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Role of Apoptosis in Acute Cadmium-Induced Hepatotoxicity

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AIM

The present study was designed in order to elucidate the mechanisms of acute cadmium-induced hepatotoxicity. In addition, the role of apoptosis in parenchymal and non-parenchymal cells in the manifestation of the toxic hepatic injury was investigated.

MATERIALS AND METHODS

Wistar male rats weighing 160-200 g were used in the present study. The experimental animals received a single intraperitoneal injection of $CdCl_2$ (6.5 mg/kg body weight) and sacrificed at 12, 16, 24, 48 and 60 hours after cadmium intoxication. One hour prior to sacrifice, the animals received 25 μCi/kg body weight of [^{3}H]thymidine intraperitoneally. Hepatic histological sections were processed routinely, HE-stained and analyzed for necrosis, peliosis, apoptosis and inflammatory infiltration. The liver cell proliferation was estimated by assaying: a) the enzymic activity of liver thymidine kinase (TK), b) the rate of [^{3}H]thymidine incorporation into hepatic DNA and c) the mitotic index in HE-sections. Serum enzyme activities of aspartic aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were assayed by automated analysis.

RESULTS

Necrosis was evident at 12 h and peaked at 48 h after cadmium intoxication. Similarly, the serum levels of AST and ALT peaked at 48 h. The time profile of apoptosis was different for parenchymal and non-parenchymal cells. The apoptotic index peaked at 48 h for non-parenchymal cells and at 60 h for hepatocytes. Hepatic peliosis for all time points examined followed apoptotic index for non-parenchymal liver cells and peaked at 48 h. The rate of hepatic regeneration monitored by [^{3}H]thymidine incorporation into DNA seemed to remain sufficiently low in contrast to the TK activity levels which were significantly increased. Therefore, on the basis of the indices used in this study, the regenerating rate seemed to peak at 48 and 60 h after cadmium administration.

CONCLUSIONS

The administration of an almost deadly dose of cadmium induces extensive necrosis and intensive apoptosis in the rat liver which participate significantly in the acute cadmium-induced hepatotoxicity in both parenchymal and non-parenchymal cells. In addition, the apoptosis of non-parenchymal cells seems to be related with the hepatic peliosis. Nuclear and mitochondrial DNA are often targets of hepatotoxins and DNA damage and mitochondrial impairment are thought to be the initiating events in induced apoptosis.