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Prolyl hydroxylase inhibition prevents graft injury during liver transplantation

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Ischemia and reperfusion injury (IRI) determines primary liver allograft function after orthotopic liver transplantation (OLT). Hypoxia inducible factor (HIF) prolyl hydroxylase enzymes (PHD1, PHD2 and PHD3) are molecular oxygen sensors and increasingly considered as putative therapeutic targets. Pharmacological inhibition of PHDs by the pan-PHD inhibitor ethyl-3,4-dihydroxybenzoate (EDHB) has been shown to reduce warm IRI. However, the specific impact of pharmacological PHD inhibition on cold IRI during OLT remains elusive. Here, it was sought to assess whether pharmacological inhibition of PHDs is a suitable strategy to mitigate liver IRI during OLT.

Rats were pre-treated with EDHB (100mg/kg), and subsequently subjected to warm or cold IRI in the framework of OLT, respectively. Following OLT, EDHB treatment was continued for 48 hours. IRI was determined by histomorphology, and by analysis of serum alanine-aminotransferase (ALT) and lactate dehydrogenase (LDH) levels. RT-PCR and Western blot analysis were applied to analyze the induction of the HIF target heme oxygenase 1 (HO-1) in EDHB-treated livers.

Five days of short-term pre-treatment with EDHB was hepato-protective by attenuation of warm IRI (serum ALT: 2055 ± 508.4 IU/L in Cx treated rats vs 731.1 ± 125 IU/L in EDHB treated rats, $P < 0.02$; necrotic area: $44.66 \pm 4.58\%$ in Cx treated rats, $12.51 \pm 2.40\%$ in EDHB treated rats, $P > 0.0001$), and cold IRI (serum ALT 12 hours after OLT: 784.4 ± 48.37 IU/L in Cx treated rats, 633.6 ± 45.53 IU/L in EDHB treated rats, $P < 0.05$; Suzuki score assessing liver injury 7.55 ± 0.7 in Cx treated rats, 3.41 ± 0.61 in EDHB treated rats). These effects were at least partly mediated by upregulation of HO-1 by EDHB on the RNA and protein levels.

In conclusions, pharmacological inhibition of PHDs using EDHB might represent a novel and innovative strategy to adapt liver allografts to hypoxia during OLT.