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MUTAGENIC AND/OR CARCINOGENIC COMPOUNDS IN MEAT AND MEAT PRODUCTS: HETEROCYCLIC AROMATIC AMINES PERSPECTIVE

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Abstract

Meat and meat products, which have a very important place in terms of nutrition, can endanger human health if they are not properly prepared and preserved. Meat and meat products except for products such as sushi, which are deliberately consumed raw, are generally consumed immediately after cooking. Cooking done properly gives meat and meat products their unique taste and aroma, increases their digestibility and makes them microbiologically safe. However, some harmful food toxicants can occur during the cooking process. Heterocyclic aromatic amines can be formed during cooking of the proteinaceous foods such as meat and meat products. Epidemiological studies have proved that heterocyclic aromatic amines are mutagenic and/or carcinogenic compounds. Therefore, having sufficient knowledge about heterocyclic aromatic amines will help to reduce the health risk posed by these compounds. In this context, in the present study, basic information about heterocyclic aromatic amines that can be formed during the heat treatment of meat and meat products was reviewed.

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Introduction

Our foods are complex mixtures of micro compounds such as vitamins and minerals and macro compounds such as protein, fat, and carbohydrates. In addition, our foods can contain antioxidants and dietary fiber that have been found to have significant effects on human health. On the other hand, studies have also proven that our food can contain very harmful substances such as microbial contaminants, toxins, or various chemicals that have negative effects on human health. Therefore, our foods, which play a role in the prevention and treatment of some diseases, are also responsible for the emergence of some diseases [1].

Cooking is a heat treatment generally applied immediately before the consumption of foods. This process takes place by heat and mass transfer, and physical, chemical, and biochemical changes occur in meat. As a result, the cooking process increases the flavor of meat, makes a product safe from the microbiological point of view, and increases its digestibility and tenderness [2]. However, if the cooking process is not done properly and carefully, it can cause the formation of some food toxicants such as heterocyclic aromatic amines (HAAs) in meat and meat products [3].

HAAs constitute a group of food toxicants that can be formed during the heat treatment (cooking) of protein-rich foods such as meat and meat products. These food toxicants, first identified in cooked meats by Japanese scientists in 1977, were named heterocyclic aromatic amines due to their chemical structure [4]. Epidemiological studies have proven that HAAs are mutagenic and/or carcinogenic compounds [5,6]. Due to the fact that foods containing these toxicants have been widely consumed in many countries and it is determined by epidemiological studies that the rate of cancer is much higher in countries that consume large amounts of meat, the number of studies done on HAAs has been increasing day by day. Therefore, it is important to have knowledge about these kinds of food toxicants. In this context, in the current study, various information about their structures, mutagenicity and carcinogenicity, formation mechanisms, and reduction of formation of heterocyclic aromatic amines was reviewed.

Chemical structures, precursors, formation mechanisms, and factors affecting formation of heterocyclic aromatic amines

HAAs are durable solids melting at 200–300 °C with a polycyclic aromatic structure, containing exocyclic amino groups [7]. All of HAAs have the characteristic UV spectrum and high extinction coefficient, while some of them have fluorescence properties. Therefore, they can be analyzed due to these properties. To date, approximately 30 different HAA compounds have been identified [8].

HAAs are divided into two main groups according to their chemical structures. The first group of these compounds is aminoimidazoazoarenes, and the second group is aminocarbolines [9]. Aminoimidazoazoarenes, which form the first group, are also called the IQ-type compounds or thermal HAAs. These compounds are usu-

