Antiviral activity and hepatoprotection by heme oxygenase-1 in hepatitis B virus infection.

BACKGROUND & AIMS: Induction of heme oxygenase-1 (HO-1) has been shown to be beneficial in immune-mediated liver damage. We now investigate the effects of HO-1 induction in models of human hepatitis B virus (HBV) infection. METHODS: Adenoviral transfer of an HBV 1.3 genome into wild-type mice was used as a model for acute hepatitis B. HBV transgenic animals were used as a model for chronic HBV infection. HBV replication was assessed by HBV viremia, antigenemia, and Southern blotting, liver damage was assessed by serum alanine aminotransferase activities and histopathology of liver sections. To investigate HO-1 effects on HBV replication at a molecular level, stably HBV-transfected hepatoma cells were used. HBV gene expression, protein stability, transcription, and replication were determined. HO-1 was induced by either cobalt-protoporphyrin-IX or over expressed by adenoviral gene transfer. RESULTS: In the acute hepatitis B model, liver injury was reduced significantly after HO-1 induction. In addition, HO-1 showed a pronounced antiviral effect, which was confirmed in stably HBV-transfected hepatoma cells and in persistently HBV replicating transgenic mice. We showed that HO-1 induction repressed HBV replication directly in hepatocytes at a posttranscriptional step by reducing stability of HBV core protein and thus blocking refill of nuclear HBV.
covalently closed circular (ccc)DNA. Small interfering RNA directed against HO-1 proved that this effect depended on the expression level of HO-1. CONCLUSIONS: Besides its hepatoprotective effect, HO-1 showed a pronounced antiviral activity in HBV infection. Therefore, induction of HO-1 might be a novel therapeutic option for inflammatory flares of hepatitis B.