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A Review on the Formation of Carcinogenic/Mutagenic Heterocyclic Aromatic Amines

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Abstract

Mutagenic and/or carcinogenic heterocyclic aromatic amines (HCAs) have been found in meat and fish cooked at temperatures over 150°C. To date, more than 25 HCAs have been isolated and identified in cooked meat and meat products as potent mutagens in the Ames/Salmonella test. HCAs are potent mutagens at ng/g levels in cooked foods and play an important role in the etiology of human cancer. Major precursors of HCAs are creatine and/or creatinine, amino acids and reducing sugars. IQ-type HCAs are formed by heat induced non enzymatic browning known as Maillard reaction which involves creati(ni)ne, amino acid and sugars whereas amino-carbolines are mainly formed by pyrolysis of amino acids and proteins at higher temperatures above 300°C. Concentrations and variety of HCAs can be dependent on many factors such as precursor level, meat type, cooking method, cooking duration, pH and water activity, heat and mass transfer, lipid level, lipid oxidation and antioxidants. Due to better understanding, formation of HCAs has been studied both in model systems and cooked foods and this review gives an overview of the studies on the formation of carcinogenic and/or mutagenic HCAs.

Introduction

Human epidemiologic and animal studies have shown that diet plays an important role in cancer development [1,2]. It has been reported that one third of human cancers are related to foods. Heterocyclic aromatic amines (HCAs) are potent mutagens at ng/g levels in cooked foods and play an important role in the etiology of human cancer [3]. The International Agency for Research on Cancer (IARC) regards some of the HCAs as possible human carcinogens (2-amino-3,4-dimethyl-imidazo[4,5-f]quinoline (MeIQ), 2-amino-3,8-dimethyl-imidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), class 2B) and one as a probable human carcinogens (2-amino-3-methylimidazo[4,5-*f*] quinoline (IQ), class 2A)[4]. The mutagenicity of HCAs in meat has been assessed by using the microsom test of Ames/Salmonella [5] and HCAs are over 100 fold more mutagenic than aflatoxin B1 and over 2,000-fold more mutagenic than benzo[*a*]pyrene [6].

Mutagenic and/or carcinogenic HCAs have been found in meat and fish cooked at temperatures over 150°C and first discovered by Japanese scientist Sugimura in 1977 [7]. To date, more than 25 HCAs have been isolated and identified in cooked meat and meat products [8]. HCAs can be classified into two main groups called IQ-type HCAs or aminoimidazoazaarenes and non IQ-type HCAs or amino-carbolines. IQ-type HCAs are formed by heat induced non enzymatic browning known as Maillard reaction which involves creati(ni)ne, amino acid and sugars whereas amino-carbolines are mainly formed by pyrolysis of amino acids and proteins at higher temperatures above 300°C [9-11]. Their formation is highly dependent on various factors such as cooking temperature, cooking method, cooking time, type of meat, fat, and moisture content [11,12], pH, sugar, free amino acid and creatinine content of meat [13]. In addition heat and mass transfer, lipid oxidation and antioxidants have effect on concentration of HCAs [13-15].

Due to better understanding, the formation of HCAs has been studied both in model systems and cooked foods. This review gives an overview of the studies on the formation of carcinogenic and/or mutagenic HCAs.

Structures and Formation of HCAs

HCAs have two major classes: aminoimidazoazoarenes (AIAs) and aminocarbolines [14]. The AIAs are the most important class in cooked foods. They have an imidazo group linked to a quinoline, a quinoxaline or a pyridine [16]. AIAs are also called imidazoquinoline (IQ)-type compounds or thermic HCAs and generated from the reaction of free amino acids creatine, creatinine and hexoses during cooking of foods at conventional cooking temperatures (150–300°C). The other amines, aminocarbolines, are formed at temperatures above 300°C [17]. Aminocarbolines are also called non-IQ-type compounds or pyrolytic HCAs. They are formed in the pyrolytic reaction of amino acids and proteins at higher temperatures [10]. Some of these carbolines contain a 2-aminopyridine moiety as a common structure. Harman and norharman are not mutagenic but are co-mutagenic since they enhance the genotoxicity of mutagenic HCAs. These compounds are included among the aminocarbolines, also sometimes grouped as polar and nonpolar according to their chemical behavior [18]. Table 1 (included as supplementary data) shows the classification of HCAs.