ally formed at temperatures between 150–300 °C. For this reason, it is stated that these kinds of HAAs can frequently occur in meat and meat products cooked at home, because cooking methods used in the home generally work at these temperatures. These compounds mostly consist of reactions between free amino acids, hexoses, and creatine/creatinine. They commonly contain either a quinoline or a quinoxaline or an imidazo group combined with pyridine. Therefore, aminoimidazoazoarenes include imidazoquinoline, imidazoquinoxaline, and phenylimidazo pyridine compounds [10]. The aminocarbolines, which form the second group, are also called the non-IQ type compounds or pyrolytic HAAs. These compounds are generally formed as a result of the pyrolysis of amino acids and proteins at temperatures above 300 °C. For this reason, it is stated that these kinds of HAAs can frequently occur in barbecued meat and meat products. They contain the 2-aminopyridine moiety as a common structure in their structure. In addition, HAAs can be classified according to their chemical behavior as polar (AIAs, Glu-P-1, and Glu-P-2) and apolar (all others) [11]. On the other hand, there are studies in the literature showing that these compounds can be formed in meat and meat products that are exposed to temperatures lower than these temperatures [12]. In addition, it has been determined that HAAs can occur not only in meat and meat products, but also in other foods such as milk and dairy products, coffee, alcoholic beverages, and tobacco products [13,14,15,16,17]. The chemical name, classification, abbreviation, and chemical structures of the most important HAAs are given in Table 1.

It is known that some precursors must be present in the environment for the formation of HAAs. In this context, it is stated that there are three major classes of the precursors; 1) creatine and/or creatinine, 2) sugars (especially reducing sugars), 3) free amino acids, dipeptides and proteins [18].

It is stated that the Maillard reaction is very important for the formation of HAAs, especially aminoimidazoazoarenes. The Maillard Reaction, which was detected by the French scientist Louis-Camille Maillard in 1912 [1], is still not a fully elucidated reaction, even after 110 years. Some Maillard reaction products are known to be anticarcinogens, but some reaction products have been determined to be mutagens and/or carcinogens. Indeed, it is very well known that as a result of the Maillard reaction, which occurs between reducing sugars and compounds containing free amino groups, taste, aroma, texture and brown pigments are formed; however, various food toxicants with mutagenic and carcinogenic properties can be formed in foods such as meat and cereals prepared for consumption [1].

Creatine, which is only present in foods of animal origin, is a non-protein nitrogenous substance. It loses one molecule of water and turns into creatine when the ambient temperature reaches about 100 °C. Creatine and creatinine are considered as important precursors in the HAA formation. It is thought that creatine forms the aminoimidazo part by cyclization and water elimination. This part is known to provide mutagenicity of aminoimidazoazoarenes and is present in all aminoimidazoazoarenes [19].

Table 1. Classification, chemical name, abbreviation, and mutagenicities of the most important HAAs

Classification and chemical name	Abbreviation	Revertants/μg	
		TA98	TA100
Aminoimidazoazoarenes (IQ-type compounds or thermal HAAs)			
2-amino-3-methylimidazo[4,5-f]quinoline	IQ	433.000	7.000
2-amino-3-methylimidazo[4,5-f]quinoxaline	IQx	75.000	1.500
2-amino-3,4-dimethylimidazo[4,5-f]quinoline	MeIQ	661.000	30.000
2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline	MeIQx	145.000	14.000
2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline	4,8-DiMeIQx	183.000	8.000
2-amino-3,7,8-trimethylimidazo[4,5-f]quinoxaline	7,8-DiMeIQx	163.000	9.900
2-amino-3,4,7,8-tetramethylimidazo[4,5-f]quinoxaline	4,7,8-TriMeIQx	na	na
2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine	PhIP	1.900	1.200
Aminocarbolines (non-IQ type compounds or pyrolytic HAAs)			
2-amino-9H-pyrido[2,3-b]indole	AαC	300	20
2-amino-3-methyl-9H-pyrido[2,3-b]indole	MeAαC	200	120
1-methyl-9H-pyrido[4,3-b]indole	Harman	—	—
9H-pyrido[4,3-b]indole	Norharman	—	—
3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole	Trp-P-1	39.000	1.700
3-amino-1-methyl-5H-pyrido[4,3-b]indole	Trp-P-2	104	1,8
2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole	Glu-P-1	49.000	3.200
2-aminodipyrido[1,2-a:3',2'-d]imidazol	Glu-P-2	1.900	1.200

na: not available

The remaining parts of the aminoimidazoazoarenes are thought to be arising from Strecker degradation products (e.g pyridines and pyrazines) formed in the Maillard reaction. Then, an aldol condensation is suggested to link these two parts together via an aldehyde or the related Schiff base [20,21,22]. This hypothesis has been verified using the model systems [23].

