FOOD-DERIVED HETEROCYCLIC AMINE MUTAGENS: VARIABLE METABOLISM AND SIGNIFICANCE TO HUMANS

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ABSTRACT:
The cooking of meat has been found to generate compounds that possess extreme mutagenicity when examined in short term tests. This observation led to the isolation and identification of a family of mutagenic chemicals, all of which are heterocyclic amines. These amines are potent bacterial and eukaryotic cell mutagens, and all of those tested have been found to induce tumors in laboratory animals. Metabolic activation of the heterocyclic amines predominantly involves CYP1-mediated N-hydroxylation and then O-esterification by phase II enzymes. In contrast, carbon oxidation, glucuronidation, and sulfation reactions at sites other than the hydroxylamine yield detoxication metabolites. In humans, the activities of these pathways are known to vary between individuals and are likely to influence susceptibility to the genetic toxicity of the heterocyclic amines. Clearly, accurate determination of human exposure to the heterocyclic amines and identification of the key enzyme systems involved and their regulation will be required for rational assessment of the risk and will help devise strategies to reduce such risk.

Epidemiological studies show that the incidence of human cancer is associated with lifestyle, occupation, iatrogenic, and cryptogenic factors (Williams, 1985). By far the most significant of these is lifestyle, particularly diet and tobacco use, which together may account for ~70% of all human cancer (Doll and Peto, 1981). Among dietary factors, high fat intake, low fiber intake, and the consumption of well cooked meat seem to predispose individuals to cancer of the colon, breast, pancreas, prostate, and the endometrium. The discovery that cooked food can be mutagenic (Commoner et al., 1978) led to efforts to isolate the mutagenic products. Groups in Japan and America showed that the cooking of food generates many compounds that are mutagenic in short-term bacterial assays including polycyclic aromatic hydrocarbons, nitrosamines, and a family of compounds that are all heterocyclic amines (HAs1) (Sugimura and Sato, 1983; Felton et al., 1986). While polycyclic aromatic hydrocarbons were shown to be the major mutagens on a mass basis, the HAs were found to be by far the more potent mutagens. These latter compounds include imidazoquinolines, imidazoquinolines, and imidazopyridines (see Fig. 1) and are found when food, particularly red meat, is cooked under normal household conditions; they are not present in uncooked food.

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1 Abbreviations used are: HA, heterocyclic amines; MelQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoline; DiMeQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoline; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; SULT, sulfotransferase.

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Human Exposure to the Heterocyclic Amines

Formation of the HAs has been investigated in model systems, and a requirement for sugars, amino acids, and creatine (or creatinine) has been established (Jagerstad et al., 1983). Three of these cooked food-derived HAs, 2-amino-3,8-dimethylimidazo[4,5-f]quinoline (MelQx), 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoline (DiMeQx), and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), are found more frequently than the others; together they account for the majority of the genotoxic potential of fried beef (Felton et al., 1986; Murray et al., 1988; Murray et al., 1993). These three compounds have been detected in beef, lamb, pork, chicken, and fish, especially when chargrilled, fried, or roasted. HAs are present in microgram per gram quantities in cooked meat; nevertheless, human exposure to the HAs, although low, is chronic since meat is consumed daily over a lifetime. Thus, depending upon dietary preferences, an individual’s daily exposure to heterocyclic amines is likely to range from microgram quantities to essentially zero in the case of vegetarians. Significantly, the incidence of cancer is approximately 60% lower in vegetarians than in nonvegetarians (Thorogood et al., 1994).

