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DISRUPTION OF BOTH *HFE* AND *TFR2* CAUSES IRON-INDUCED LIVER INJURY

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Hereditary haemochromatosis (HH) is a common iron overload disorder caused by mutations in *HFE* or *TFR2*, which impair the liver iron regulatory hormone, hepcidin (*Hamp*). This study aimed to examine the effects of disruption of *Hfe* and *Tfr2* on liver iron loading and injury in mouse models of HH. Methods: Iron status was determined in single mutant ($Hfe^{-/-}$ and $Tfr2^{Y245X}$) and double mutant ($Hfe^{-/-}$x$Tfr2^{Y245X}$) mice (10-14 weeks of age) by measuring plasma and liver iron concentration. *Hamp* expression was measured by real-time PCR. Liver injury was evaluated by measuring serum alanine transaminase (ALT) activity, hepatic histology, collagen deposition (Sirius red) and iron levels (Perls). Hepatic oxidative stress was determined by measuring F2-isoprostane, a marker of lipid peroxidation, by gas chromatography-mass spectrometry and anti-oxidant enzyme, superoxide dismutase (SOD). Results: $Hfe^{-/-}$x$Tfr2^{Y245X}$ mice had significantly elevated hepatic iron levels (1.5-fold; P<0.01) with a periportal iron distribution, increased plasma iron (1.7-fold; P<0.01) and transferrin saturation (1.3-fold; P<0.01) compared with $Hfe^{-/-}$ and $Tfr2^{Y245X}$ mice, which in turn, were increased compared with wild-type mice. *Hamp* was significantly reduced in $Hfe^{-/-}$ and $Tfr2^{Y245X}$ mice to 30% (P<0.01) and in $Hfe^{-/-}$x$Tfr2^{Y245X}$ mice to 1% (P<0.01) compared with wild-type mice. $Hfe^{-/-}$x$Tfr2^{Y245X}$ mice had elevated serum ALT activity (2 fold; P<0.001) compared with the other types of mice. $Hfe^{-/-}$x$Tfr2^{Y245X}$ mice had scattered lobular aggregates of mononuclear inflammatory cells, steatosis and increased portal tract collagen deposition. By contrast, $Hfe^{-/-}$ and $Tfr2^{Y245X}$ mice showed minimal hepatic inflammation, with no increased collagen deposition in $Tfr2^{Y245X}$ mice. F2-isoprostane levels were significantly elevated in $Hfe^{-/-}$x$Tfr2^{Y245X}$ (4.2-fold; P<0.001), $Tfr2^{Y245X}$ mice (3.2-fold; P<0.001) and $Hfe^{-/-}$ mice (2.0-fold; P<0.01) and SOD was increased in $Hfe^{-/-}$x$Tfr2^{Y245X}$ (1.5-fold; P<0.05) compared with wild-type mice. Conclusion: The disruption of *Hfe* or *Tfr2* causes hepatic iron loading and lipid peroxidation. However, the disruption of both *Hfe* and *Tfr2* produces more severe hepatic iron overload and lipid peroxidation, with inflammation, portal fibrosis and steatosis. $Hfe^{-/-}$x$Tfr2^{Y245X}$ mice provide a novel model of iron-induced liver injury.

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