Species Differences in Metabolism of Heterocyclic Aromatic Amines, Human Exposure, and Biomonitoring

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Heterocyclic aromatic amines (HAAs) are animal carcinogens and suspected human carcinogens which are formed in cooked foods at the low parts per billion level. HAAs in cooked meats were purified by either immunofinity chromatography or solid phase tandem extraction, which allowed for the simultaneous analysis of 11 HAAs by HPLC. The metabolism of two prominent HAAs, 2-amino-3,8-dimethylimidazo[4,5-f]quinoline (MelQx) and 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), was investigated in animal models and in vitro with human tissues to develop strategies for human biomonitoring. MelQx and IQ are rapidly absorbed from the gastrointestinal tract of rodents and transformed into several detoxification products which are excreted in urine and feces. Metabolites result from cytochrome P450-mediated ring oxidation at the C-5 position followed by conjugation to sulfate or β-glucuronide. Other major metabolites include the phase II conjugates, Nβ-glucuronide and Nβ-sulfamate. A metastable Nβ-glucuronide conjugate of the genotoxic metabolite of N-hydroxy-MelQx was also detected in urine and bile. The binding of both carcinogens to blood proteins was low and suggests that human biomonitoring through protein adducts may be difficult. These metabolic pathways exist in nonhuman primates and several of these pathways also occur in vitro with human liver. The urinary excretion of MelQx in seven human subjects following consumption of cooked beef or fish ranged between 2 and 22 ng in 12 hr when determined by negative ion chemical ionization GC–MS. After acid hydrolysis of urine, the amount of MelQx increased 4- to 10-fold in 6 of the 7 subjects. These acid labile metabolites were identified as the Nβ-sulfamate and Nβ-glucuronide following column chromatography and HPLC purification. Thus, amine sulfonation and Nβ-glucuronidation are important routes of detoxification of MelQx in rodents, nonhuman primates, and humans. — Environ Health Perspect 102(1Suppl 6):47–51 (1994)

Key words: food mutagens, heterocyclic aromatic amines, metabolism, human biomonitoring

Introduction

More than a dozen heterocyclic aromatic amines (HAAs) have been identified in cooked foods at the low part per billion level (1) and all HAAs tested so far are carcinogenic in rodent bioassays (2). One of these food-borne mutagens, 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), is also a potent hepatocarcinogen in nonhuman primates (3). Metabolic studies with human tissues show that humans activate HAAs at appreciable levels. Activities for some substrates are comparable to those observed in rodents (4–8). Thus, despite the occurrence of HAAs in only trace amounts, their presence in many common foods suggests that human exposure can be significant and that HAAs may be involved in the etiology of human cancers.

The risk evaluation of genotoxins such as HAAs is based on quantitative estimates of exposure and on the formation of toxicologically active metabolites in target tissues. In recent years, both DNA and protein adducts have been used successfully as biologic markers to measure human exposure and to estimate the formation of the genotoxic metabolites of a variety of environmental and dietary carcinogens (9,10). The most direct evidence of recent exposure and genetic damage is through the measurement of DNA adducts in cells and their excretion products in urine; whereas measurement of protein adducts may provide an index of long-term exposure over the lifetime of the protein. Analysis of urinary metabolites of xenobiotics may also provide important biologic data. For example, human acetyltransferase and cytochrome P450IA2 metabolic phenotype activity can be determined by analysis of caffeine metabolites in urine and may be used as biomarkers of cancer susceptibility (11,12). The analysis of urinary metabolites of genotoxins, such as HAAs, may also provide important information on the ability of humans to metabolically activate or detoxify these precarcinogens and may aid in risk evaluation. Our recent data on the quantification of HAAs in cooked foods, the metabolism of IQ and 2-amino-3,8-dimethylimidazo[4,5-f]quinoline (MelQx) in experimental animals, and our preliminary data on human metabolism are presented in this article.

Methods

Quantification of HAAs in Cooked Foods

HAAs were isolated from cooked meats and fish by solid-phase tandem extraction using an Extrelut-20 column in series with a propylsulfonic acid silica cartridge and quantified with multiple internal standards (13,14). HAAs were quantified by HPLC employing a Hewlett-Packard 1090M system containing both a UV diode array detector and a fluorimeter. A Vydac 201H552 narrow bore reverse-phase column was used for increased sensitivity and resolution.

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Metabolism Studies in Animal Models
Metabolism studies were performed with male Sprague-Dawley rats. MelQx was administered by gavage as its acetate salt. In some instances, animals were pretreated with a single ip injection of Aroclor 1254 in corn oil 24 hr prior to dosing (15). Metabolites were isolated from biologic fluids and reference standards were prepared either biosynthetically using rat hepatocytes or through chemical syntheses (16). Urine and bile were obtained from nonhuman primates undergoing carcinogen bioassays as IQ and MelQx (3) and metabolites were purified and spectroscopically characterized as previously reported (17).