In studies of the fate of administered HAs, it was found that irrespective of the route of administration, oral, intraperitoneal, or intravenous, similar amounts of administered HA radiolabel were excreted in the urine and the feces (Gooderham et al., 1987). This and the fact that most of the radioactivity was eliminated in the first 24 h indicated that the HAs were rapidly and extensively absorbed (Gooderham et al., 1987, 1991). Analysis of the excreted material showed that the majority of an administered dose of heterocyclic amine was biotransformed but that a small proportion (2–5%) was excreted in the urine as unchanged parent amine. Subsequently, similar results were obtained in studies of human volunteers fed fried beef meals (Murray...
Metabolism of the Heterocyclic Amines

The rapid elimination of HA radiolabel and that only a small amount of amine was excreted unchanged in the urine suggested that these compounds are likely to be extensively metabolized (Gooderham et al., 1987, 1991). In vitro studies with MeIQx and PhIP using liver microsomal preparations from rats, mice, and rabbits showed that at least two oxidative metabolites were formed from each compound, a ring-hydroxylated product and the N-hydroxy derivative (Gooderham et al., 1987; Turesky et al., 1988, 1991; Sjödin et al., 1989; Turteltaub et al., 1989; Watkins et al., 1991a, b; Rich et al., 1992; Zhao et al., 1994). In vivo studies using a variety of different approaches have shown that the genotoxic N-hydroxylation pathway of these amines involves primarily members of the CYP1A subfamily (Watanabe et al., 1982; McManus et al., 1989; Turesky et al., 1988, 1991; Watkins et al., 1991a, b; Rich et al., 1992; Zhao et al., 1994). Clearly, there are species differences in the oxidative metabolism of HAs since experimental animals are able to both activate and detoxify these amines, whereas humans convert them predominantly to their reactive genotoxic metabolite.

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There are reports that CYP1A1, CYP1B1, CYP3A4, CYP2C9, and CYP2A3 are all capable of metabolizing HAs to their genotoxic N-hydroxy derivatives (McManus et al., 1989; Yamazaki et al., 1993; Edwards et al., 1994; Crofts et al., 1997; Hellmold et al., 1998). However, all of these P450 isoforms are less active toward HA substrates than CYP1A2. An illustrative comparative study has been reported by Crofts et al. (1998) in which human P450 isoforms were expressed in insect cells and the kinetic constants of PhIP N-hydroxylation determined under comparable conditions (Table 2). CYP1A1 and CYP1A2 had comparable N-hydroxylation activity, while CYP1B1 was much less active. CYP1A1 had the highest 4-hydroxylation activity. Levels of CYP1A2 in human liver can vary considerably (Sesaric et al., 1990); thus, hepatic metabolism of heterocyclic amines such as PhIP will vary within the human population. CYP1A2 expression is almost exclusively hepatic, whereas CYP1A1 and PhIP, respectively, with little if any aromatic hydroxylation (Rich et al., 1992; Zhao et al., 1994). Clearly, there are species differences in the oxidative metabolism of HAs since experimental animals are able to both activate and detoxify these amines, whereas humans convert them predominantly to their reactive genotoxic metabolite.
CYP1B1 have been detected in a variety of extrahepatic organs, usually after exposure to inducing agents. Hence, the hepatic oxidative metabolism of the HAs will be CYP1A2-dependent, whereas in extrahepatic tissues metabolism is likely to be supported by CYP1A1 and to a lesser extent by CYP1B1. Again, variations in the expression of these extrahepatic enzymes will contribute to variation in the overall disposition and toxicity of these compounds.

It has recently been shown that human urinary metabolites of the HAs MeIQx and PhIP include glucuronides and sulfate esters (Turesky et al., 1995; Lewis et al., 1998). Three of the sulfotransferases (SULTs 1A2, 1A3, and 1E1) have been shown to sulfate heterocyclic amines and their hydroxylamine derivatives (Buonarati et al., 1990; Ozawa et al., 1994; Lewis et al., 1998; Turesky et al., 1998). The latter isoform, SULT1E1, is known to be hormonally regulated and readily inducible by progesterone. This suggests that sulfation activity could vary, for example during the luteal phase of the menstrual cycle when there is a surge in progesterone levels and SULT1E1 activity may be elevated (Lewis et al., 1998). Since the sulfoxy ester of N-hydroxy-PhIP is an unstable product, its detection in biological samples is likely to be very difficult. However, the 4'-PhIP-sulfate ester, a detoxication product, has been detected in humans, thus demonstrating the involvement of sulfotransferase in PhIP metabolism (Malfatti et al., 1999).

