

Molecular mechanisms of methimazole cytotoxicity in isolated rat hepatocytes

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Background and Aims: Methimazole is an anti-thyroid drug widely used in the treatment of hyperthyroidism. Administration of this drug, often in a chronic manner, is associated with several adverse drug reactions in humans, including life-threatening hepatotoxicity. This study attempted to investigate the cytotoxic mechanism(s) of methimazole toward isolated rat hepatocytes. In addition, the role of proposed methimazole intermediary metabolites, such as N-methylthiourea and glyoxal, in the toxicity induced by this drug was evaluated.

Methods: Isolated hepatocytes were prepared by collagenase enzyme perfusion method. The cells were treated with methimazole, N methylthiourea and other chemicals and markers such as cell viability, mitochondrial membrane potential, reactive oxygen species (ROS) formation, lipid peroxidation, and cellular glutathione content were measured.

Results: Methimazole-induced cytotoxicity was accompanied by collapse in mitochondrial membrane potential, increase in reactive oxygen species formation and lipid peroxidation. Furthermore, methimazole caused reduction in glutathione reservoirs and the cytotoxic effect of the drug was much more severe in glutathione-depleted cells. N methylthiourea caused toxicity in lower concentrations than methimazole and reduced hepatocytes glutathione content. The specific flavin containing monooxygenase (FMO) inhibitor, N,N-dimethylaniline attenuated toxicity induced by N-methylthiourea. Administration of glyoxal trapping agents such as metformin, hydralazine, or N-acetyl cysteine effectively prevented methimazole toxicity in intact or glutathione depleted rat hepatocytes.

Conclusions: This study indicates that methimazole reactive metabolites are responsible for the cytotoxicity induced by this drug but the role of glyoxal as a metabolite, which causes ROS formation, lipid peroxidation, and mitochondrial injury is predominant since the glyoxal trapping agents diminished these adverse effects.

Keywords: Methimazole; Glyoxal; N-methylthiourea; Hepatotoxicity; Glutathione; Mitochondria; ROS formation