Rethinking the Role of Intestinal Microflora in Bioactivation of Food-Borne Heterocyclic Amine Carcinogens

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Since the discovery that mutagenic and carcinogenic heterocyclic amines are formed during the cooking of foods (1,2), it has been widely hypothesized that intestinal microflora are likely to play an important role in the bioactivation of these amines (3), leading to tumor induction in the colon of humans and experimental animals. In this issue of the Journal, Weisburger et al. (4) provide strong data to the contrary. 2-Amino-3-methyl-3H-imidazo[4,5-f]quinoline (IQ), a typical food-borne heterocyclic amine that is effective as a colon carcinogen in rats and as a liver tumorigen in mice, had previously been shown to be metabolized readily by intestinal bacteria to a 7-hydroxy-IQ (7-OHIQ) derivative. The discovery that 7-OHIQ is also a potent direct-acting mutagen in Salmonella typhimurium suggested that its formation in the colon lumen may represent a final metabolic activation step resulting in DNA adduct formation and carcinogenesis (5). However, Weisburger et al. (4) have now shown that, unlike IQ, 7-OHIQ does not have genotoxic activity in the Williams hepatocyte DNA repair test and is essentially inactive as a carcinogen in rats after intrarectal infusion or in mice after neonatal intraperitoneal injection followed by dietary administration, with the exception of a low yield of liver tumors that was statistically significant only in female mice. Thus, it appears highly unlikely that IQ metabolism by intestinal microflora is a significant bioactivation pathway.

Similar conclusions have also been reached recently in parallel studies (Kaderlik KR, Minchin RF, Mulder GJ, et al: manuscript submitted for publication) aimed at examining the role of bacterial deconjugation as a necessary step in the bioactivation of another heterocyclic aromatic amine carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). Like IQ and other heterocyclic amines, PhIP undergoes N-oxidation by hepatic cytochrome P4501A2 to N-hydroxy-PhIP, which is regarded as a proximate carcinogenic metabolite. However, N-hydroxy-PhIP is also effectively conjugated by hepatic UDP-glucuronosyltransferases to two isomeric N-glucuronides (Kaderlik KR, Mulder GJ, Turesky RJ, et al: manuscript submitted for publication), one of which is secreted in the bile and then readily cleaved back to N-hydroxy-PhIP by bacterial β-glucuronidases.

Thus, it has long been hypothesized that another bioactivation pathway for amine colon carcinogens involves their hepatic N-oxidation and subsequent N-glucuronidation and biliary transport to the colon lumen, where deconjugation by intestinal bacteria releases the N-hydroxy metabolite. Nevertheless, the recent studies (Kaderlik KR, Minchin RF, Mulder GJ, et al: manuscript submitted for publication) with PhIP have shown that DNA adduct formation in the colon and in other extrahepatic tissues is unaffected by bile duct ligation, and intravenous infusion and oral-dosing experiments have indicated that either N-hydroxy-PhIP or its N-acetoxy derivative is transported through the circulation to the various target tissues. In addition, Davis et al. (6) have just published results showing that the N-hydroxy metabolites of IQ, PhIP, and 2-amino-3,8-dimethylimidazo[4,5-f]quinoline (MelQx) are further activated not only by O-acetylation but also by other phase II esterifying enzymes in the colon, heart, kidney, and liver. In conclusion, it would now appear that, although intestinal microflora may play an important role in the promotional stages of colon carcinogenesis (7), there is little evidence for their involvement in metabolic activation through oxidation or deconjugation reactions.

References


Notes

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*See "Notes" section following "References."