Food-derived Mutagens and Carcinogens

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Abstract

Cooked food contains a variety of mutagenic heterocyclic amines. All the mutagenic heterocyclic amines tested were carcinogenic in rodents when given in the diet at 0.01–0.08%. Most of them induced cancer in the liver and in other organs. It is noteworthy that the most abundant heterocyclic amine in cooked food, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, produced colon and mammary carcinomas in rats and lymphomas in mice but no hepatomas in either. 2-Amino-3-methylimidazo[4,5-f]quinoline induced liver cancer in monkeys. Forma- tion of adducts with guanine by heterocyclic amines is presumably involved in their carcinogenesis. Quantification of heterocyclic amines in cooked foods and in human urine indicated that humans are continuously exposed to low levels of them in the diet. These low levels of heterocyclic amines are probably insufficient to produce human cancers by themselves. However, a linear relationship between DNA adduct levels and a wide range of doses of a heterocyclic amine was demonstrated in animals. It suggests that even very low doses of heterocyclic amines form DNA adducts and may be implicated in the development of human cancer under conditions in which many other mutagens-carcinogens, tumor promoters, and factors stimulating cancer progression exist.

Introduction

Diet plays an important role in cancer development: high intakes of total calories and fat enhance cancer development, excessive intake of sodium chloride promotes carcinogenesis in the stomach, whereas, in contrast, fiber, carotene, and vitamins protect against cancer development (1, 2). Foods also contain mutagenic and/or carcinogenic substances as very minor components: mycotoxin contaminants, nitrosamines, polycyclic aromatic hydrocarbons, and plant alkaloids (3).

A series of mutagenic-carcinogenic substances have been found in cooked meat and fish in the last 15 years. New heterocyclic amine compounds were isolated by monitoring the fractionation and purification of mutagens by using microbial mutation assays (4–7). These compounds have much higher mutagenic activity than other typical mutagens-carcinogens and were later shown to be carcinogenic in rodents and nonhuman primates. This review deals mainly with mutagenic and carcinogenic heterocyclic amines that are produced under ordinary cooking conditions.

In 1939, Widmark (8) reported that organic solvent extracts of broiled horse meat induced tumors in mammary glands when repeatedly painted on the backs of mice. In the 1970s we became interested in whether the smoke produced by broiling meat and fish contained mutagenic and carcinogenic activity, because cigarette smoke condensate was known to contain many mutagens. We found that a smoke condensate obtained by broiling fish and trapping the smoke on glass fiber filters exerted mutagenic activity toward Salmonella typhimurium TA98 after microsomal metabolic activation (9, 10). TA98 was more sensitive than TA100, indicating that the mutagenic compounds have planar structures that can be inserted between the base pairs of double-stranded DNA. Charred parts of broiled fish and meat were also found to be mutagenic to TA98 after metabolic activation (9, 10). These findings led to the isolation of the mutagenic compounds, IQ (11), MelQ, MelQx from broiled fish and meat (5–7). Later PhIP was also isolated as member of this class of mutagens (11). These heterocyclic amines were formed by heating mixtures of creatinine, sugars, and amino acids, which are present in raw meat and fish (12–16). More recently identified mutagens have been found to contain oxygen atoms (17–19). Before the discoveries of imidazoquinoline and imidazoquinoxaline compounds, pyrolysates of food components, amino acids, and proteins were shown to contain mutagenic substances. These findings led to the identification of pyridoindole, dipyridoimidazole, phenylpyridine, and tetraaza-fluoranthene derivatives as new mutagenic heterocyclic amines in pyrolysates of amino acids and of amino-ω-carbone derivatives as mutagenic compounds in a pyrolysate of protein (4–7). Some of the heterocyclic amines that were originally isolated from pyrolysates of amino acids and proteins were also recovered from cooked foods (6).