Precursors and factors of HCAs formation

Several studies reported that major precursors of HCAs creatine and/or creatinine, amino acids and reducing sugars [20,21]. But some studies have shown that sugar is not obligatory for the formation of AIAs [22,23]. Adding small amount of reducing sugar to model systems

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and meat before cooking resulted in increased production of mutagens [24]. On the other hand, the addition of glucose in amounts greater than half the molar concentration of amino acids and creatine has been shown to reduce the formation of cooked food mutagens in model systems [24,25]. Creatine, free amino acids and hexoses, present in raw meat, were suggested the precursors of IQ-compounds. Creatine was postulated to form the 2-amino-3- methylimidazo (2-aminoimidazo) moiety of AIAs by cyclization and water elimination, a reaction that takes place spontaneously when the temperature is raised above 100°C. This part of the molecule is a common moiety of all IQ- compounds and is also responsible for the mutagenicity of IQ substances. Without this part, and especially its 2-amino group, the mutagenicity becomes almost negligible [11,26].

The remaining parts of IQ-compounds are assumed to arise from Strecker degradation products, such as pyridines or pyrazines, formed in the Maillard reaction between hexoses and amino acids. Aldol condensation is believed to link the two parts together via an aldehyde [12]. Figure 1 shows suggested pathway for the formation of IQ-type and IQx-type compounds.

Muscle meats contain creatine and creatinine, which can react with free amino acids and sugars during cooking [28]. Creatine is therefore basically responsible for the mutagenic activity of meat [29]. During cooking of meat or fish, creatine is converted to creatinine, which then forms the imidazo part of AIAs [26]. Higher cooking temperatures lead to a more rapid decrease in creatine and increase in creatinine. In addition, creatinine has been shown to produce about 50% more mutagenicity than creatine when heated with certain amino acids and glucose in model systems [10,24]. Mutagen production is strongly dependent on the amount of moisture initially present in the meat above approximately 40% [30]. Water-soluble mutagenic agent precursors migrate with water toward the surface of food [29].

Imidazoquinoxaline type HCAs are formed in the model mixture consist of glucose, glycine and creatinine through free radical Maillard intermediates, a pyrazine cation radical and carbon-centered radicals [31-34]. In the initial stage of Maillard reaction of glucose with glycine, both pyrazine cation radical and cation centered radicals are generated and in the presence of phenolic antioxidants they are scavenged [31]. In the model mixture composed of glucose, glycine and creatinine has shown that epigallocatechin gallate and flavonoids prevent the HCAs formation [35]. Moreover, iron is a well-known catalyst of lipid oxidation at lower temperatures and Johansson and Jägerstad [33] reported that the addition of iron (Fe^{2+} and Fe^{3+}) to creatine, glycine, glucose model system, increased the formation of IQx, MeIQx and DiMeIQx approximately two fold.

Several studies have reported that natural and synthetic antioxidants decreased mutagenic activity or inhibited the formation of HCAs. Spices are source of natural antioxidants and their effects on the formation of HCAs were investigated. Rosemary oleoresin [35], rosemary extract added to virgin olive oil [36], oleoresin or grape seed extract [37], spice-containing marinades [38], adding red and black pepper [39,40] can be effective inhibitors of HCAs formation. Marinating is another method can decrease the concentration of HCAs and several studies have shown reduced effect of marinated chicken before grilling on concentration of HCAs [41,42].