The aminocarbolines are thought to be formed via free radicals. Pyrolysis occurs at temperatures above 300 °C and produces many reactive fragments by free radical reactions, and these fragments condense to form new compounds. In addition, it is reported that tryptophan is one of the most important precursors for this kind of heterocyclic amines and aminocarbolines have an indole moiety that comes from tryptophan [10]. On the other hand, there are studies indicating there are other precursors than tryptophan and pyrolysis is not the only way to the formation of aminocarbolines [24,25]. Figure 1 shows the formation mechanisms of IQ-type HAAs, PhIP, and norharman as aminocarboline.

It is stated that types and concentrations of HAAs that can be formed in foods that are subjected to heat treatment using different methods and temperature-time combinations depend on factors such as type of a product being heat treated, the temperature used during cooking, cooking time, cooking conditions, pH, water activity, carbohydrates, free amino acids, creatine, as well as heat and mass transfer, fats, fat oxidation and antioxidants [1,16,26,27].

Mutagenicity and carcinogenicity of HAAs

It is stated that meat that has not been subjected to heat treatment does not show the mutagenic activity. However, heat treatment causes the mutagenic activity in meats [28]. Short-term bacterial tests are used for the determination of the mutagenic activities of HAAs [29]. Substances with genotoxic potential are detected by the Ames test [30]. HAAs are very strong mutagens in the Ames test leading to mutations and chromosomal damage in cells of *Salmonella typhimurium* bacteria and carcinogens in animal experiments [31]. It is stated that they are 100 times more muta-

