena Salas, Alen A. Litta, Virginia S. Schuck, Anabela C. Medeot, Romina B. Andermatten, Cecilia L. Basiglio, Fernando A. Crocenzi[1].
[1]*Instituto de Fisiología Experimental (IFISE)*

Estradiol 17β-D-glucuronide (E17G) alters canalicular secretion via several kinase-mediated signaling pathways which induce endocytosis and intracellular retention of canalicular transporters, the MEK-ERK1/2 pathway contributing to the second process. Previously, we found that NADPH oxidase (NOX)-generated reactive oxygen species (ROS) are partly responsible for the impairment of canalicular Mrp2 transport activity induced by E17G, and that NOX shares the MEK-ERK1/2 signaling pathway, downstream these kinases. We aimed to evidence that E17G-induced NOX-mediated functional impairment of Mrp2 transport is dependent on its internalization. Intracellular distribution of Mrp2 was assessed by immunofluorescence and confocal microscopy analysis in sandwich cultured rat hepatocytes (SCRH). First, SCRH were treated with vehicle (DMSO, control), E17G (200 μM, 20 min) or pre-treated with apocynin (Apo, NOX inhibitor, 100 μM, 30 min) prior to E17G. Then, SCRH were fixed, permeabilized, and incubated with a specific antibody to Mrp2, and then with a secondary antibody and Alexa Fluo 568-conjugated phalloidin for F-actin staining, which is mainly pericanalicular (demarcating the canaliculi) and barely evident in the basolateral membrane. Mrp2 internalization was evaluated in confocal images (n=12 canaliculi, from 3 independent cultures) by calculating the percentage of Mrp2-associated staining within the canaliculi to total cellular staining. Mrp2, mainly confined to the canaliculi in controls, was internalized to intracellular vesicles by E17G. Apo prevented this alteration, showing a control-like distribution pattern. Apo, which inhibits migration of the cytosolic p47phox subunit of NOX, impeding the formation of the active NOX complex in the plasma membrane, prevents internalization of Mrp2 by E17G. This finding supports the location of NOX in the MEK-ERK1/2 signaling pathway, which is involved in E17G-induced internalization of canalicular transporters such as Mrp2.

138. (549) **ANTICANCER EFFECTS OF GLYCOSYLATED 4-METHYLUMBELLIFERONE ON HEPATOCELLULAR CARCINOMA THROUGH REGULATION OF APOPTOSIS AND MIGRATION**

Gisela Weiz, Alina L Gonzalez, Iara Mansilla, Javier D. Breccia, María I. Molejón
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Liver cancer, more specifically hepatocellular carcinoma (HCC), is the second leading cause of cancer-related death and its incidence is increasing globally. We have recently reported that 4-methylumbelliferilrutinose (4MUR), an enzymatically synthetized compound, exhibit antitumoral effect on HCC. 4MUR could be used as HCC targeted therapy, without damaging non-tumoral cells or other organs. In this work we aim to understand the molecular processes involved in 4MUR-related antitumor efficacy. First, we evaluated its effect on cell death using HCC tumoral cell lines. The percentage of apoptotic Huh7 cells exposed to 4MUR significantly increased as compared with 4MU ($p < 0.001$). We next performed wound healing assays to examine the effect of the glycosylated drug on the migration of tumoral cells. 4MUR significantly inhibited the migration of Huh7 cells in a dose-dependent manner compared to the untreated group. Based on the evidence that hyaluronic acid (HA) and its receptors play an important role in tumor migration we quantified by RT-PCR the HA synthases (HAS2 and HAS3) and HA-receptor expression. In Huh7 cells, the expression of HAS2 was significantly reduced upon 4MUR treatment ($p<0.05$), while HAS3 was not significantly affected. On the other hand, 4MU treatment did not affect the expression of HAS2 but up-regulated HAS3 by around 3.5-fold. Whereas, no differences were obtained in CD44 expression. The results of this study revealed that 4MUR effectively induces apoptosis cell death in HCC cells. In addition, 4MUR treatment exerted anti-migration effects on HCC cells. The underlying mechanisms suggested that HCC progression was promoted via HA-dependent pathway, independently of HA-receptos inhibition. Thus, we propose that treatments interfering HA metabolism with 4-MUR may represent effective strategies for HCC treatment in the future.

139. (696) **ANTIOXIDANT ACTIVITY OF ATRIAL NATRIURETIC PEPTIDE (ANP) IN THE EXOCRINE PANCREAS**

Courreges, Ana P[1], Alvarez Guadalupe I[1], Ochoa Federico[2], Lairion Fabiana[3], Zotta Elsa[2], Repetto Marisa[3], Vatta Marcelo S[1,4], Bianciotti Liliana G[1,4].
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We previously reported that ANP is produced by the exocrine pancreas and that it plays a beneficial role in the outcome of acute pancreatitis (AP). It reduces trypsinogen activation and the inflammatory response and restores glutathione depletion. In the present study we assessed different parameters of oxidative stress and antioxidant defenses in Sprague Dawley rats with AP induced by four repetitive cerulein injections (40µg/Kg). Thirty minutes before the first cerulein injection animals were infused with either saline (control) or ANP (1µg/Kg/h) for 60 min. Following euthanasia (60 min after the last cerulein injection) pancreatic samples were harvested. ANOVA followed by a Student Newman Keuls was used for statistical analysis. Results are expressed as the mean±SD and $p<0.05$ or less were considered statistically significant (*). ANP reduced NADPH oxidase activity (U/ug protein) (2180±256 vs. 1410±216**). As ANP increased Nrf2 nuclear translocation (0.158±0.2 vs. 0.398±0.02*) superoxide dismutase (SOD) and catalase expression were assessed by western blot and qRT-PCR. ANP increased SOD protein and mRNA expression (0.9±0.08 vs; 1.20±0.11*; 0.63±0.12 vs. 2.29±0.19*). Catalase showed no protein or mRNA changes as expected. Carbonyl content was decreased by ANP (5.60±0.6 vs. 3.60±0.9*) and TBARS showed no changes in any experimental group. The oxidized form of coenzyme Q9 (isoform in rodents) was also reduced by ANP (477.9±56.9vs. 254.7±86.4*). These results further support previous findings showing that ANP enhances the antioxidant capacity of the pancreas in AP. Current evidence suggests that targeting only oxidative stress would not be sufficient to stop the progression of AP, a pathology characterized by a sudden onset and an unpredictably clinical course. In this sense ANP, which it is produced in the exocrine pancreas, would be beneficial since it not only improves the redox status of the pancreas but also significantly reduces premature trypsinogen activation and the local inflammatory response

140. (744) **LIPOTOXIC EFFECT OF CAFETERIA DIET AND 3-METHYLCHOLANTRENE ON THE LIVER OF RATS**

Marina Labiano[1], Jeremías Pablo Flores-Quiroga [1], Florencia Heinecke [1], María Agustina Meneghini [1], Alicia Graciela Fale-