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Review

Metabolism and toxicology of heterocyclic aromatic amines when consumed in diet: Influence of the genetic susceptibility to develop human cancer. A review

Maite Sanz Alaejos *, Verónica Pino, Ana M. Afonso

Department of Analytical Chemistry, Nutrition and Food Science, University of La Laguna, 38205-La Laguna (Santa Cruz de Tenerife), Spain

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Abstract

There is not sufficient scientific evidence to support the hypothesis that human cancer risk is specifically due to the intake of heterocyclic aromatic amines (HAAs) in diet. Epidemiological evidence appears to imply two main factors in the HAAs carcinogenicity. These factors are the very high frequency of consumption of red meats, and very darkly browned meats from cooking, which are HAAs-containing foods. The present review focuses on the fact that the cancer risk is notably enhanced when certain genotypes related to HAAs metabolism are present. Thus, genetic predisposition seems to be the main factor in cancer development related to HAAs, and possibly the co-presence of other mutagenic compounds in diet.

Keywords: Heterocyclic aromatic amines; Genetic aspects; Genetic susceptibility; Human cancer

Contents

* Corresponding author. Tel.: +34 922318012; fax: +34 922318090.
E-mail address: mtsanz@ull.es (M.S. Alaejos).

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1. Introduction

Heterocyclic aromatic amines (HAAs) are in general formed during heating process of organic products containing nitrogenous compounds, mainly proteins. This formation is mainly temperature-dependent. HAAs formed at temperatures between 100 and 300 °C are known as "thermic HAAs", IQ type or aminoimidazoazarenes. The ones formed at higher temperatures, above 300 °C, are known as "pyrolytic HAAs" or non-IQ type. Thermic HAAs are generated from the reaction of free amino acids, creatin(in)e and hexoses. Table 1 shows their structures, chemical and abbreviated names.

To date, more than 20 heterocyclic aromatic amines (HAAs) have been isolated as potent mutagens in the Ames/*Salmonella* test, and have been characterized. HAAs are mutagenic compounds for bacteria and for some mammalian cell systems, and can produce chromosomal aberrations and sister chromatid exchanges in cultured cells. Some of them show higher mutagenic activity in bacteria and certain animals than typical mutagens/carcinogens such as benzo(a)pyrene or aflatoxin B_1.

Cooking processes of meat at high temperatures produce polycyclic aromatic hydrocarbons (PAHs) and acrylamide, in addition to HAAs. Processed meats can also contain nitrosamines. Altogether with these compounds, there are other substances and factors that can contribute to the etiology of cancer as well, e.g., high fat or salt intake, physical activity, etc. Thus, there are few epidemiological studies in which an exclusive association between HAAs and human cancer can be assumed.

A recent review (Sanz Alaejos, González, & Afonso, 2008) shows the relationships between the intake of HAAs and human cancer risk, discussing aspects as red meat intake, doneness, and cooking methods. Some conclusions on the investigations carried out by International Organisms related to the possible carcinogenicity of HAAs were also included. The role of HAAs in carcinogenicity has been attributed to two main factors: very high frequencies of consumption of: (1) red meats, and (2) very darkly browned meats. Nevertheless, there is not sufficient scientific evidence to support the hypothesis that human cancer risk is due specifically to the consumption of HAAs in diet.

The present review shows the metabolic and toxicological aspects of HAAs in humans, and collects bibliographic data on the possible relationships among the intake of HAAs contained (or formed) in foods, the genetic predisposition and the human cancer risk, over the last years.

2. Metabolic aspects of HAAs and possible implication with cancer risk development

The metabolic activation of HAAs is catalyzed by enzymes that are polymorphic in humans, leading to inter-individual differences in metabolizing capacity (Turesky, 2002). This may result in significant differences in cancer risk susceptibility among individuals. However, the genetic variation in a human population is not the exclusive factor that plays a role in eventual cancer risk. Food preparation methods determine the kind and amount of HAAs to be ingested, and the intake of HAAs varies widely from day to day due to individual dietary and cooking preferences (Moonen et al., 2004).

The metabolism and biochemistry of HAAs have recently been reviewed (Turesky, 2007). It is remarkable that the metabolism of the more than 25 HAAs has not been completely elucidated, and some steps are still questionable. A representative diagram of the metabolism of HAAs is shown in Fig. 1. In general, metabolism of HAAs can be summarized as follows: The major pathway for the metabolic activation of HAAs starts with the *N*-hydroxylation of the exocyclic amino group, catalyzed mainly by cytochrome P450 1A2 (CYP1A2). Although these metabolites may directly react with DNA, this *N*-hydroxylation step is usually followed by sulphation or acetylation steps by means of sulfotransferase 1A1 (SULT1A1) or *N*-acetyltransferases (NAT), respectively.

NAT1 and NAT2 genes encode NAT enzymes. NAT2 is involved in both the *N*-acetylation of aromatic amines and the *O*-acetylation of the *N*-hydroxylated derivatives. In general, the *N*-acetylation is a detoxification mechanism whereas the *O*-acetylation is usually an activation step. The phenotype distinguishes between rapid and slow *N*-oxidizers and *O*-acetylators. These activated esters are electrophiles able to react with DNA to form adducts, or with proteins and other cellular constituents. The resulting products can be unstable, and spontaneously degrade to 5-OH-PhIP and other metabolites. Some metabolites can be conjugated by sulphation and glucuronidation mechanisms by means of glutathione *S*-transferase and UDP-glucuronosyltransferase, respectively. The formed polar compounds coming from the glutathione *S*-transferase are readily excreted through bile or urine. They can also be transported to extrahepatic tissues where further metabolism can occur. The formed polar compounds coming from the UDP-glucuronosyltransferase are not reactive and are excreted by urine.

On the other hand, multiple genes encoding for biotransformation enzymes such as CYP1A2 and NAT2 display polymorphic distribution in the human population. These enzyme activities are therefore liable to inter-individual variation, leading to a specific metabolizing capacity profile for each person (Moonen et al., 2004). Thus, there are several common genes polymorphisms in the cytochrome P450 (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2C9, CYP2C19 and CYP2D6), glutathione *S*-transferase (GSTM1, GSTP1, and GSTT1), sulfotransferase (SULT1A1 and SULT1A2), and *N*-acetyltransferase (NAT1 and NAT2), among others.

2.1. Cytochrome P450

This way, several polymorphisms in the encoding gene have been described for CYP1A2, being its activity inducible