2017

# medicina

BUENOS AIRES VOL. 77 Supl. I - 2017

MEDICINA

Volumen 77, Supl. I, págs. 1-616

by PRL. These findings suggest the possibility of altered pharmacokinetics of xenobiotics substrates of Pgp in PP period, including therapeutic agents.

*Keywords*: Prolactin, P-glycoprotein, liver, hepatic transporter, lactating rats

(1490) **THE ABSENCE OF SPARC (SECRETED PROTEIN ACIDIC AND RICH IN CYSTEINE) ATTENUATES LIVER INFLAMMATION AND FIBROSIS IN NON-ALCOHOLIC STEATOHEPATITIS MICE MODELS**

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Non-alcoholic fatty liver (NAFLD) consists of fat accumulation in hepatocytes. It encompasses a set of clinical conditions ranging from fatty liver, hepatocyte damage and inflammation (steatohepatitis or NASH) and its subsequent complications: liver fibrosis, cirrhosis and hepatocellular carcinoma. SPARC is a matricellular protein associated with inflammatory processes, tissue remodeling, regulation of fibrillar collagen deposits, among other biological functions.

The aim of this project was to study the role of SPARC in the context of two NASH models: 1) the streptozotocin-induced NASH model (STAM); 2) and the diet-induced obesity (DIO) model. For STAM model, 2 days old SPARC$^{-/-}$ and SPARC$^{+/+}$ mice were subcutaneous injected with 200 mg streptozotocin (SZT) and fed with high fat (HF) or control (LF) diet since weaning for 8 weeks. For DIO model, SPARC$^{-/-}$ and SPARC$^{+/+}$ mice were fed for 20 weeks with HF. SPARC and pro-inflammatory cytokines expression were assessed by qPCR. The degree of NASH was measured using the NAS score; and fibrosis was assessed by picrosirius red staining. Triglycerides, cholesterol and serum transaminases were also measured.

Liver SPARC expression was increased in HF-fed mice in both experimental models. In the STAM model weight curves demonstrated that SPARC$^{+/+}$ and SPARC$^{-/-}$ mice, either LF or HF, increased their weight equally; in contrast, DIO model shows weight difference between LF and HF fed-mice. HF-fed SPARC$^{-/-}$ mice in STAM model developed less fibrosis, as well as HF-fed SPARC$^{-/-}$ mice from DIO model. According to NAS score, HF-fed mice from STAM model developed NASH after 8 weeks, whereas in DIO model only HF-fed SPARC$^{-/-}$ mice develop incipient NASH. Inflammatory cytokines expression were increased in HF-fed SPARC$^{+/+}$ mice compared to SPARC$^{-/-}$ mice from both experimental models.

We present novel evidences that demonstrate a role for SPARC in the development of NASH. SPARC could play a key role as a target for prevention of NASH progression.

Keywords: Sparc / Nash / Stam / Dio

(1278) **THE ROLE OF SPARC (SECRETED PROTEIN ACIDIC AND RICH IN CYSTEINE) IN THE LIVER SINUSOIDAL ENDOTHELIUM IN AN EXPERIMENTAL MODEL OF ACUTE LIVER FAILURE.**

