

The role of oxidant stress and reactive nitrogen species in acetaminophen hepatotoxicity.

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Acetaminophen (AAP) overdose can cause severe hepatotoxicity and even liver failure in experimental animals and humans. Despite substantial efforts over the last 30 years, the mechanism of AAP-induced liver cell injury is still not completely understood. It is widely accepted that the injury process is initiated by the metabolism of AAP to a reactive metabolite, which first depletes glutathione and then binds to cellular proteins including a number of mitochondrial proteins. One consequence of this process may be the observed inhibition of mitochondrial respiration, ATP depletion and mitochondrial oxidant stress. In the presence of sufficient vitamin E, reactive oxygen formation does not induce severe lipid peroxidation but the superoxide reacts with nitric oxide to form peroxynitrite, a powerful oxidant and nitrating agent. Peroxynitrite can modify cellular macromolecules and may aggravate mitochondrial dysfunction and ATP depletion leading to cellular oncotic necrosis in hepatocytes and sinusoidal endothelial cells. Thus, we hypothesize that reactive metabolite formation and protein binding initiate the injury process, which may be then propagated and amplified by mitochondrial dysfunction and peroxynitrite formation. This concept also reconciles many of the controversial findings of the past and provides a viable hypothesis for the mechanism of hepatocellular injury after AAP overdose.