Chemistry of Heterocyclic Amines in Foods

The heterocyclic amines reported so far are listed in Table 1 with their chemical names, abbreviations, and sources (11, 17, 18, 20–29). They are classified as IQ-type compounds, in which the amino group is not changed by treatment with 2 mM sodium nitrite, and as non-IQ-type compounds, in which the amino group is converted to a nitro group with 2 mM sodium nitrite (30). The amino group of IQ-type heterocyclic amines is converted to a nitro group with 50 mM sodium nitrite and the resulting compound shows a similar mutagenicity to the original compound in the absence of S9 mix (31). Most of these heterocyclic amines have been synthesized in large quantities for use in long-term experiments in rodents (6, 32). These compounds remain stable in experimental diets if these diets are kept cold and dry. They are also sufficiently stable in dilute aqueous solution for biological experiments.

The structures of heterocyclic amines are shown in Fig. 1. A heterocyclic amine containing oxygen, namely aminomethylimidazo[4,5-f]pyridopyrimidine, can exist as four possible isomers because there are two possible positions for both the oxygen and N-aminogroups. IQ-type heterocyclic amines have been found to contain oxygen atoms and as non-IQ-type compounds, in which the amino group is not changed by treatment with 2 mM sodium nitrite, and as non-IQ-type compounds, in which the amino group is converted to a nitro group with 2 mM sodium nitrite (30). The amino group of IQ-type heterocyclic amines is converted to a nitro group with 50 mM sodium nitrite and the resulting compound shows a similar mutagenicity to the original compound in the absence of S9 mix (31). Most of these heterocyclic amines have been synthesized in large quantities for use in long-term experiments in rodents (6, 32). These compounds remain stable in experimental diets if these diets are kept cold and dry. They are also sufficiently stable in dilute aqueous solution for biological experiments.

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Mutagenesis

As described briefly in the introduction, heterocyclic amines are more mutagenic toward S. typhimurium TA98 than TA100. The specific mutagenicities of some heterocyclic amines are much stronger than those of typical mutagens-carcinogens such as aflatoxin B1, 4-nitroquinoline 1-oxide, and benzo[a]pyrene. Moreover, imidazoquinoline and imidazoquinoxaline derivatives, including IQ, MeIQ, and MelQx are much more mutagenic than AaC, MeAaC, and PhiP, as shown in Table 2 (4–7). However, these marked differences between heterocyclic amines and other typical mutagens-carcinogens were not found in cultured mammalian cell systems, such as Chinese hamster lung cells with diphtheria toxin resistance (33) and repair-deficient Chinese hamster ovary cells with 6-thioguanine resistance (34, 35). Results with these mammalian mutation systems closely reflect carcinogenic potencies, the carcinogenic potencies of IQ, MeIQ, and MelQx being almost the same as those of AaC, MeAaC, and PhiP. One factor responsible for the differences between bacterial systems and mammalian systems would be esterifying enzymes such as acetyltransferase and sulfotransferase. Heterocyclic amines induce chromosomal aberrations (36) and sister chromatid exchanges (34, 37–39) in cultured cells in vitro. Heterocyclic amines were also positive in a wing spot test with Drosophila melanogaster (40).

Carcinogenesis

Long-term animal experiments with rats and mice fed a diet containing heterocyclic amines have been carried out, in most cases with the maximum tolerable doses (MTD) of the compounds. The results are summarized in Table 3 (41–53). In BALB/c × DBA/2 F1, mice tumors developed in the liver, forestomach, lung, blood vessels, hematopoietic system, and lymphoid tissue (42, 44, 46, 48, 50, 52, 53). In F344 rats tumors developed in the liver, intestine, skin, oral cavity, mammary gland, Zymbal gland, and clitoral gland (41, 43, 45, 47, 49, 51, 53). Most heterocyclic amines were hepatocarcinogens. However, PhiP did not induce hepatomas in rats or mice but instead induced colon cancers preferentially in male rats, mammary gland cancers in female rats (47), and lymphomas in mice of both sexes (48).