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Acute liver failure (ALF) is characterized by a rapid deterioration of liver function. Liver sinusoidal endothelial cells (LSEC) have a key role during ALF. Different pathological agents can target LSEC, disrupting sinusoidal endothelium and facilitating T-cell migration into liver parenchyma. SPARC is a matricellular protein involved in many processes including cell-cell interaction and adhesion. After injury, SPARC is overexpressed in EC inducing different cellular processes. We have observed that SPARC$^{-/-}$ mice are protected from ALF damage. In this work, we study the role of SPARC in sinusoidal endothelial injury. In an *in vivo* approach of ALF, SPARC$^{+/+}$ and SPARC$^{-/-}$ mice were subjected to conA injury and LSEC monolayer morphology was studied by electronic microscopy. LSEC primary cultured from SPARC$^{+/+}$ and SPARC$^{-/-}$ were used to study the effects of conA *in vitro*. SPARC expression, cytoskeletal structure, cell morphology and activation were assessed. Microscopic analysis revealed that LSEC monolayer was well preserved and less activated in conA-treated SPARC$^{-/-}$ mice compared to SPARC$^{+/+}$. SPARC$^{-/-}$ LSEC phenotype and endocytic capacity were conserved. SPARC expression was increased in conA-treated LSEC (7.3±1 vs 1±0.1). In addition, SPARC$^{-/-}$conA-treated LSEC showed a marked decrease in VCAM-1 expression; cell morphology was more preserved and no alterations in actin cytoskeleton organization in SPARC$^{-/-}$ mice; contrarily, SPARC$^{+/+}$LSEC showed a clear disturbance in cell appearance and actin filament architecture. Consistently, qPCR analysis showed that SPARC$^{-/-}$conA-treated LSEC increased their expression of *capzb* (1.7±0.1 vs 1.2±0.1), a regulator of actin filament dynamics, and decreased *tubb2b* expression (0.01±0.1 vs 2.4±0.01), a major component of microtubules, compared with SPARC$^{+/+}$conA-treated LSEC. Our results suggest that SPARC plays an interesting role in LSEC under conA damage. Inhibition of SPARC merits further investigation as a potential therapeutic target.

Liver sinusoidal endothelial cell (LSEC) – SPARC – Acute liver failure (ALF)

(767) **UNRAVELING THE ROLE OF PROHIBITIN-1, A NOVEL LIGAND OF GALECTIN-1 IN HEPATOCELLULAR CARCINOMA CELL VIABILITY**

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Galectin-1 (Gal1) is a glycan-binding protein overexpressed in hepatocellular carcinoma (HCC). We demonstrated that Gal1 upregulation in human HCC cells induces cell proliferation, epithelial-mesenchymal transition, tumor growth and metastasis. By proteomics we have identified prohibitin-1 (PHB) as a new Gal1 ligand in HCC cells. PHB has multiple functions depending on its subcellular localization. Its role in cancer is controversial, it was found downregulated in most human HCC tissues analyzed but in other HCC samples its overexpression was observed. Liver-specific PHB knockout (KO) mice develop HCC spontaneously suggesting that PHB functions as tumor suppressor, although when highly expressed it promotes HCC cell migration *in vitro* showing its involvement in tumor progression. Thus, we aimed to elucidate PHB role in HCC cell viability and to analyze if PHB expression is regulated by Gal1. By immunofluorescence, we observed that PHB localizes in a punctate pattern in human HepG2 and HuH-7 HCC cells, both in nucleus and cytoplasm. By siRNA transfection, we downregulated PHB expression in these cells: HepG2-siPHB 31±15 vs HepG2-siControl 76±19% ($p<0.05$ n=3); HuH7-siPHB 36±9 vs HuH7-siControl 96±19% ($p<0.05$ n=7) at 72 h post-transfection (Western blot, Wb). Cell viability (MTT) at 72 h decreased in HuH7-siPHB cells (85±5%) compared to HuH-7-si-Control cells (100%, $p<0.05$ n=7) whereas the opposite effect was observed in HepG2-siPHB cells (118±9 vs control cells 100% n=3). PHB expression increased in Gal1 overexpressing HepG2-Gal1 cells (181±36% $p<0.05$ n=5) and decreased in HepG2 cells transfected with Gal1 shRNA (13±2% $p<0.01$ n=3) respect to the corresponding controls (Wb). In the liver of 2-week old-Gal1 KO mice PHB expression also decreased (63±7% n=4 vs wild-type mice 107±21% n=3). In conclusion, PHB modulates HCC cell viability in a cell line-dependent manner and Gal1 regulates PHB expression both in normal and tumor hepatocytes. CONICET PIP647-UBA-20020150100005BA.

