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Formation and biochemistry of carcinogenic heterocyclic aromatic amines in cooked meats

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Abstract

Heteroyclic aromatic amines (HAAs) are a class of hazardous chemicals that are receiving heightened attention as a risk factor for human cancer. HAAs arise during the cooking of meats, fish, and poultry, and several HAAs also occur in tobacco smoke condensate and diesel exhaust. Many HAAs are carcinogenic and induce tumors at multiple sites in rodents. A number of epidemiologic studies have reported that frequent consumption of well-done cooked meats containing HAAs can result in elevated risks for colon, prostate, and mammary cancers. Moreover, DNA adducts of HAAs have been detected in human tissues, demonstrating that HAAs induce genetic damage even though the concentrations of these compounds in cooked meats are generally in the low parts-per-billion (ppb) range. With recent improvements in sensitivity of mass spectrometry instrumentation, HAAs, their metabolites, and DNA adducts can be detected at trace amounts in biological fluids and tissues of humans. The incorporation of HAA biomarkers in epidemologic studies will help to clarify the role of these dietary genotoxicants in the etiology of human cancer.

Keywords: Dietary carcinogens; Heterocyclic Aromatic amines; Metabolism; Biomarkers

1. The formation of HAAs in cooked meats

Heteroyclic aromatic amines (HAAs) were first discovered in cooked foods by Professor Sugimura and his collaborators more than 25 years ago (Sugimura et al., 1977, 2004). Since that time, more than 20 HAAs have been identified in cooked meats. The structures of the principal HAAs present in these cooked staples are presented in Fig. 1. There are two classes of HAAs formed in cooked meats. HAAs that contain the *N*-methyl-2-aminoimidazole moiety are proposed to form through the reaction of pyridine or pyrazines, which are heat-catalyzed degradation products of amino acids, with sugars and creatine, a key precursor present in muscle-meats, to produce the "IQ- and IQx-type" compounds (Skog et al., 1998). These compounds form in meats heated at 150 °C or higher temperature, and their formation has been characterized in model systems (Skog et al., 1998). The second class of HAAs, which include 2-amino-9*H*-pyridole[2,3-*b*]indole (AαC), 2-amino-3-methyl-9*H*-pyridole[2,3-*b*]indole (MeAαC), the glutamic acid and tryptophan pyrolysate mutagens, are formed in proteins or produced directly from pyrolysis of these two amino acids heated at high temperature (>250 °C) (Matsumoto et al., 1981).

The formation of HAAs in cooked meats is dependent upon the type of meat and the temperature and duration of cooking; accordingly, concentrations of HAAs can vary by more than 100-fold. Prolonged cooking time and high-temperature cooking surfaces produce the highest quantities of HAAs (Knize et al., 1994). The concentrations of HAAs formed in meats prepared