Injection s.c. of Trp-P-1 resulted in the formation of fibrosarcomas at the injection site in F344 rats and Syrian golden hamsters (54). Intragastric intubation of IQ resulted in development of tumors in the mammary gland, liver, and ear duct of SD rats (55). Intestinal tumors developed much more rapidly in analbuminemic congenic F344 strain rats (F344-Á/Á rats) than in F344 rats, when IQ was given with the diet. Albumin-deficient SD rats (NAR rats) were also very sensitive to induction of intestinal tumors by PhiP (56). Hepatocellular carcinomas also developed in cynomolgus monkeys (Macaca fascicularis) after repeated administration of IQ by gavage (57).

Metabolism of Heterocyclic Amines and Their Modification of DNA

Heterocyclic amines are metabolically activated by cytochrome P450s with conversion of an amino group to a hydroxyamino group (58–63). The principal cytochrome P450 isoform responsible for this conversion is induced in rat liver by 3-methylcholanthrene. Recent investigations using cloned complementary DNAs for various molecular species of cytochrome P450s driven by vaccinia virus expression vector indicated that cytochrome P450IA2 is the most effective for metabolic activation of heterocyclic amines (64). Hydroxyamino derivatives of heterocyclic amines are further activated by forming esters with acetic acid, sulfonic acid, and proline. These esters may be the ultimate forms producing DNA adducts (58, 61, 65). The formation of the IQ-guanine adduct is shown schematically in Fig. 2 (66). The structures of guanine adducts with Trp-P-2 and Glu-P-1 were also elucidated (67, 68). These DNA adducts should be responsible for the genetic alteration leading to carcinogenesis. In vitro experiments using the hydroxyamino derivative of Glu-P-1 and a plasmid containing the human c-Ha-ras-1 protooncogene sequence demonstrated the hot spots for mutation in the region of the CCGG sequence, corresponding to codons 11 (GCC) and 12 (GCG) (69). The c-Ha-ras...
adducts as those in the liver, but these organs show no histological precancerous changes, although nephro- and cardiotoxicological effects might appear much later (74, 75). Furthermore, the formation of DNA adducts alone may not be sufficient to produce cancers. This is suggested from a linear relation found between levels of MelQx-DNA adducts in the liver of rats and doses ranging from 0.4 ppm to the dose used in a carcinogenicity test, 400 ppm (75). However, the hepatocarcinogenic response of mice to various doses (20, 60, 200, and 600 ppm) of MelQx seemed to be nonlinear (76). These results suggest that the genetic alterations produced by heterocyclic amines are enhanced by liver regeneration induced by heterocyclic amines themselves at higher doses. The linearity of the dose response for carcinogenesis in the intestine and other organs has not been examined.

The pharmacokinetics of heterocyclic amines are important. Ingested heterocyclic amines are absorbed from the intestine, and their metabolic activation and inactivation occur mainly in the liver. Hydroxylation of ring carbons followed by conjugation leads to their inactivation, and detoxified forms of heterocyclic amines are excreted in the urine and feces (77-79). However, the pattern of in vivo metabolism differs for different heterocyclic amines. PhIP is absorbed from the intestine and most of it is excreted as PhIP in the bile and feces in rats (80). However, in mice treated with polychlorinated biphenyls, little unmetabolized PhIP is detected in the feces (81).

Quantification of Heterocyclic Amines and Consideration of Their Risk for Cancer Development

Methods have been developed for quantitating heterocyclic amines in various materials such as cooked foods, cigarette smoke condensate, and urine (6,82–84). The procedures consist of blue-cotton treatment, HCl-methylene dichloride partition, and conventional and high-performance liquid chromatography. An electrochemical method is effective for detecting imidazoquinoline and imidazoquinoxaline derivatives (82). Some examples of analytical data are given in Table 4 (6, 76). PhIP mutations were frequently observed in squamous cell carcinomas of the Zymbal gland of rats induced by IQ, MelIQ, and MelIQx (70). Most of the mutations were found in codon 13 and were due to transversions of G to T or G to C.

