Carbon monoxide and liver failure after hepatectomy; a toxic gas or maestro of liver regeneration

Liver failure remains the main cause of mortality after major liver resection. Inducible Heme Oxygenase (HO - 1), an enzyme critical for heme catabolism, is also involved in cellular response to oxidative stress. We have previously shown that induction of HO-1 expression in response to limb ischemia confers pulmonary cellular protection against oxidative stress suggesting a systemic factor; however, the mechanism of this protection is unclear. Our follow-up study showing that carbon monoxide (CO) the product of heme catabolism by HO-1, can mimic this protection suggests that CO itself may be the important active molecule. Recent animal work has independently shown that HO-1 induction may also influence cellular regeneration in the liver following partial hepatectomy. Independently, CO has emerged as growth-promoting signal molecule with anti-apoptotic effect that protects hepatocytes from hypoglycemia-induced cytotoxicity. Further, administration of CO significantly improved the survival of mice after initiation of fulminant hepatitis and enhances rapid and early hepatocytes proliferation after partial hepatectomy, when mice lacking functional HO-1 were unable to mount an appropriate regenerative response. Collectively, these data suggest that the heme oxygenase - CO offers either direct or indirect protection against cellular injury and may promote regeneration in the liver.