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Hepatoprotective effect of sodium (*S*)-2-hydroxyglutarate against ischemia-reperfusion injury in Wistar rats

E. Cienfuegos-Pecina [1,2], D.P. Moreno-Peña [1], L. Torres-González [1], D. Garza-Villarreal [1], O.H. Mendoza-Hernández [1], R.A. Flores-Cantú [1], B.A. Samaniego-Sáenz [1], L.E. Muñoz-Espinosa [1], P. Cordero-Pérez [1]

[1] *Hepatology Center, Internal Medicine, University Hospital "Dr. José E. González", Monterrey, México*
[2] *Clinical Pathology, University Hospital "Dr. José E. González", Monterrey, México*

Background and aim: Ischemia-reperfusion (IR) injury is one of the leading causes of early graft dysfunction in liver transplantation. Techniques such as ischemic preconditioning protect the graft through the activation of the hypoxia-inducible factors, which are the main regulators of oxygen homeostasis and are downregulated by the EGLN prolyl-hydroxylases. The inhibition of EGLN has a therapeutic effect against IR injury. Our aim was to evaluate the effect of the EGLN inhibitor sodium (*S*)-2-hydroxyglutarate [(*S*)-2HG] against liver IR injury in Wistar rats.

Material and methods: (*S*)-2HG was synthesized from L-glutamic acid by diazotization/alkaline hydrolysis, and its structure was confirmed by nuclear magnetic resonance. Thirty-one female Wistar rats were used, weighing 250 – 300 g, randomly divided in the following groups, following the specifications of the NOM-062-ZOO-1999: IR (n = 7, ischemia: 20 minutes, reperfusion: 60 minutes), sham (SH, n = 7, laparotomy without IR), non-toxicity (HGTox, n = 6, 25 mg/kg, *p.o.*, twice per day for two days, laparotomy without IR), and (*S*)-2HG + IR (HGIR, n = 7, same dose as HGTox group + IR induction). Serum levels of ALT, AST, LDH, ALP, glucose, and total bilirubin, were assessed. Tissue levels of IL-1β, IL-6, TNF-α, malondialdehyde, SOD, and glutathione peroxidase were also evaluated. This project was approved by the Ethics and Research Committee of our institution (Registration number: HI19-00003).

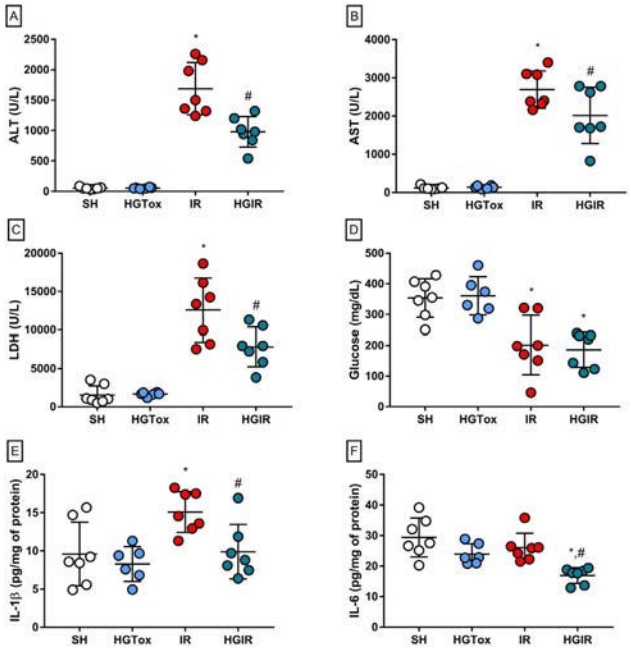

Figure. Liver injury and inflammatory biomarkers. (A) Serum alanine aminotransferase; (B) Serum aspartate aminotransferase; (C) Serum lactate dehydrogenase; (D) Serum glucose; (E) Tissue interleukin 1β; (F) Tissue interleukin 6. One-way ANOVA with Tukey *post hoc* test, $^{*}p < 0.05$ versus SH; $\#p < 0.05$ versus IR.

Results: A difference in the levels of ALT, AST, LDH, glucose, IL-1β, and IL-6 was observed among the groups (Figure). No hepatotoxic effect was observed when comparing the HGTox group versus the SH group. There were also no differences in the other biomarkers assessed.

Conclusions: (*S*)-2HG showed a hepatoprotective effect, decreasing the levels of liver injury and inflammation biomarkers. No hepatotoxic effect was observed at the tested dose.

Conflicts of interest: The authors have no conflicts of interest to declare.

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Cellular and molecular characterization of the pirfenidone effects on an hepatocarcinogésis experimental model

J.A. Silva-Gómez [1], H.C. Monroy-Ramírez [1], M. Galicia-Moreno [1], A. Santos-García [2], J. Armendáriz-Borunda [1,2]

[1] *Department of Molecular Biology and Genomics. Institute for Molecular Biology in Medicine and Gene Therapy, Health Sciences University Center, University of Guadalajara, México*
[2] *Tecnológico de Monterrey, Campus Guadalajara, Zapopan, Jalisco, México*

Background and aim: Hepatocellular carcinoma (HCC) is a primary neoplasm of the liver with high recurrence and high mortality rate. The etiological factors are hepatitis B and/or C virus infections, non-alcoholic steatohepatitis, alcohol consumption, and aflatoxin b1 exposition. These factors promote inflammation, fibrosis, and cirrhosis, and alter the expression of genes and molecular mechanisms, initiating hepatocarcinogenesis. The modified resistant hepatocyte model (MRHM) has been established which simulates the stages of carcinogenesis. Pirfenidone (PFD) has shown antifibrotic, anti-inflammatory and antioxidant effects in liver damage models, so the aim was to evaluate the administration of PFD on histopathological alterations and the expression of key proteins in the development of hepatocarcinogenesis in MHRM.

Material and methods: Longitudinal experimental study. 30 Wistar rats were divided into 3 groups: control group, carcinogenic damage group, and carcinogenic damage group plus daily administration of PFD. The physical and clinical data of the animals were analyzed at 30 days. All tissues were subjected to H&E, and Masson trichrome histological assays, and analysis of proteins involved in liver fibrosis, acute and chronic inflammation, apoptosis, cell division, tumor promotion/suppression, and cell metabolism using Western-Blot tests and microscopy confocal. Experiments for triplicate were performed; data were analyzed and plotted in GraphPad Prism 7.

Results: Morphological analysis: damage group shows dense, pale brown and inflamed livers compared to control and PFD groups. PFD administration prevents damage in the hepatocyte architecture, reduces periportal fibrosis and prevents inflammation overexpression markers (NFkB, IL-6, and TNFalpha) and cell