DNA adduct formation by carcinogenic heterocyclic amines was detected by the 32P-postlabeling method (71–75). All heterocyclic amines examined except PhIP produced higher levels of DNA adducts in the liver than in other organs: with PhIP, which is not a hepatocarcinogen, the adduct level in the liver was lower than in the other organs, including the lung, pancreas, and heart (74). Furthermore, the DNA adduct levels of various heterocyclic amines in rat liver correlated well with the carcinogenic potencies of these compounds in the liver. Thus, the levels of DNA adducts formed by carcinogenic doses of heterocyclic amines in the liver are probably reliable indicators of their hepatocarcinogenicities.

Some organs in which the heterocyclic amines form DNA adducts may develop cancers unless animals die from the first dominant tumor. The presence of DNA adducts and histopathological changes in the pancreas and salivary glands of rats treated with 0.08% MeAßC, which induces atrophy of these organs and is toxic to rats, suggest that lower doses of this compound can produce tumors in these organs (71). However, DNA from the kidney and heart of animals given heterocyclic amines contains relatively high levels of the same kinds of DNA adducts as those in the liver, but these organs show no histological precancerous changes, although nephro- and cardiotoxicological effects might appear much later (74, 75). Furthermore, the formation of DNA adducts alone may not be sufficient to produce cancers. This is suggested from a linear relation found between levels of MelQx-DNA adducts in the liver of rats and doses ranging from 0.4 ppm to the dose used in a carcinogenicity test, 400 ppm (75). However, the hepatocarcinogenic response of mice to various doses (20, 60, 200, and 600 ppm) of MelQx seemed to be nonlinear (76). These results suggest that the genetic alterations produced by heterocyclic amines are enhanced by liver regeneration induced by heterocyclic amines themselves at higher doses. The linearity of the dose response for carcinogenesis in the intestine and other organs has not been examined.

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FOOD-DERIVED MUTAGENS AND CARCINOGENS

Table 3 Carcinogenicities of heterocyclic amines in rats and mice

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Species</th>
<th>Concentration (%)</th>
<th>Target organs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td>Rats</td>
<td>0.03</td>
<td>Liver, small &amp; large intestines, Zymbal gland, clitoral gland, skin</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>0.03</td>
<td>Liver, forestomach, lung</td>
<td>42</td>
</tr>
<tr>
<td>MeIQ</td>
<td>Rats</td>
<td>0.03</td>
<td>Large intestine, Zymbal gland, skin, oral cavity, mammary gland</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>0.04, 0.01</td>
<td>Liver, forestomach</td>
<td>44</td>
</tr>
<tr>
<td>MeIQx</td>
<td>Rats</td>
<td>0.04</td>
<td>Liver, Zymbal gland, clitoral gland, skin</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>0.06</td>
<td>Liver, lung, hematopoietic system</td>
<td>46</td>
</tr>
<tr>
<td>PhIP</td>
<td>Rats</td>
<td>0.04</td>
<td>Large intestine, mammary gland</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>0.04</td>
<td>Lymphoid tissue</td>
<td>48</td>
</tr>
<tr>
<td>Trp-P-1</td>
<td>Rats</td>
<td>0.015</td>
<td>Liver</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>0.02</td>
<td>Liver</td>
<td>50</td>
</tr>
<tr>
<td>Trp-P-2</td>
<td>Mice</td>
<td>0.02</td>
<td>Liver</td>
<td>50</td>
</tr>
<tr>
<td>Glu-P-1</td>
<td>Rats</td>
<td>0.05</td>
<td>Liver, small &amp; large intestines, Zymbal gland, clitoral gland</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>0.05</td>
<td>Liver, blood vessels</td>
<td>52</td>
</tr>
<tr>
<td>Glu-P-2</td>
<td>Rats</td>
<td>0.05</td>
<td>Liver, small &amp; large intestines, Zymbal gland, clitoral gland</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Mice</td>
<td>0.05</td>
<td>Liver, blood vessels</td>
<td>52</td>
</tr>
<tr>
<td>AaC</td>
<td>Mice</td>
<td>0.08</td>
<td>Liver, blood vessels</td>
<td>52</td>
</tr>
<tr>
<td>MeAaC</td>
<td>Mice</td>
<td>0.08</td>
<td>Liver, blood vessels</td>
<td>52</td>
</tr>
</tbody>
</table>

