**5708**
**Topic Category:** 4073-ASIP Liver injury and inflammation

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**First Author Degree:** PhD, DSc, or equivalent

**Presentation Preference:** Indifferent

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**Keywords:** 1. ischemia 2. phosphodiesterase

# PDE4 Inhibitor Rolipram Mitigates Liver Ischemia Reperfusion Injury in a Rat Model by Preventing Neutrophil Accumulation

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BACKGROUND/INTRODUCTION:

Ischemia-reperfusion (IR) injury is caused by a transient loss of blood flow (ischemia) followed by return of blood flow (reperfusion), which initiates an inflammatory response. IR injury occurs in organ transplantation, sepsis, respiratory failure, hemorrhage, trauma, stroke, cardiac arrest, and shock. Ischemia reperfusion, as a primary cause of post graft non-function, is a limiting factor in the success of liver transplantation. Due to a crucial shortage of donor livers, there are about 17,000 people on the waiting list for a liver transplant, and 1,500 a year will die while waiting for an organ (American Liver Foundation). Pharmacological attenuation of the IR-induced inflammatory response could improve graft function and survival. We investigated the potential of using the phosphodiesterase (PDE) inhibitor, rolipram, in hepatic ischemia reperfusion injury. PDEs are the only enzymes that can hydrolyze cyclic adenosine monophosphate (cAMP). Higher cAMP levels can initiate and sustain anti-inflammatory signaling. Therefore, we hypothesized that suppression of the inflammatory response by rolipram would reduce liver damage following IR injury.

METHODS:

Male Sprague-Daley rats were randomized to six groups (n=6-8 per group): 1) sham, 2) sham + 3 mg/kg rolipram, 3) 40% ischemia reperfusion, 4) 40% ischemia reperfusion + 3 mg/kg rolipram, 5) 70% ischemia reperfusion, and 6) 70% ischemia reperfusion + 3 mg/kg rolipram. Two different levels of severity of IR injury were achieved by clamping either 40% (left lobe) or 70% (left and median lobes) of the liver. In both cases, occlusion was for 1 hour followed by 3 hours of reperfusion. Treatment was given I.V. at the end of the ischemic period. Blood and tissue were collected. Blood chemistry was assayed on a Vetscan 2 (Abaxis). Paraffin embedded liver sections were stained for H&E (morphology), intercellular adhesion molecule 1 (ICAM-1) (neutrophil adhesion molecule), and chloroacetate esterase (CAE, stains neutrophils). Liver myeloperoxidase (MPO, from neutrophils) and tumor necrosis factor alpha (TNF-α) and serum hyaluronate (a marker of vascular damage) were assessed by ELISA.

RESULTS:

Blood chemistry revealed that IR significantly ($p=0.01$) elevated serum alanine aminotransferase (ALT), an indicator of liver damage, in both the 40% and 70% models. Rolipram lowered serum ALT levels in the 40% model. Inflammation-induced neutrophil infiltration is a major source of IR damage. Histology showed areas of coagulative necrosis and increased neutrophil infiltration, which were ameliorated by rolipram, in both 40% and 70% models. Liver ICAM-1 was reduced by rolipram treatment in both models. MPO was significantly increased by 70% but not 40% IR, and rolipram did not lower it. Liver TNF-α showed no difference between sham and IR groups, but rolipram seemed to lower it independently of IR. Rolipram treatment showed a trend towards decreasing serum hyaluronan in both models.

CONCLUSION:

Mechanisms still remain to be determined, but overall, these data suggest that inhibition of PDE reduces hepatic IR injury by decreasing neutrophil recruitment. We conclude that rolipram might have therapeutic potential in ischemia reperfusion injury.