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A novel anti-hypoglycemic role of liver inducible nitric oxide synthase

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This study was designed to elucidate the role of inducible nitric oxide synthase (iNOS) in septic fatty livers with the accentuation on glucose metabolism. Herein, wild type (WT) and iNOS-knockout ($iNOS^{-/-}$) mice were fed with a high cholesterol diet (HCD, 1%w/w) for 6 weeks. Following diet period, mice were injected with LPS (5 mg/Kg). Chronic consumption of HCD led to non alcoholic steatohepatitis (NASH) in WT and $iNOS^{-/-}$ mice. LPS administration caused marked liver damage only in cholesterol-fed mice, which was further exacerbated in the absence of iNOS. Enhanced liver injury in $iNOS^{-/-}$ mice was in association with a fatal hypoglycemia. Glycogen contents were significantly retained in $iNOS^{-/-}$ mice while Hypoxia-inducible factor-1 (HIF1) signaling was markedly attenuated compared to control WT. The role of iNOS and HIF1 in hepatic glucose metabolism was further confirmed in-vitro. Hepatic glucose output was augmented by overexpression of HIF1 or by using NO-donor in AML12 hepatocytes. Results also demonstrated increased oxidative stress and reduced heme oxygenase-1 mRNA in the livers of $iNOS^{-/-}$ mice. Furthermore, the amounts of *plasma tumor necrosis factor*-α (TNFα) and intrahepatic TNFα mRNA were significantly elevated in the absence of iNOS. Taken together, these data highlight the essential role of iNOS/HIF1 axis in the glycemic response to LPS in NASH and argues for the beneficial effects of iNOS.

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