Table 4 Amounts of heterocyclic amines in cooked foods

<table>
<thead>
<tr>
<th>Sample</th>
<th>IQ</th>
<th>MelIQ</th>
<th>MeIQx</th>
<th>4,8-DiMeIQx</th>
<th>PhIP</th>
<th>Trp-P-1</th>
<th>Trp-P-2</th>
<th>AaC</th>
<th>MeAaC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broiled beef</td>
<td>0.19</td>
<td>2.11</td>
<td>0.64</td>
<td>0.12</td>
<td>15.7</td>
<td>0.21</td>
<td>0.25</td>
<td>1.20</td>
<td></td>
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<tr>
<td>Fried ground beef</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broiled chicken</td>
<td>2.33</td>
<td>0.81</td>
<td>0.67</td>
<td>3.62</td>
<td>42.5</td>
<td>0.15</td>
<td>2.50</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Broiled mutton</td>
<td>1.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Food-grade beef extract</td>
<td>3.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fried cod fish</td>
<td>0.16</td>
<td>0.03</td>
<td>6.44</td>
<td>0.10</td>
<td>69.2</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*See Table 1 for abbreviations.

is a relatively abundant heterocyclic amine in cooked food. The calculated average intake of carcinogenic heterocyclic amines is about 0.4–16 μg per day, per capita. Carcinogenic heterocyclic amines have been detected in all urine samples examined from healthy volunteers eating normal diets but not in the urine of postoperative patients receiving parenteral alimentation (85). This indicates that humans are normally continuously exposed to heterocyclic amines in foods and that some level of exposure to heterocyclic amines is unavoidable.

The amounts of individual heterocyclic amines consumed daily are too small to explain human carcinogenesis, assuming that the susceptibility of humans to heterocyclic amines is the same as that of rodents. However, the results of medium-term experiments in which five heterocyclic amines were administered simultaneously, each at one-fifth and one-twenty-fifth of their carcinogenic dose, suggest that the carcinogenic effects of heterocyclic amines are additive or synergistic (86). This may also be true for other environmental carcinogens. The total exposure to more than 10 heterocyclic amines formed in cooked food could be, at most, several 100-fold less than the TD50 values of the individual carcinogenic heterocyclic amines (76). Painting a limited amount of Trp-P-2, which itself was not carcinogenic, on mouse skin resulted in skin tumor formation when the skin was treated with a tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (87). Similarly, a combination of a limited amount of IQ and a sufficient amount of phenobarbital induced liver tumors in rats, although the same amount of IQ alone did not induce tumors (88). A strain of Long-Evans rats with cinnamon-like coat color (LEC), which develops hepatitis spontaneously 5 months after birth and hepatomas 14 months after birth, is much more sensitive than normal Long-Evans rats to induction of hepatomas by MelIQx.5 Such findings indicate that the carcinogenic potency of heterocyclic amines is readily modified by various factors.

Humans are continuously exposed to various mutagens-carcinogens, both autobiotic and xenobiotic. The multiple genetic alterations present in human cancer cells could be produced by many kinds of xenobiotic mutagens-carcinogens, each at a very
low level. In addition, autotrophic formation of oxidative agents in vivo and cell replication increase the chances of genetic alteration.

Total avoidance of exposure to heterocyclic amines is impossible, but reducing the exposure level as much as possible is advisable. For example, charring of food during cooking should be avoided. Direct contact of meat and fish with a naked gas flame or charcoal is also not recommended: a microwave oven may be preferable. Cooking meat and fish in aluminum foil would reduce charring, and a simple method for removing heterocyclic amines is mechanical separation of charred parts of broiled fish and meat from edible portions. Soybean protein suppresses mutagen formation in fried hamburger (89). It is desirable to limit the intake of heterocyclic amines to a minimum. This principle also holds for any kind of food containing mutagens and carcinogens. The measures to be followed need to be realistic and not tedious. Inconvenient measures may not be accepted by the public.

References


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