Protection against acetaminophen toxicity in CYP1A2 and CYP2E1 double-null mice.

Abstract:
Acetaminophen (APAP) hepatotoxicity is due to its biotransformation to a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), that is capable of binding to cellular macromolecules. At least two forms of cytochrome P450, CYP2E1 and CYP1A2, have been implicated in this reaction in mice. To test the combined roles of CYP1A2 and CYP2E1 in an intact animal model, a double-null mouse line lacking functional expression of CYP1A2 and CYP2E1 was produced by cross-breeding Cyp1a2-/- mice with Cyp2e1-/- mice. Animals deficient in the expression of both P450s developed normally and exhibited no obvious phenotypic abnormalities. Comparison of the dose-response to APAP (200-1200 mg/kg) indicated that double-null animals were highly resistant to APAP-induced toxicity whereas the wild-type animals were sensitive. Administration of 600 to 800 mg/kg of this drug to male wild-type animals resulted in increased plasma concentrations of liver enzymes (alanine aminotransferase, sorbitol dehydrogenase), lipidosis, hepatic necrosis, and renal tubular necrosis. In contrast, when APAP of equivalent or higher dose was administered to the double-null mice, plasma levels of liver enzymes and liver histopathology were normal. However, administration of 1200 mg of APAP/kg to the double-null mice resulted in infrequent liver lipidosis and mild kidney lesions. Consistent with the protection from
hepatotoxicity, the expected depletion of hepatic glutathione (GSH) content was significantly retarded and APAP covalent binding to hepatic cytosolic proteins was not detectable in the double-null mice. Likewise, in vitro activation of APAP by liver microsomes from the double-null mice was approximately one tenth of that in microsomes from wild-type mice. Thus, the protection against APAP toxicity afforded by deletion of both CYP2E1 and CYP1A2 likely reflects greatly diminished production of the toxic electrophile, NAPQI.