

Effect of ribose cysteine pretreatment on hepatic and renal acetaminophen metabolite formation and glutathione depletion.

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Ribose cysteine (2(R,S)-D-ribo-(1',2',3',4'-tetrahydroxybutyl)thiazolidine-4(R)-carboxylic acid) protects against acetaminophen-induced hepatic and renal toxicity. The mechanism for this protection is not known, but may involve inactivation of the toxic electrophile via enhancement of glutathione (GSH) biosynthesis. Therefore, the goal of this study was to determine if GSH biosynthesis was required for the ribose cysteine protection. Male CD-1 mice were injected with either acetaminophen or acetaminophen and ribose cysteine. The ribose cysteine cotreatment antagonized the acetaminophen-induced depletion of non-protein sulfhydryls in liver as well as GSH in kidney. Moreover, ribose cysteine cotreatment significantly increased the concentration of acetaminophen-cysteine, hepatic acetaminophen-mercapturate in liver and renal acetaminophen-GSH metabolites in kidney 4 hr after acetaminophen. To determine whether protection against acetaminophen-induced liver and kidney damage involved ribose cysteine dependent GSH biosynthesis, buthionine sulfoximine was used to selectively block gamma-glutamylcysteine synthetase (gamma-GCS). Plasma sorbitol dehydrogenase (SDH) activity and blood urea nitrogen from mice pretreated with buthionine sulfoximine and challenged with acetaminophen indicated that both liver and kidney injury had occurred. While co-treatment with ribose cysteine had previously protected against acetaminophen-induced liver and kidney injury, it did not diminish the acetaminophen-induced damage to either organ in the buthionine sulfoximine-treated mice. In conclusion, ribose cysteine serves as a cysteine prodrug that facilitates GSH biosynthesis and protects against acetaminophen-induced target organ toxicity.

