

Cytotoxic effects of methamphetamine in rat hepatocytes

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Background and Aims: Methamphetamine is a highly addictive and toxic drug of abuse that has potent central and peripheral sympathomimetic effects. Methamphetamine affects multiple organs including: brain, heart, lung and kidneys. Different studies also reported pathological findings in the livers of methamphetamine abusers. However, the whole mechanistic picture involved in methamphetamine toxicities is yet poorly understood. Moreover, the precise role of free radicals in methamphetamine cytotoxicity has not yet been completely elucidated. The major objective of this study was to determine the role of oxidative stress in methamphetamine cytotoxic mechanisms in isolated rat hepatocytes using accelerated cytotoxicity mechanisms screening (ACMS) techniques.

Method: Hepatocytes were obtained by collagenase perfusion of the liver and viability was assessed by plasma membrane disruption determined by trypan blue (0.2 w/ v) exclusion test. To determine the rate of hepatocyte reactive oxygen species (ROS) generation induced by cumene hydroperoxide, dichlorofluorescein diacetate (DCFH-DA) was added to the hepatocytes. The latter then reacts with ROS to form the highly fluorescent dichlorofluorescein (DCF), which effluxes the cell. The fluorescence intensity of DCF was measured.

Results: In the first step the EC₅₀_{2h} concentration (i.e., 50% membrane lysis in 2 h) of methamphetamine was found. Methamphetamine caused hepatocyte membrane lysis as determined by trypan blue uptake. In addition, when hepatocytes were incubated with methamphetamine at this EC₅₀ concentration, ROS formation determined by the oxidation of dichlorofluorescein diacetate to dichlorofluorescein was significantly increased. These toxic effects were prevented by antioxidants and ROS scavengers.

Conclusions: Our results showed that methamphetamine could induce sharp rise in ROS formation after its incubation and cell membrane lysis (cytotoxicity). These data also indicated that methamphetamine-induced cytotoxicity is directly related to ROS generation which could be a key player in the mechanism underlying methamphetamine-induced liver injury.