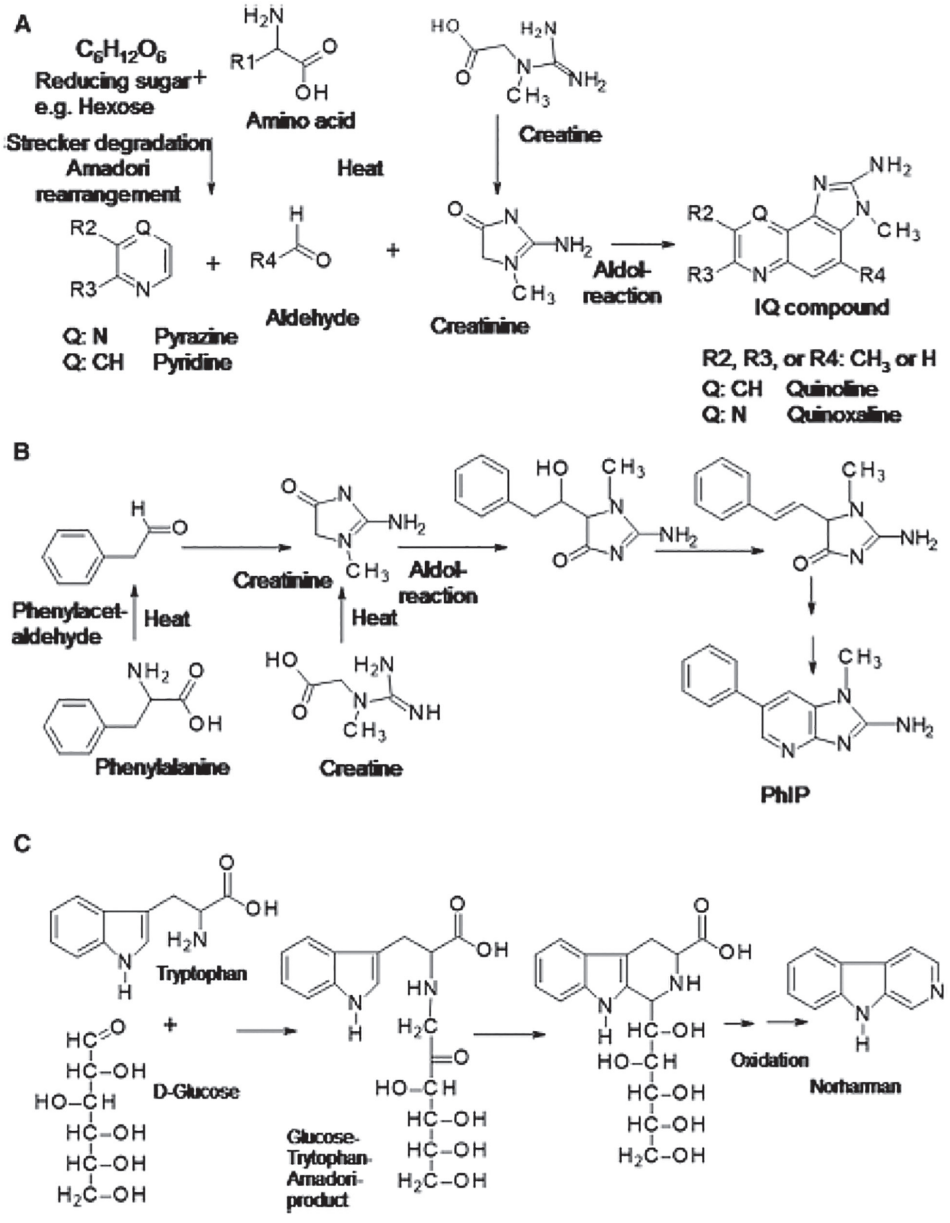

Figure 1. Formation mechanisms of IQ-type HAAs, PhIP, and norharman [16]

genic than aflatoxin B1 and 2000 times more mutagenic than benzo[a]pyrene [32]. The aminoimidazoazoarenes are especially highly mutagenic to *Salmonella typhimurium* TA98, ranging from 1.800 to 660.000 revertants/μg [10]. Data on the mutagenicities of the HAAs in *Salmonella typhimurium* histidine auxotroph TA98 and TA 100 are also given in Table 1. On the other hand, it is stated that the harman and norharman compounds in the aminocarbolines class do not show mutagenic activities, but they are co-mutagenic because they increase the mutagenicity and genotoxicity of other HAAs [33].

Epidemiological studies have shown that lifestyle factors, including a diet, have a significant impact on human cancers [34]. F344 rats and CDF_1 mice are generally used for the carcinogenicity tests for HAAs [34]. However, further studies are needed to reveal the effect of HAAs on human cancers. Epidemiological studies have proven a positive correlation between high consumption of meat (especially well done) and fish and cancers of the pancreas, breast, colon, colorectal, prostate, and ureter [27]. In addition, the International Agency for Research on Cancer (IARC) has identified HAAs as a probable human carcinogen (IQ, class 2A) and a possible human carcinogen (MeIQ, MeIQx, PhIP, AαC, MeAαC, Trp-P-1, Trp-P- 2 and Glu-P-1, class 2B) [35]. Therefore, it has been suggested that the accepted daily consumption amount should be 0–15 μg/day for a person [36].

Levels of the HAA formation in meat and meat products

It is very difficult to predict the exact amount of HAAs that can occur in heat-treated meat and meat products, based on the cooking method, cooking temperature, and cooking time without analysis, because as mentioned before, many factors affect the HAA formation in cooked meat and meat products. However, it can be stated that cooking methods using low cooking temperatures such as boiling, sous-vide cooking, in general, may cause less HAA formation. On the other hand, when eating meat in a restaurant, it can be a boring question to think about what level of HAA compounds was formed in that meat. However, in general, it can be thought of as the more darkened meat surface, the higher internal temperature of the meat, and even the more flavor of the meat, the more HAAs can be formed.

