Up-regulation of heme oxygenase-1 by sevoflurane is not dependent on Kupffer cells and associates with ERK1/2 and AP-1 activation in the rat liver

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Sevoflurane is a potent non-toxic inducer of the hepatoprotective enzyme heme oxygenase-1 (HO-1). So far, little is known about the underlying molecular mechanism. Therefore the aim of this study was to characterize the respective signal transduction pathway and in particular to elucidate the role of Kupffer cells in this context. Rats were treated with or without sevoflurane. The effects on hepatic HO-1 gene expression, mitogen-activated protein kinases and transcription factors were studied by Northern and Western blot analyses, immunostaining, electrophoretic mobility shift assays, and enzymatic activity assays. Kupffer cells were depleted by administration of clodronate liposomes in vivo to characterize their role in HO-1 signal transduction. In additional in vitro experiments, HO-1 mRNA expression in primary rat hepatocytes and HepG2 cells was assessed. Sevoflurane up-regulated HO-1 gene expression in pericentral hepatocytes and increased HO enzyme activity in vivo. This was associated with activation of ERK1/2 and activator protein-1. We identified c-jun/AP-1, JunD, c-fos, and Fra-1 as active subunits of the activator protein-1 complex. Administration of clodronate liposomes to rats led to depletion of Kupffer cells without affecting sevoflurane induced HO-1 expression. Moreover, sevoflurane up-regulated HO-1 mRNA in primary rat hepatocytes but not in HepG2 cells. Our results suggest that sevoflurane induced HO-1 gene expression in pericentral hepatocytes does not depend on Kupffer cells and is associated with activation of ERK1/2 and activator protein-1. Since we could recently demonstrate significant hepatoprotective effects of HO-1 induced by isoflurane, the present results may help to establish new concepts in hepatic organ protection.