

## Toxicity of hepatotoxins: new insights into mechanisms and therapy.

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Liver injury caused by hepatotoxins, such as carbon tetrachloride (CCl<sub>4</sub>), ethanol, and acetaminophen (APAP), is characterised by varying degrees of hepatocyte degeneration and cell death via either apoptosis or necrosis. The generation of reactive intermediate metabolites from the metabolism of hepatotoxins, and the occurrence of reactive oxygen species (ROS) during the inflammatory reaction account for a variety of pathophysiologic pathways leading to cell death, such as covalent binding, disordered cytosolic calcium homeostasis, glutathione (GSH) depletion, onset of mitochondrial permeability transition (MPT) and associated lipid peroxidation. The metabolism of hepatotoxins by cytochrome P-450 enzyme subtypes is a key step of the intoxication; therefore, enzyme inhibitors are shown to minimise the hepatotoxin-associated liver damage. Understanding the function of transcription factors, such as nuclear factor kappaB (NF-kappaB) in acute liver injury, may provide some answers as to the molecular mechanisms of toxic insults. Moreover, substantial evidence exists that MPT is involved in ROS-associated hepatocellular injury and new findings offer a novel therapeutic approach to attenuate cell damage by blocking the onset of MPT. Thus, oxidant stress and lipid peroxidation are crucial elements leading to hepatotoxin-associated liver injury. In addition to specific treatment for a given hepatotoxin, the general strategy for prevention and treatment of the damage includes reducing the production of reactive metabolites of the hepatotoxins, using anti-oxidative agents, and selectively targeting therapeutics to Kupffer cells or hepatocytes for on-going processes, which play a role in mediating a second phase of the injury.