N-Hydroxylation of the HAs, the primary metabolic pathway in humans, is also the primary route of HA genotoxicity. For some HAs, the N-hydroxy metabolite reacts poorly with DNA, but it can be converted to highly reactive derivatives by esterification, e.g., to form N-acetoxy, N-sulfonyloxy, N-propyloxy, and N-phosphatyl derivatives (Schut and Snyderwine, 1999). Studies with bacterial strains that are deficient, proficient, and overexpress acetyltransferase enzymes

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td><strong>Effect of furafylline on the metabolism of MeIQx and PhIP</strong></td>
</tr>
<tr>
<td>In vitro N-hydroxylation by human liver microsomal fraction*</td>
</tr>
<tr>
<td>MeIQx control</td>
</tr>
<tr>
<td>MeIQx + furafylline</td>
</tr>
<tr>
<td>PhIP control</td>
</tr>
<tr>
<td>PhIP + furafylline</td>
</tr>
<tr>
<td>Excretion of unchanged amine in human urine*</td>
</tr>
<tr>
<td>MeIQx (placebo)</td>
</tr>
<tr>
<td>MeIQx (furafylline)</td>
</tr>
<tr>
<td>PhIP (placebo)</td>
</tr>
<tr>
<td>PhIP (furafylline)</td>
</tr>
</tbody>
</table>

* Values are mean ± S.D. (n = 4) pmol of N-hydroxy HA min⁻¹ mg of microsomal protein⁻¹.

* Values are mean ± S.D. (n = 6) percent of the ingested dose excreted as unchanged amine.
Like the activation of the heterocyclic amines to bacterial mutagens (see Fig. 4), this reaction affects the comparative genotoxicity of these compounds. The importance of this acetyltransferase activity in the metabolic activation of the heterocyclic amines to genotoxic derivatives (Edwards et al., 1994).

The molecular nature of PhIP-induced mutation has also been examined in an in vivo transgenic model, MutaMouse, in which 80 copies of the lacZ bacterial transgene gene are present in every cell (Lynch et al., 1996). The MutaMouse mice were administered oral PhIP (20 mg/kg per day) for 4 days and then examined for mutation in the intestinal tissue. Molecular analysis of the mutations confirmed a remarkable similarity to those found in XEMh1A2 cells (see Table 3), viz., mainly G:C to T:A transversions with a significant number of −1 G:C base pair deletions (Table 3), in monotonous runs of G. The preponderance of these guanine-based mutations occurred on the nontranscribed strand of the lacZ transgene that was expressed in the colon (Yadollahi-Farsani et al., 1996).

The molecular nature of PhIP-induced mutation has also been examined in an in vivo transgenic model, MutaMouse, in which 40 copies of the lacZ bacterial transgene gene are present in every cell (Lynch et al., 1996). The MutaMouse mice were administered oral PhIP (20 mg/kg per day) for 4 days and then examined for mutation in the intestinal tissue. Molecular analysis of the mutations confirmed a remarkable similarity to those found in XEMh1A2 cells (see Table 3), viz., mainly G:C to T:A transversions with a significant number of −1 G:C base pair deletions (Lynch et al., 1997). Nearest neighbor analysis of PhIP-induced mutations showed that in both models there was a preferred motif for mutation, a 5′-GGA-3′ sequence. These three characteristics of PhIP-induced mutation, i.e., G:C to T:A transversion, −1 G:C frame-shift mutation, and preference for 5′-GGA-3′ motifs may constitute a mutational “signature” that is diagnostic of the involvement of PhIP (Gooderham et al., 1997). Whether it is possible to use mutational signatures to assess the involvement of compounds such as PhIP in human disease remains to be established.