It can be seen from the literature that there are very different results in various studies. For example, several studies that used heat treatment with the same method and almost the same temperature and time did not reveal HAA formation in meat samples, while a very high level of HAA formation was detected in some samples in other studies under similar conditions. In addition, cooking methods were not discussed in detail in some studies, while in others, meat samples were cooked to increase HAA formation generally. It is stated in the studies that the lowest individual HAA amounts were below the detection limits. On the other hand, the maximum amounts of some individual HAAs determined in the meat samples analyzed in some studies were as follows: IQ 303.06 ng/g in beef meatball [37], IQx 3.48 ng/g in beef [38], MeIQ 16.6 ng/g in fish [39], MeIQx 270 ng/g in beef [39], 4,8-DiMeIQx 15 ng/g [39], 7,8-DiMeIQx 5.3 ng/g in fish [39], PhIP 480 ng/g in chicken [39], AαC 106 ng/g in pork [39], MeAαC 3.2 ng/g in pork [39], harman 200 ng/g in pork [39], norharman as 186.1 ng/g in pizza [40].

In the studies carried out, it was determined that the highest individual HAA content (PhIP) in heat-treated meats (cooked chicken) was up to 480 ng/g. This is an important source of risk, because this amount belongs to only one compound in one gram of meat. On the other hand, considering that 100 g of meat is eaten as a portion and approximately 30 different HAA compounds have been isolated and identified from foods until today, and this number may increase, it will be possible to take more HAA compounds into the body than the maximum acceptable daily consumption amount (15 μg). For this reason, studies on reducing the formation levels of these compounds are gradually increasing. However, there is no legal regulation regarding the maximum availability limits of HAAs in foods in any country, which is considered an important disadvantage.

Methods of reducing HAAs in cooked meat

It is known that the world population is close to 8 billion as of now [41]. On the other hand, the United Nations has estimated that the world population will be 9.7 billion in 2050 and 11.2 billion in 2100 [42]. As it can be understood from these data, the world population is increasing day by day, despite the recent epidemics (for example, the COVID-19 pandemic). In addition, when the studies in the literature are examined, it is seen that the amount of meat consumption is increasing day by day in parallel with the increase in the world population. For example, per capita meat consumption was 23.1 kg per capita in 1961 [43], reached 42.4 kilograms in 2021 and is expected to increase to 43.7 kilograms by 2030 [44]. Therefore, studies on the complete inhibition or reduction of the formation levels of these kinds of compounds in heat-treated meat and meat products are very valuable, because meat consumption has been increasing day by day and the mutagenicity and carcinogenicity of HAAs have been proven as a result of epidemiological studies. In the studies on the reduction of HAA formation in heat-treated meat and meat products, the following recommendations have been made in general:

- Conventional cooking methods used in the cooking of meat and meat products should be modified and boiling or steaming methods including lower temperature should be preferred instead of frying or grilling;
- Meat and meat products should be pre-cooked for a short time using microwaves, to ensure, if possible, that HAA precursors are removed from meat. After this

short pre-cooking process, it will be healthier to subject meat to the other cooking process;
- Meats such as fish and chicken should be cooked with their skins. By this means, their skin will be a protective shield during the cooking of this kind of meats in terms of the HAA formation. After cooking, the skin should be removed from meat and the meats should be consumed;
- Nowadays, in many steakhouses, waiters ask their customers how they prefer their meat cooked. When faced with such a question, we should prefer medium and well done meats, because rare meats pose a risk in terms of microbiology, while very well done meats pose a risk in terms of heat treatment contaminants such as HAAs;
- If there are blackened/extremely burned parts on the surface of heat-treated meats, meat definitely should not be consumed before these parts are separated from meat;
- If meats are barbecued, meat should be as far away from the heat source as possible and should not come into direct contact with the source if possible;
- It is recommended to consume meat with salad or similar garniture due to the fact that the antioxidant compounds present in these products can interfere with the HAA formation and reduce the amount of meat in the portion. In addition, the use of spices with the antioxidant activity during the cooking of meat and meat products can reduce the HAA formation.

Conclusion

Heterocyclic aromatic amines are among the main food mutagens and/or carcinogens found in cooked meat and meat products. In this current study, the basic information about heterocyclic aromatic amines was reviewed. The most important issue about heterocyclic aromatic amines is that these compounds can also occur in normally cooked meat and meat products. Due to their mutagenicities and/or carcinogenicities, their formation in meat and meat products should be reduced. In this context, there is a need to increase the number of studies on reducing the formation levels of these compounds in different meat and meat products.

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