Metabolism Studies in Humans
Analysis of MelQx and its metabolites in human urine was done by negative ion chemical ionization gas chromatography–mass spectrometry (NICI–GC–MS) after derivatization with 3,5-bis(trifluoromethyl)benzyl bromide (18). Trideuterolated (N-Cd3)-MelQx was used as an internal standard. Each of the seven subjects consumed 1 lb (before cooking) of panfried fish or beef. Urine collections were made 0 to 12 hr postmeal. Aliquots of urine were analyzed for unchanged MelQx before and after acid hydrolysis (1 N HCl at 70°C for 6 hr) which cleaves the N2-glucuronide and N2-sulfamate conjugates with quantitative recovery of MelQx (19). The samples, both nonhydrolyzed and acid hydrolyzed, underwent solvent partitioning and immunoaffinity chromatography prior to NICI–GC–MS analyses (Hewlett-Packard 5987 GC–MS system and an HP-1 capillary column) (20). MelQx and the deuterated internal standard were detected and quantified by selective ion monitoring of the ions at m/z 438 and m/z 441, respectively (corresponding to the M-227 ions of the [di(3,5-(bis-trifluoromethyl)benzyl] derivatives). The N2-sulfamate and the N2-glucuronide were isolated from human urine as described (15) except that solid phase extraction steps with both C-18 and aminopropyl resins were included after the organic precipitation of urine. The urine extract was dissolved in 30 ml 50 mM ammonium acetate, pH 6.8, and then applied to a Partisil (C-18) column. After washing with this buffer, metabolites were eluted in 50% methanol and dried. The residue was dissolved in water, its pH adjusted to 8.0 and then applied to a propylamine cartridge. The eluent was dried, redissolved in 1 ml of 50 mM ammonium acetate (pH 6.8), diluted with 9 ml acetonitrile and applied to the propylamine cartridge in normal phase mode. The sulfamate was eluted with 30% ammonium acetate buffer and 70% acetonitrile and then the N2-glucuronide was eluted with 50 mM ammonium acetate containing 2% ammonium hydroxide (vol/vol). This extraction procedure enabled partial separation of the N2-sulfamate from the N2-glucuronide conjugate (20), which was verified by HPLC (15) and by NICI–GC–MS.

Results
The solid phase tandem extraction procedure is highly selective for the purification of HAAs and enables quantification at levels approaching 1 ppb. HAA content was determined in several cooked foods with this extraction procedure and the data is presented in Table 1. The production of these genotoxins in cooked foods varied greatly and depended on the type of meat, cooking temperature and manner of preparation. High levels of HAAs were also detected in cooking grill scrapings, which are often used as a gravy base. A typical chromatogram of purified HAAs in from grill scrapings is shown in Figure 1.

MelQx and IQ metabolism were investigated in animal models to develop strategies for human biomonitoring. In the rat, MelQx metabolism and disposition were

### Table 1. Heterocyclic amines in cooked meats and fish.

| Sample identification | MelQx | SE | 4.8-DiMelQx | SE | PhiP | SE | AA | SE |
|-----------------------|-------|----|-------------|----|------|----|----|----|
| Grilled meat 2 x 3 min | 0.8   | ND | ND          | 0.7 | ND   | ND |
| Grilled meat 2 x 5 min | 2.0   | 0.1| ND          | 3.2 | 1.7  | ND |
| Grilled meat 2 x 7 min | ND    | ND | ND          | ND  | ND   | ND |
| Grill residue        | 29    | 3  | 4.2         | 0.2 | 144  | 38 | 76.5 | 5.6 |
| Pan fried fish 2 x 3 min | 1.4  | 0.01| ND          | 1.7 | 0.7  | ND |
| Pan fried fish 2 x 5 min | 5    | 0.3 | ND          | 23  | 7    | 4.6 |
| Pan fried fish 2 x 7 min | 4.7   | 0.2| ND          | 14  | 2.8  | 8  |
| Pan fried fish 2 x 12 min | 3.7   | 0.2| ND          | 17  | 0.6  | 9  |
| Barbecued turkey 2 x 2 min | ND   | 1.5 | 0.4        | ND | 7    | 1.2 | 6.4 | 0.7 |
| Barbecued turkey 2 x 4 min | 1.5 | 0.4 | ND          | 50.6 | 6.3  | 103 | 11 |