**Carcinogenicity.** All the heterocyclic amines examined thus far have been shown to be carcinogenic in bioassays (Ohgaki et al., 1991). Both MeIQx and PhIP are carcinogenic in both mice and rats (Kato et al., 1988; Esumi et al., 1989; Ito et al., 1991). In the mouse, MeIQx induces liver and lung tumors, lymphomas, and leukemias, whereas in the rat it causes tumors in the liver, the skin, the zymbal gland, and the clitoral gland (Kato et al., 1988). In the mouse, PhIP induces predominantly lymphoma (Esumi et al., 1989), but interestingly in the rat it induces tumors of the colon and the prostate in the male and the colon and breast in the female (Ito et al., 1991), the sites of the most common diet-related cancers found in humans in the Western world. Molecular analysis of the colon tumors induced in human beings shows that these tumors are caused by PhIP (Thompson et al., 1987). Interestingly, PhIP, a weaker bacterial mutagen than MeIQx, is a particularly potent eukaryotic cell mutagen (Thompson et al., 1987; Felton and Knize, 1990). To explore the molecular nature of PhIP-induced mutation, we have used Chinese hamster V79 cells and the hprt gene as a surrogate marker. Since V79 cells have no intrinsic CYP1A2 activity, culture with PhIP failed to increase the mutation frequency above background spontaneous rate. However a V79 cell line variant, engineered to express human CYP1A2 activity, culture with PhIP failed to increase the mutation frequency above background spontaneous rate. However a V79 cell line variant, engineered to express human CYP1A2 activity, culture with PhIP failed to increase the mutation frequency above background spontaneous rate.

**TABLE 2**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>$V_{\text{max}}$ (nmol min$^{-1}$)</th>
<th>$K_m$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>7.7 ± 0.5</td>
<td>16.1 ± 0.9</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>1.5 ± 0.15</td>
<td>89.9 ± 8.6</td>
</tr>
<tr>
<td>CYP1B1</td>
<td>2.2 ± 0.4</td>
<td>45.2 ± 1.2</td>
</tr>
</tbody>
</table>

$V_{\text{max}}/K_m$ intrinsic clearance (taken from Crofts et al., 1998).

**TABLE 3**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Percentage of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>hprt (Hamster)</td>
<td>lacZ (Mouse)</td>
</tr>
<tr>
<td>GC→TA</td>
<td>64</td>
</tr>
<tr>
<td>GC→AT</td>
<td>15</td>
</tr>
<tr>
<td>GC→CG</td>
<td>5</td>
</tr>
<tr>
<td>AT→G</td>
<td>0</td>
</tr>
</tbody>
</table>

**Frameshifts**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Percentage of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1 G:C base pair</td>
<td>12.5</td>
</tr>
<tr>
<td>+1 G:C base pair</td>
<td>0</td>
</tr>
<tr>
<td>−1 A:T base pair</td>
<td>0</td>
</tr>
<tr>
<td>+1 A:T base pair</td>
<td>0</td>
</tr>
<tr>
<td>Complex mutation</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Acetyltransferase activity is high in *S. typhimurium* YG1024 strain, lower in TA98, and very low in TA98DNP.

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show the importance of this esterification reaction in the metabolic activation of the heterocyclic amines to bacterial mutagens (see Fig. 4). Like the N-hydroxy sulfate esters, the acetyl esters of the N-hydroxy heterocyclic amines are extremely reactive and readily damage DNA.

**Genotoxicity**

**Mutation.** In Ames *S. typhimurium* mutagenicity tests, the HAs have been found to be extremely powerful promutagens causing both frameshift and point mutation (Felton and Knize, 1990). The requirement for metabolic activation and substantial species differences in this reaction affects the comparative genotoxicity of these compounds. Whereas the mouse is good at activating PhIP and MeIQx to genotoxic derivates, other species such as the rat are poor (Davis et al., 1993). However, activation of the HAs to genotoxic derivatives is very efficient in humans due to high hepatic CYP1A2 activity (Edwards et al., 1994). Species differences in the ability to activate HAs are particularly pronounced between humans and cynomolgus monkey, since the liver of the latter is almost devoid of CYP1A2 expression and is consequently very poor at activating HAs to genotoxic derivatives (Edwards et al., 1994).

