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tivation at different levels of the inflammasome cascade. UBACyT 20020170100586BA, PIP-CONICET 11220170100585CO, PICT 2018-03052.

NEFROLOGÍA

182. (103) **ELIGLUSTAT PROTECTS FROM DAMAGE CAUSED BY SHIGA TOXIN TYPE 2 IN HUMAN RENAL TUBULAR EPITHELIAL CELLS**

Sánchez DS[1], Fischer Sigel LK[1], Balestracci A[2], Ibarra C[1], Amaral MM[1], Silberstein C[1].
1. IFIBIO HOUSSAY, Departamento de Cs. Fisiológicas, Facultad de Medicina, Universidad de Buenos Aires.
2. Hospital General de Niños Pedro de Elizalde.

Shiga toxin-producing *Escherichia coli* is responsible for Hemolytic Uremic Syndrome (HUS), a cause of renal failure in children. We have previously shown that C-9 and Eliglustat (EG), inhibitors of glucosylceramide synthase and globotriaosylceramide (Gb3), prevent the cytotoxic effects of Shiga toxin type 2 (Stx2), in human cortical renal tubular epithelial cells (HRTEC) primary cultures and HK2 cell line. The aim of this work was to evaluate the efficacy of EG, elucidating EG treatments necessary to achieve total protection against Stx2 in HRTEC and HK2. Cells were incubated with Stx2 (1 ng/ml, 24 and 72 h) and pre-incubated with or without EG (1-500 nM, 6 and 24 h), followed by co-incubation with same dilutions of EG and Stx2 (24 and 72 h). Total number of cells stained with Hoechst was counted in microphotographs and compared with cell viability measured by neutral red uptake. Early and late apoptosis and necrosis was evaluated by annexin V/propidium iodide staining. Tubulogenesis was evaluated in HRTEC grown on matrigel. Treatment of cells with Stx2 significantly decreased cell confluence and viability and the number of cells attached ($p<0.001$). In HRTEC, Stx2 increased early and late apoptosis, and necrosis compared to non-treated cells ($p<0.01$). Furthermore, Stx2 inhibited cell aggregation and tubulogenesis on matrigel. HRTEC preincubated with EG (50 nM, 24 h or 500 nM, 6 h) totally prevented Stx2 effects on HRTEC measured as cell count, viability, apoptosis, necrosis and tubulogenesis ($p<0.05$). Preincubation of HK2 cells with EG (1 nM, 24 h or 10 nM, 6 h) totally prevented Stx2 effects on cell viability and confluence. EG alone did not produce cytotoxic effects *per se*. In conclusion, EG protects human renal tubular epithelium against Stx2 cytotoxicity being HRTEC more sensitive than HK2. Treatment with EG could be a novel substrate inhibition therapy to neutralize Stx2 action and prevent renal damage in patients with HUS. Study supported by PUE0041, CONICET.

183. (284) **EFFECTS OF SHIGA TOXIN TYPE 2 IN PREGNANT AND NON-PREGNANT FEMALE RATS**

Fischer Sigel LK[1], Sacerdoti F[1], Ibarra C2, Zotta E[1], Silberstein C[1].
1.IFIBIO Houssay (UBA-CONICET) Dpto de Cs Fisiologicas, Facultad de Medicina, UBA.

Shiga toxin-producing *Escherichia coli* causes acute renal failure and Hemolytic Uremic Syndrome. It was reported that inhibition of nitric oxide (NO) by Shiga toxin type 2 (Stx2) enhanced renal damage in mice and baboon models of Stx-mediated HUS. The aim of the work was to study the evolution of the damages caused by Stx2 in P compare with NP rats. Pregnant Sprague-Dawley rats, at day 8 of gestation, and NP rats were ip inoculated with 0.5 ng Stx2/g body weight (PS, NPS) or diluent (PC, NPC). Some PS and PC rats were treated with 1mg/ml L-NAME, NO inhibitor, in drinking water (PLS, PLC) from 24h before ip injection to 4 days post-injection (dpi). Rats were individually housed, checked for water and food intake, and weighted every 24h until 30 dpi. At 4 dpi, blood and 24h-urine samples were collected to determine urinary flow and free water clearance (C_{H20}). Then, rats were euthanized and kidneys were removed for histopathological observations. NPS and PS rats showed a decrease in food intake and weight with respect to controls ($p<0.05$). PS rats increased food intake and recovered weight at 5 dpi, while NPS rats showed an improvement at 14 dpi. The water intake increased in NPS and PS rats compared to controls until 7 dpi ($p<0.05$). In NPS at 4 dpi, the rise in water intake coincided with an increase in urinary flow and C_{H20} respect to NPC ($p<0.05$), different from what was observed in PS. The renal cortex of NPS presented significantly more necrosis and atrophied tubules than PS ($p<0.05$). Preliminary results in PLS rats showed that L-NAME significantly increased renal necrosis compared with PLS and PLC rats ($p<0.05$). In conclusion, PS rats suffered less renal damage and recovered from the Stx2 effect faster than NPS rats. L-NAME increased Stx2 effect in PLS suggesting that physiology changes caused by pregnancy, like increasing in NO production, may contribute to protect maternal kidney from Stx2 effects.