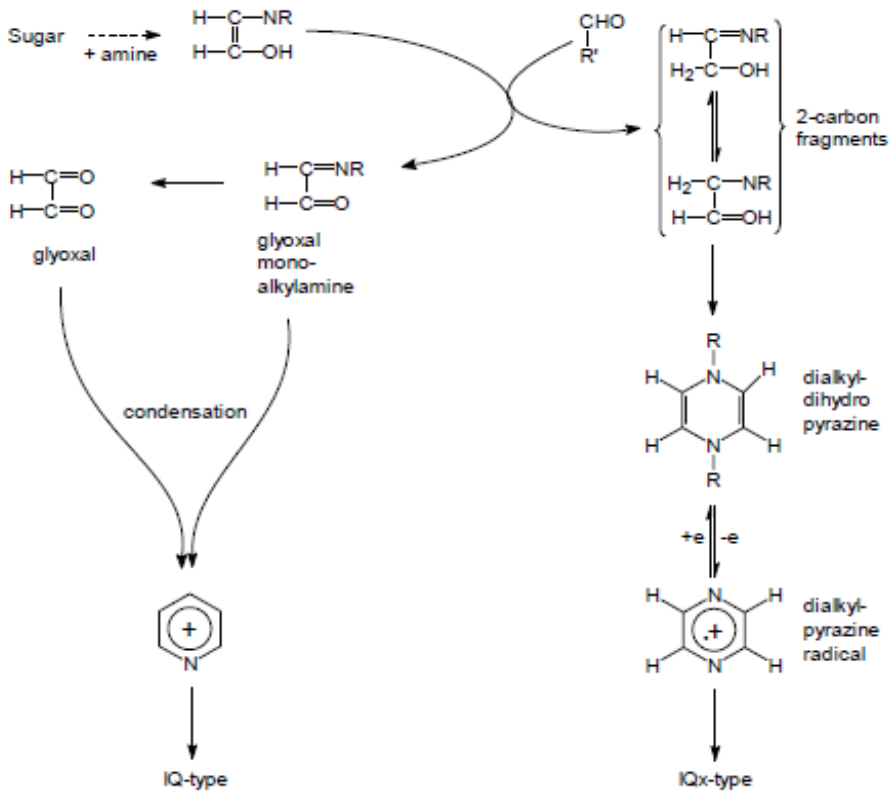

Figure 1: Suggested pathway for the formation of IQ-type and IQx-type compounds [27].

It was shown that phenylalanine, creatinine and glucose were probable precursors of PhIP [27]. PhIP may also be produced from creatine heated together with leucine, isoleucine and tyrosine. Glucose seems not to be a necessary precursor using dry heating conditions [34]. But glucose have a considerable influence, either enhancing or inhibiting depending on its concentration, on the formation of PhIP from phenylalanine and creatine in both a liquid model system and during dry heating [24]. It has been reported that erythrose is the most active in the formation of PhIP, when phenylalanine and creatinine dissolved in water is heated at temperatures of 37 and 60°C. The other carbohydrates namely arabinose, ribose, glucose and galactose are not as active [43].

Although mutagenic activity was first reported in proteinaceous foods, no mutagenic activity was detected when proteins instead of amino acids were reflux-boiled in a model system [12]. Studies with model systems showed that amino acids or short-chain peptides were absolutely necessary for the formation of AIAs [45]. Knize and others [46]. reported that different amino acids were precursors for one mutagenic compound. Refluxing carnosine (b-alanine + L-histidine) with creatinine and glucose at 130°C for 2 h produced similar mutagenic activity to many other amino acids. This result showed that a dipeptide can contribute to the mutagenic activity. However, the highest mutagenic activity was reported for threonine, followed by glycine and lysine [10]. The presence of sugars is necessary for the formation of mutagenic activity in meat. Very low mutagenic was detected in the crust of meat after beef patties (with low glucose) were fried. The patties lacked the meat aroma and also a brown color was not developed in the crust as a result of the Maillard reaction. However, the mutagenic activity increased twofold to threefold when a small amount of glucose was added to the meat before frying [10].