*Key words: Galectin-1, hepatocellular carcinoma, prohibitin-1*

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(57) ***Acacia aroma*** **HIDORALCOHOLIC LEAF EXTRACT: A PROPHYLACTIC EFFECTIVE TREATMENT FOR ETHANOL-INDUCED GASTRIC LESIONS IN RATS**

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The pathophysiology of peptic ulcers results from an imbalance between some aggressive and defensive factors. *Acacia aroma* Gill ex Hook&Arn (Tusca) is a native northwestern's Argentinian plant; it has been used traditionally to treat ulcers and wounds. The aim of this study was to evaluate the gastric effect of Tusca leaves hidroalcoholic extract (HAE) on an ulcer experimental model. A qualitative and quantitative phytochemical analysis was carried out on 10% HAE (in ethanol 70º) and its antioxidant activity was also studied. Extract's ability to bind gastric mucosa was determined too. Ethanol induced gastric ulcer model using male Wistar rats was carried out. Experimental design (n=6 animals/group) 1. Control group received 0.9% NaCl, 2. Positive control group received Sucralfate (100mg/Kg, orally) 3. Treated group, received HAE 150mg/kg orally. Mucus content was determined by Alcian Blue method. Macroscopic (Number of ulcers, severity and percentage of ulcerated area) and microscopic (histologic and histochemical) studies of stomachs obtained from each group were carried out. The activity of catalase and the levels of reduced glutathione and malondialdehyde were quantified in gastric homogenates. Tusca HAE showed a significant ($p \leq 0.05$) free radical scavenging activity *in vitro* compared to Quercetin and also had the ability to bind gastric mucosa. The animal group treated with the HAE exhibited a decrease in ulceration percentage, and an increase in mucus content compared with the untreated group. The oxidative stress parameters of Tusca treated group approached to normality. In summary, HAE is effective to protect the gastric mucosa from ethanol induced injury by binding to its surface and strengthening mucus layer. This effect is also linked to extract´s antioxidant property. Future studies will be necessary to determine the active compounds and additional mechanisms involved.

Keywords: *Acacia aroma,* gastroprotective.effect, hidroalcoholic extract.

(622) **GASTROPROTECTIVE ACTIVITY OF *Aristolochia argentina*: ROLE OF PROSTAGLANDINS, NITRIC OXIDE AND INTERACTION WITH COX**

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*Aristolochia argentina* (Aristolochiaceae) is popularly known as "charrúa", "charruga", "patito", "buche de pavo". The roots of this plant are used in folk medicine for the treatment of ulcers. Previously, we have demonstrated that *A. argentina* prevented the gastric ulcer induced by several necrotizing agents (ethanol, HCl, NaOH). Allantoin was isolated from the roots of *A. argentina*. The aim of the study was to evaluate the mechanism of action and the role of sulfhydryl groups, nitric oxide and prostaglandins in the gastroprotection of *A. argentina*, and the structural basis of interaction of the principle active allantoin with cyclooxigenases ($COX_1$ and $COX_2$). The effects of *A. argentina* lyophilized extract (AALE) on ethanol-induced gastric ulcer were studied in Wistar rats. The activity of AALE on ethanol-induced lesions continued even after the inhibition of endogenous sulfhydryls following pretreatment with NEM (N-ethymaleimide). Both indomethacin, a prostaglandins synthesis inhibitor, and L-NNA (Nω-nitro-L-arginine), a nitric oxide synthase inhibitor, antagonized AALE gastroprotective activity ($p<0.001$). Moreover, the docking of allantoin into the crystallographic structure of $COX_1$ and $COX_2$ was done using AUTODOCK4. The allantoin docking with $COX_1$ showed that it binds to the protein active site, a long and deep hydrophobic channel, between C6 and C11. The allantoin docking with $COX_2$ showed that it binds to the protein active site between C8 and C11. Allantoin occupies a similar region as several NSAIDs in the crystal structure of these complexes with $COX_2$. The interaction of allantoin with $COX_2$ active site may indicate that has a role in the antiulcer mechanism. Present findings suggest the possible involvement of prostaglandins and nitric oxide, at least in part, in the antiulcer effect of AALE.

