Induction of hepatotoxicity by sanguinarine is associated with oxidation of protein thiols and disturbance of mitochondrial respiration

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摘要

Abstract

Sanguinarine (SANG) has been suggested to be one of the principle constituents responsible for the toxicity of Argemone mexicana seed oil. In this study, we focused on the possible mechanism of SANG-induced hepatotoxicity. The serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) activities, hepatic vacuolization, lipid accumulation and lipid peroxidation of the liver were increased, and triglyceride (TG) was decreased in SANG-treated mice (10 mg kg-1 i.p.), indicating damage to the liver. SANG induced cell death and DNA fragmentation, in a concentration- (0-30 μM) and time-dependent (0-24 h) manner, and the cytotoxicity of SANG (15 μM) was accompanied by an increase in reactive oxygen species and a lessening in protein thiol content; these outcomes were reversed by glutathione, N-acetyl-L-cysteine and 1,4-dithiothretol, and slightly improved by other antioxidants in hepatocytes. SANG can affect the function of mitochondria, leading to the depletion of the mitochondrial membrane potential and adenosine 5'-triphosphate content of hepatocytes. SANG caused an uncoupling effect of the respiratory chain at lower concentrations, but inhibited the respiratory chain at higher concentrations in mitochondria isolated from rat liver. In conclusion, the data suggest that SANG is a liver toxin that induces cytotoxicity in liver cells, possibly through oxidation of protein thiols, resulting in oxidative stress on the cells and disturbance of mitochondrial function