Dolara and others [47] reported that the external surface of cooked meat show greater levels of mutagenic activity than the inner parts. It has been reported that cooking temperature and duration have a much greater influence on the formation of HCAs than the present of precursors (creatine, sugars, and free amino acids) or the amount of water of food [48,49]. Cooking temperature has been reported to be the most important parameter [34,50]. The concentrations of AIAs generally increased with cooking temperature [34,50]. In aqueous model system consisted of creatine, glucose and a blend of amino acids were heated at 150-225°C for 0.5 to 120 min in order to investigate the relation between temperature and time in the formation of HCAs led to rapid formation of IQx, MeIQx, 4,8DiMeIQx and PhIP but not IQ or MeIQ [50]. Most model system studies have been performed at 125-300°C. In liquid model systems for the formation of PhIP from phenylalanine, creatinine and glucose, the concentration of PhIP was increase when the temperature was increased from 180 to 225 C [51]. In meat or model systems, mutagenic activity or the formation of AIAs increased with processing time at 150–170°C. However, the concentrations of HCAs increased during the initial period of processing and then decreased at higher temperatures (190–250°C) [24,52]. Formation of HCAs can be minimized if the cooking temperature is kept low and constant. In domestic cooking, temperature is generally below 200°C. Increase in cooking time and temperature lead to increase the amounts of HCAs and PhIP level is higher at higher cooking temperatures and in longer cooking time [12,50,53,54]. Bjeldanes and others [30,55] reported that mutagenic activity in grilled meat increased rapidly during the initial 10 min and then decreased. They declared that the decreasing might be due to the formation of an obvious, distinct crust on the meats, which appears to inhibit further heat transfer to the interior of the meat. In addition coating foods with breadcrumbs before frying may reduce the formation of HCAs because of the insulating effect of coating [50].

Cooking method is another factor for the HCAs formation [56]. Investigations of various cooking methods have shown pan-frying and grilling/ barbecuing to generally yield higher levels of HAAs than oven roasting, deep-fat frying, boiling or microwaving [57,58]. High concentrations of HAAs are formed during pan-frying, especially at temperatures, above 225°C [21]. Similarly Oz and others [59] reported that the highest total HCAs amount found in pan fried fish and no HCAs detected in fish fillet cooked with microwave or hot plate. Microwave, oven and hot plate cooking to all various doneness degrees in beef samples did not cause HCAs formation whereas barbecuing and pan frying led to HCAs formation in beef samples [60].The heat transfer by air may be the explanation of the lower amounts of HAAs formed during oven cooking. In oven cooking also less mutagenic activity was formed in the presence of steam which affected the heat transport and decreased the surface temperature of products [34]. Oz et al. [61] found that microwaved cooked chicken had the lowest total HCAs amount and emphasized microwave pretreatment instead of direct microwave cooking. Microwave pretreatment of meat before frying decreases HCAs formation due to loss of HCAs precursors with the meat juice [28].

The lipid content of meat is also important for the formation of mutagenic activity in crust. However, the role played by lipids is not clear in the development of mutagenic activity. Most authors agree that there is an optimum lipid level for maximum formation of HCAs; in the case of grounded meat, this level is between 10% and 20% [44]. Using added fats (butter, margarine or oils) in cooking dramatically increased the amounts of mutagenic compounds at above 200°C [62]. This also indicates that lipids are effective heat transfer agents.

Conclusion

HCAs are potent mutagens and/or carcinogens at ng/g levels in cooked foods and play an important role in the etiology of human cancer. Their formation is highly dependent on various factors such as cooking temperature, cooking method, cooking time, type of meat, fat, moisture content, pH, sugar, free amino acid and creatinine content of meat. In addition, heat and mass transfer, lipid oxidation and antioxidants have effect on concentration of HCAs. After evaluations based on high dose, long term animal studies and in vitro and in vivo genotoxicity tests IARC concluded that several HCAs present in cooked foods are possibly (2B) and probably (2A) carcinogenic to humans. But there is insufficient scientific evidence that these toxicants really cause human cancer. There is no general agreement on the role of HCAs regarding human health. However the authorities of Western countries recommend minimizing their formation in our diet.

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