Chemically induced mutation in bacterial cells is sometimes not manifest in mammalian cell systems. Since the HAs are such powerful bacterial mutagens, it was important to confirm their genotoxicity in eukaryotic cells. A variety of Chinese hamster cells, both DNA repair-proficient and -deficient have been used to study HA-induced mutagenicity (Thompson et al., 1987). Interestingly, PhIP, a weaker bacterial mutagen than MeIQx, is a particularly potent eukaryotic cell mutagen (Thompson et al., 1987; Felton and Knize, 1990). To explore the molecular nature of PhIP-induced mutation, we have used Chinese hamster V79 cells and the hprt gene as a surrogate marker. Since V79 cells have no intrinsic CYP1A2 activity, culture with PhIP failed to increase the mutation frequency above background spontaneous rate. However a V79 cell line variant, engineered to express human CYP1A2 activity, culture with PhIP failed to increase the mutation frequency above background spontaneous rate. However a V79 cell line variant, engineered to express human CYP1A2 activity, culture with PhIP failed to increase the mutation frequency above background spontaneous rate.
male rats given PHP showed that 5 of 8 had a mutation in the Apc gene (Kakuchi et al., 1995); in every case the mutation was a −1 G:C base pair frameshift in a 5′-GGGA sequence. Interestingly, mutation of Apc is a very common and early event in human colon cancer (Powell et al., 1992). Thus, the molecular nature of the mutations detected in these PhIP-induced tumors was identical to the PhIP mutational signature in cultured cells and transgenic mice.

**Conclusions**

There is now no doubt that humans who regularly consume cooked meat are exposed to heterocyclic amines on a daily basis. These compounds are readily absorbed and bioavailable and are extensively, but variably, metabolized to derivatives that include the proximal genotoxic N-hydroxyamine compounds. Further metabolism of the HAS generates conjugated metabolites that include glucuronides and sulfate and acetyl esters, the esters being reactive derivatives capable of damaging DNA by forming adducts predominantly with guanine bases. The consequence of this reaction with guanine is a characteristic pattern of mutation. In the case of PhIP, the reproducibility of the nature and sequence context of these mutations are such that they form a mutational signature that is diagnostic of its involvement. Such mutational signatures may be a means of detecting the involvement of heterocyclic amines in mutating critical gene targets such as cancer-associated genes.

The significance of these processes to the etiology of human cancer requires further investigation. Within a population, exposure to the heterocyclic amines will vary depending upon cooking practices and preferences, the level of cooked meat consumption, and the degree of affluence. The genotoxic potential of ingested HAS will depend upon the balance between metabolic activation and detoxication, and the involvement of polymorphic enzymes in some of these reactions would be expected to influence susceptibility to the genotoxic outcome. Subsequently, the site and extent of DNA damage incurred will depend upon the efficiency of DNA repair mechanisms and the genetic predisposition of the individual to accommodating or adapting to the genetic damage. In line with these observations, in a study of acetylation phenotype, meat intake, and risk for adenoma/colon cancer, it was reported that fast acetylators have a higher odds ratio than slow acetylators and that the odds ratio increases to >3 in fast acetylators who have a high meat consumption (Roberts-Thomson et al., 1996). In a separate study, Lang et al. (1994) reported that the combination of rapid acetylation, rapid CYP1A2 activity, and consumption of well done meat markedly increased the risk of colon cancer (odds ratio, >6). Thus, the significance to humans of exposure to the heterocyclic amines is likely to depend upon what combination of these factors pertain to a particular individual, and by estimating the relative contribution of each factor, we may be able to obtain better estimates of overall risk.

**References**


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