

Effect of acetaminophen administration on hepatic glutathione compartmentation and mitochondrial energy metabolism in the rat.

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Changes in cell energy metabolism and mitochondrial dysfunction have been observed after acetaminophen administration. Because consumption of hepatic glutathione is closely related to acetaminophen toxicity, we investigated the kinetics of: 1. glutathione depletion in liver mitochondria and cytosol; 2. State 3 and 4 respiratory rates of succinate-supplemented mitochondria; 3. rate of ATP synthesis; 4. oligomycin-sensitive ATP hydrolase activity and passive proton conductivity of inside-out vesicles of the inner mitochondrial membrane; and 5. changes in hepatic and mitochondrial malondialdehyde in the rat after in vivo acetaminophen administration. Two hours after acetaminophen injection, hepatic glutathione decreased and malondialdehyde increased. In the same interval, an increase in both State 3 and 4 respiratory rates of succinate-supplemented mitochondria was observed. This was accompanied by a decrease in the rate of ATP synthesis and the P/O ratio and by an increase in the passive proton permeability of the inner mitochondrial membrane, which was insensitive to oligomycin. No significant change in oligomycin-sensitive ATP hydrolase activity was observed. Four hours after APAP injection, the respiratory rates, as well as the proton conductivity, decreased, the rate of ATP synthesis was restored, and the mitochondrial glutathione started to increase; the cytosolic levels of glutathione were still low and the cytosolic and mitochondrial levels of malondialdehyde remained high for 2 more hr. The concentrations of these indices were completely restored 24 hr postdosing. Our findings suggest that acetaminophen administration selectively depletes (within 2 hr) mitochondrial glutathione, and produces local toxicity by altering membrane permeability and decreasing the efficiency of oxidative phosphorylation. This renders mitochondria more susceptible to oxidative damage, especially during increased free radical production, as in the case of enhanced mitochondrial respiration in State 4. The concomitant restoration of mitochondrial respiration, oxidative phosphorylation, membrane permeability, and glutathione levels is consistent with the importance of the mitochondrial glutathione pool for the protection of the mitochondrial membrane against oxidative damage.