Abstract

The present study examined the effects of butylated hydroxyanisole (BHA) on acetaminophen-induced hepatotoxicity and metabolism in vivo with emphasis on possible changes in the glucuronidation pathway. Female Swiss-Webster mice received BHA in the diet (1% w/w) for 12 days (600 to 800 mg/kg/day). BHA prevented acetaminophen hepatotoxicity (600 mg/kg, ip), based on serum alanine and aspartate aminotransferase activities and histopathological examination. The rate of elimination of acetaminophen from blood was 10-fold higher in BHA-fed mice (clearance, 49 ml/min/kg) than in controls (4.4 ml/min/kg). In general, the urinary metabolite excretion patterns in control and BHA-treated mice were the same. However, the rates of acetaminophen conjugation via the sulfation, glucuronidation, and mercapturic acid pathways were enhanced with the rate of glucuronide formation, the major biotransformation pathway of acetaminophen, increased sevenfold in BHA-treated mice (0.041 min-1) compared to controls (0.006 min-1). BHA increased hepatic UDP-glucuronosyltransferase activity twofold, as well as hepatic UDP-glucuronic acid concentrations. In addition, after acetaminophen administration, UDP-glucuronic acid in BHA-treated mice was depleted to a lesser extent and returned to control values more rapidly than in untreated animals. BHA had a similar but less pronounced effect on hepatic glutathione levels. The findings indicate that the rate of acetaminophen glucuronidation is increased in vivo during BHA feeding to mice. This effect appears to play a role in the enhanced excretion of acetaminophen as well as protection against acetaminophen-induced hepatotoxicity.

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