Abbreviations: ND, not detectable (below 0.5 ng/g); SE, standard error. No SE are given for values below 1 ng/g. 
*Values given in ng/g cooked meat or fish and are corrected for incomplete recovery during extraction. Surface temperature of grill or barbecue measured using a thermocouple was 250°–270°C. Pan temperature was 200°C (14).
dependent upon dose and animal pretreatment with PCB. At the 20 mg/kg treatment approximately 50% of the dose was excreted in urine within 24 hr while at the lowest dose tested 20 to 25% of the dose was recovered in urine and the remainder recovered in feces (15). The 5 major metabolites excreted in urine and bile are the sulfate and β-glucuronate conjugates of the 5-hydroxy derivative of MeIQx, the N2-glucuronate and the N2-sulfamate phase II conjugates, and the N2-glucuronate conjugate of the procarcinogenic metabolite, N-hydroxy-MeIQx (Figure 2) (15). At the highest dose tested, N2-sulfamate formation was the major route of detoxification and urinary elimination of MeIQx in noninduced animals. However, other metabolic pathways, such as 5-hydroxylation of MeIQx and N2-glucuronidation, were more prominent both at lower doses and in animals pretreated with PCB (Figure 3). In animals treated with MeIQx at 0.01 mg/kg, each of the above metabolites accounted for 0.5 to 4% of the total dose in urine whereas unmetabolized MeIQx accounted for 0.5 to 2% of the dose. Notably, the formation and excretion of the metastable N2-glucuronate conjugate of N-hydroxy-MeIQx was relatively more important at low-dose exposure.

Urine samples (8 hr collections) from rats dosed with MeIQx (0.01 mg/kg) were analyzed before (Figure 4) and after hydrolysis, which resulted in cleavage of all the characterized metabolites. MeIQx recovery in urine after acid hydrolysis increased from 2 to approximately 7% of the dose in non-induced animals and from 0.5% to nearly 6% of the dose in PCB pretreated animals (n = 4 animals). This increase in MeIQx was commensurate to the amount of cleaved sulfamate and N2-glucuronate. The 5-hydroxy derivative of MeIQx and the genotoxic metabolite, N-hydroxy-MeIQx, the initial hydrolysis product of the N-hydroxy-N2-glucuronide, are unstable under these acid hydrolysis conditions and were not analyzed.

These metabolism pathways also occur in the rodent for the structurally related food mutagen IQ after high dose exposure; however, the N2-glucuronide conjugate of N-hydroxy-IQ was not detected (21,22). These pathways also have been detected in nonhuman primates undergoing carcinogenic bioassays with MeIQx (23) and IQ (3,17). In the case of IQ, several other metabolic routes were reported (17) including N-demethylation and bacterial mediated oxidation at the C-7 position of the heterocyclic nucleus.

We sought to determine whether humans detoxify MeIQx by phase II conjugation reactions, such as sulfamation and N2-glucuronidation, and, thus, analyzed MeIQx in urine, both before and after acid hydrolysis, from seven subjects who consumed fried beef or fish (Figure 5). The values of MeIQx recovered within 12 hr ranged between 2 and 22 ng. Following acid hydrolysis, the amounts of MeIQx in urine increased 4- to 10-fold in six of the subjects, while there was little change in the amount of MeIQx in the urine of one subject. The acid labile metabolites of two subjects were purified by solid phase extraction with the aminopropyl cartridges, and the N2-sulfamate and the N2-glucuronide phase II conjugates accounted for essentially all of the acid labile material recovered as MeIQx. This data was supported by isolating urinary fractions by HPLC at retention times corresponding to the respective conjugates followed by NICI–GC–MS analysis of MeIQx after acid hydrolysis (15). Further work is being carried out to confirm directly the identity of the conjugates by mass spectrometry.
**Discussion**

To assess human exposure to HAAs, rapid and reliable analytical methods are required to quantitate these compounds in foods. We demonstrated previously that immunoaffinity chromatography rapidly isolates HAAs from complex mixtures (24). However, due to the high selectivity of monoclonal antibodies, analysis and quantification of HAAs are limited to the compound against which the antibody is raised (and possibly several structurally related compounds). Consequently, a broad panel of antibodies is required for immunoaffinity purification of the many structurally diverse HAAs found in cooked foods. Therefore, we developed a more general analytic method that could be used to detect a wide range of HAAs. With this solid phase tandem extraction procedure, it is possible to analyze simultaneously 11 HAAs formed in cooked foods at the low parts per billion level by HPLC (13,14).

We have seen that grill scrapings, often used as a gravy base, may contain high levels of HAAs. This is in agreement with high levels of mutagenicity reported in gravy (25) and indications that the critical precursors of HAA formation are present in the meat juice (26).