KeyWords: *Aristolochia argentina*; ulcer; cyclooxigenase

(1181) **IN VITRO ACTIVITY OF *Jodina rhombifolia* LEAVES AND BARK AQUEOUS EXTRACTS ON ISOLATED RAT THIN INTESTINE**

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The leaves and bark of *Jodina rhombifolia* (Hook. & Arn.) Reissek (Santalaceae) are usually employed in Argentine folk medicine for a great variety of digestive tract affections, however, few studies have evaluated the effect of this specie on gastrointestinal functions. In our previous *in vivo* studies, these aerial parts have demonstrated a reduction of intestinal transit. Therefore, the aim of this work was to evaluate the activities of bark and leaves extracts, by separate, on *in vitro* intestinal contractility of rats. Effects were evaluated through contractile concentration-response curves (CRC) induced by Carbachol and $CaCl_2$ in isolated rat thin intestine segments that were suspended in tissue baths to measure the antispasmodic activity. Leaves and bark aqueous extracts were obtained by infusion and decoction at 10%w/v, respectively, and subsequently concentrated and lyophilized. The effects of CRC in the presence and absence of extracts were statistically compared by two-way ANOVA [treatment (extract dose); Carbachol or $CaCl_2$ concentration]. In dose-dependent manner, extracts reversibly and non-competitively antagonized the contractions provoked by spasmogenic agents (Carbachol and $CaCl_2$); ANOVA indicated a significative effect of treatment ($p<0.001$), as well as Carbachol ($p<0.001$) and $CaCl_2$ concentration ($p<0.001$). The extracts of leaves and bark inhibited the CRC of Carbachol with $IC_{50}$ = 10.57 ± 1.38 and 16.20 ± 1.21 mg/ml, respectively, and the CRC of $CaCl_2$ with $IC_{50}$ = 8.29 ± 1.54 and 8.58 ± 1.52 mg/ml, respectively. The results obtained suggest that leaves extract is more potent than bark extract as intestinal antispasmodics, while both similarly inhibit CRC of $Ca^{+2}$. This suggests that the non-competitive interference with $Ca^{+2}$ influx to smooth muscle is the cause of the antispasmodic effect of the two fractions. This study provides novel evidence to validate the folk use in digestive pathologies, due to their antispasmodic properties.

(1247) **ORAL ADMINISTRATION OF *Zuccagnia punctata* EXTRACT HAS BENEFICIAL EFFECTS IN HYPERCHOLESTEROLEMIC RABBITS**

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The consumption of flavonoids has been shown to prevent cardiovascular diseases (CD) including atherosclerosis. In turn, extracts from *Zuccagnia punctata* have demonstrated to be rich in flavonoids. **Purpose:** To study the effects of oral treatment with *Z. punctata* extract (ZpE) on clinical parameters: lipid profile, oxidative stress status and vascular function in a rabbit model of hypercholesterolemia. **Methods:** Rabbits were separated in five groups: fed standard chow untreated (CD) or treated with 2.5 mg GAE/day ZpE (CD-ZpE); fed 1% cholesterol-enriched chow untreated (HD), treated with 2.5 mg GAE/day ZpE (HD-ZpE) or with 2.5 mg Rosuvastatin (HD-R), during 6 weeks. Body weights (BW), mean blood pressure (MAP), heart rate (HR), visceral abdominal fat (VAF) were determined. Total cholesterol (TC), triglycerides (TG), fasting glucose (FG), aspartate amino transferase (AST), alanine amino transferase (ALT), bilirubin, creatinine, thiobarbituric acids reactive substances (TBARS) and glutathione reduced/oxidized index were measured in serum. Abdominal aorta was excised and vascular function was assessed by acetylcholine (Ach) relaxation and contractile response to norepinephrine (NE) and angiotensin II (Ang II). **Results:** ZpE reduced