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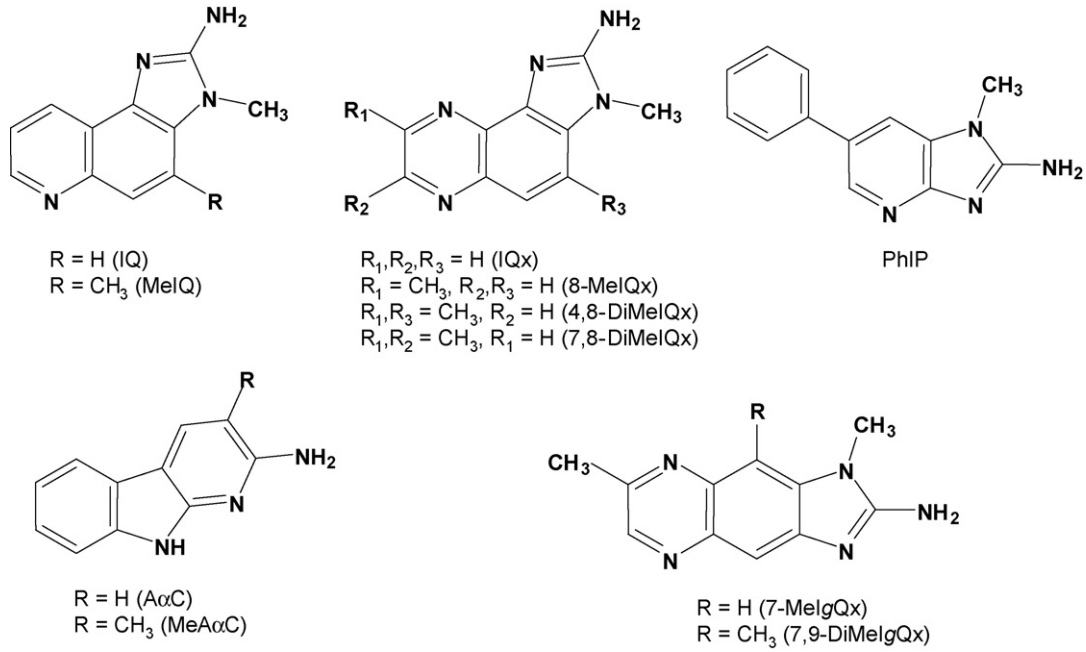

Fig. 1. Chemical structures of representative HAAs formed in cooked meats. More than 20 HAAs have been identified in cooked meats.

by common household cooking practices are generally in the low parts-per-billion (ppb) range, although concentrations in meats or poultry that are cooked well-done (Skog et al., 1998), or the grilled pan scrapings often used for gravy, can be as high as 500 ppb (Skog et al., 1998). 2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (8-MeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) are the most abundant of the HAAs formed in grilled beef, bacon, fish, and poultry (Knize et al., 1994; Skog et al., 1998). AαC also forms in appreciable quantities in some meats cooked well-done (Matsumoto et al., 1981). 2-Amino-3-methylimidazo[4,5-*f*]quinoline (IQ) and 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ) occur in broiled salmon at the low ppb range and form at several hundred ppb in beef extract; however, neither compound is formed at appreciable concentrations (<0.1 ppb) in grilled ground beef or poultry (Skog et al., 1998).

The early studies on the identification and quantification of HAAs were done by isolating HAAs from kilogram quantities of cooked meat, employing multiple chromatography steps. The mutagens were monitored at each purification step by the Ames bacterial mutagenesis assay (Sugimura et al., 2004, Wakabayashi et al., 1995). The purified mutagenic fractions were characterized by ^{1}H NMR and mass spectrometry for elucidation of structures. These methods were extremely labor intensive. Thereafter, more simplified extraction schemes were devised for the isolation of HAAs from cooked meats. The tandem-solid phase extraction method developed by Gross (Gross and Gruter, 1992), which employs a silica-based resin and mixed cation exchange/hydrophobic resins placed in series, has been routinely used to isolate HAAs from a variety of meat products. The method is rapid and permits the quantification of HAAs at the low ppb concentration in only several grams of cooked meat, using HPLC with UV diode array or fluorescence for detection. More recently, this tandem-solid phase extraction technique has been employed in combination with electrospray ionization tandem mass spectrometry (LC/ESI–MS/MS) to measure HAAs in cooked meats in the low parts-per-trillion range; analysis by LC/ESI–MS/MS has lead to the discovery of several novel HAAs (Turesky et al., 2005, 2006).

2. Mutagenicity and carcinogenicity of HAAs

MeIQ, IQ, and 8-MeIQx are among the most potent mutagens ever tested in the Ames bacterial reversion assay (Sugimura et al., 2004). The strong propensity of these HAAs to induce frameshift revertant mutations in *Salmonella typhimurium* TA98 and TA1538 tester strains is attributed to a preference by these HAAs to react about 9 base pairs upstream of the original CG deletion in the *his*D^{+} gene, in a run of GC repeats