Protein dosimetry has been used to monitor human exposure to several classes of carcinogens (10). The rodent model is a good surrogate for blood protein adduct formation of several different carcinogens, including the alylamine 4-amino-biphenyl, where over 5% of a dose binds to hemoglobin via an acid labile sulfonamide linkage. This adduct is also formed in humans at comparable levels and results from a series of reactions between the hemoprotein and the carcinogenic N-hydroxy metabolite (10). However, the binding of MeIQx to hemoglobin in the rat is below 0.01% of the dose and induction of cytochrome P450 actually resulted in lower levels of protein binding (15). Blood protein binding of the HAA analog, IQ, is also very low in rodents (27) and in nonhuman primates (17). Hemoglobin sulfonamide adducts of IQ and MeIQx are formed in vitro using enzymatically generated or synthetic N-hydroxy derivatives (27) indicating that these genotoxic metabolites are sufficiently stable to penetrate the erythrocyte and react with the hemoprotein. The absence of this adduct in vivo suggests that very low levels of the N-hydroxy metabolites are excreted by the liver into the blood stream. Thus, based on animal models, human monitoring of these two mutagens by protein dosimetry may be difficult. In support of this conclusion, a preliminary study assaying for hemoglobin sulfonamide adducts of MeIQx in humans showed that the adducts, if present, were below levels of detection using NICI–GC–MS (28). An IQ sulfonamide-serum albumin adduct has been detected in rodents (27) and this linkage may be formed for many aromatic and heterocyclic aromatic amines as well (10). However, in the case of IQ and MeIQx, the levels are low and protein dosimetry with such an adduct may prove difficult.

MeIQx is rapidly absorbed and extensively metabolized in the rat to form five principal metabolites which are excreted in urine. Four of these metabolites are detoxification products, while the fifth is a metastable N2-glucuronide conjugate of the genotoxic metabolite N-hydroxy-MeIQx (15). At the lowest dose of MeIQx administered (0.01 mg/kg), the N2-sulfamate and N2-glucuronide excreted in urine accounted for approximately 25% of the urinary excretion of MeIQx and its metabolites (corresponding to approximately 5% of the total dose). This dose is only several hundred-fold greater than daily human exposure to MeIQx (1). Sulfamate formation and N2-glucuronidation are two of the major routes of MeIQx and IQ detoxification. In rodent (15,19,21,22,29), nonhuman primate (23) and human liver also appear to catalyze these reactions in vitro ([30]; R Turesky, unpublished observations).

In preliminary experiments with humans, six of seven subjects excreted MeIQx metabolites as acid labile phase II conjugates, while there was no evidence of acid labile metabolite formation in the remaining subject. The 4- to 10-fold increase in MeIQx content in human urine following acid hydrolysis is comparable to the increase of MeIQx detected in urine of rodents given MeIQx at 0.01 mg/kg following acid treatment. We isolated these acid labile metabolites from two human subjects, and nearly all of the acid labile material recovered as MeIQx is attributed to the N2-sulfamate and the N2-glucuronide conjugates. With the development of internal standards for these metabolites, a better estimation of their relative contribution to MeIQx metabolism and detoxification can be determined. Rodents, nonhuman primate, and humans appear to have at least two common metabolic routes of MeIQx detoxification.

Recently, the thermostable phenolsulfotransferase (TS PST) in human liver was shown to catalyze the sulfamation of 2-naphthylamine (31). This sulfotransferase also appears to be responsible for the metabolic activation of several N-hydroxy aromatic and heterocyclic aromatic amines to reactive DNA binding species (32,34). Thus, sulfotransferase has a dual role in HAA metabolism and is involved both in metabolic activation as well as detoxification. TS PST activity varies greatly in individuals and exhibits a genetic polymorphism (31,33). Consequently, studies are required to assess the role of human sulfotransferases in HAA carcinogenesis.

Human liver metabolically activates MeIQx and other HAAs through cytochrome P450-mediated N-oxidation and subsequent esterification reactions to produce the ultimate carcinogenic metabolites (4–7,32,34). Analytic developments are underway to quantify the N-hydroxy-N2-glucuronide conjugate of MeIQx, an index of metabolic activation of this procarcinogen, in human urine. This method will be used to evaluate better both the metabolic activation and detoxification of MeIQx and, therefore, to assess health risk of this dietary mutagen.

**Note Added in Proof**

We recently have identified a glucuronide conjugate of MeIQx in urine and bile of nonhuman primates undergoing carcino- gene assays (23). 1H-NMR and FAB-MS spectroscopy support the structure as a N2-glucuronide (Turesky RJ, Welti DH, Fay LB, Snyderwine EG, unpublished observations). The relative contribution of this metabolite, which has very similar chromatographic properties to MeIQx-N2-glucuronide, in human detoxification of MeIQx remains to be established.
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