184. (359) **MOLECULAR MECHANISMS INVOLVED IN RENAL ALTERATIONS TRIGGERED BY ENDOTHELIN INHIBITION IN THE RAT DURING THE POSTNATAL PERIOD**

Marinoni, RC[1]; Oronel, LH[1]; Yarza, C[1]; Ortiz, MC[1]; Albertoni Borghese, MF[1] and Majowicz, MP[1]
[1]. Cátedra de Biología Celular y Molecular, Departamento de Ciencias Biológicas, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires.

We had previously shown that Endothelin (ET) inhibition during the early postnatal period (PNP) with bosentan (20 mg/kg/day), a dual ET receptor antagonist (ERA), leads to alterations in both ET-1 and ET receptors expressions in adult rats during a high sodium intake. We had also shown that ET inhibition during PNP increases apoptosis in the kidney and this could be a consequence of an imbalance between nitric oxide (NO) and superoxide (O_2^-). It is known that the delicate balance between NO and O_2^-, besides contributing to development, is important for renal sodium handling.
The aim of this work was to evaluate in 7 day old rats (male and female controls and ERA-treated rats): renal mitochondrial NO/O_2^- ratio, nitric oxide synthase (NOS) activity in different renal structures estimated by NADPH-diaphorase technique, renal NOX4, ET_A and ET_B expressions by Westernblot and renal pre-pro ET-1 by real time PCR. Four experimental groups were studied: control males (Cm), males treated with bosentan (ERAm), control females (Cf) and females treated with bosentan (ERAf). Two-way ANOVA was used for statistics.
We found an effect of sex for pre-pro ET-1 expression ($p<0.05$), being higher in m than in f and for ETB expression ($p<0.02$), being higher in f than in m. However ET_A/ET_B ratio was not significantly different between groups.
On the other hand, we found a decrease in NADPHd activity in immature cortical renal structures only in ERAm ($p<0.05$) and in macula densa in both ERAm and ERAf vs their controls ($p<0.05$) and a clear tendency to decrease NO/O_2^- ratio in ERA-treated animals. NOX4 expression also had a tendency to increase in both ERAm (0.70 ± 0.18 vs 0.87 ± 0.17) and ERAf (0.64 ± 0.18 vs 0.86 ± 0.06) vs their respective controls. This tendency could explain the tendency to decrease NO/O_2^- ratio in ERA-treated animals. The expression of renal pre-pro ET-1 and ETB receptor has sex differences in early life but it is not affected by ET inhibition at this stage.

185. (378) **EFFECTS OF ESTROGENS ON RENAL PROXIMAL TUBULE EPITHELIAL CELLS**

Jove P1, Vlachovsky SG2, Sánchez DS[1], Azurmendi PJ2, Oddo EM2, Ibarra FR[1,2], Silberstein C1
1. Departamento de Ciencias Fisiológicas, Instituto de Fisiología y Biofísica Bernardo Houssay (IFIBIO-Houssay) UBA-CONICET, Facultad de Medicina, Universidad de Buenos Aires
2. Laboratorio de Nefrología Experimental y Bioquímica Molecular, Instituto de Investigaciones Médicas Alfredo Lanari, Facultad de Medicina, Universidad de Buenos Aires

We have previously demonstrated that 17β-Estradiol (17βE) stimulates cell proliferation through classic estrogen receptors (ER) and the G protein-coupled estrogen receptor 1 (GPER-1), in primary cultures of human renal cortical tubular epithelial cells (HRTEC). We also observed that 17βE decreases the expression of Na+ K+ ATPase (NKA) in primary cultures. The aim of the present work is to study the effects of 17βE on cell proliferation and the expression of