EDITORIALS

Heterocyclic Amines in Cooked Foods: Candidates for Causation of Common Cancers

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This issue of the Journal has a report by Weisburger et al. (1) who have contributed much to our knowledge about chemical carcinogenesis as well as nutrition and its association with cancer prevention. Weisburger et al. describe the bacterial metabolite 2-amino-3,6-dihydro-3-methyl-7H-imidazo[4,5-f]quinoline-7-one (7-OHIQ), which is formed from a cooked food mutagen and carcinogen, 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (IQ). Although 7-OHIQ was suspected to induce colon cancer in rodents in vivo, no such result was obtained in this study. In contrast, IQ itself was shown to produce colon cancers by oral administration in rats in our experiments (2). It seems appropriate at this point to comment on the significance of recently found carcinogens existing in cooked food, i.e., heterocyclic amines (HCAs), which are possible candidates for producing commonly occurring human cancers.

HCAs Produced by Cooking Meat

Ames et al. (3) established a mutation test, known as the Ames test, that first used Salmonella typhimurium TA1538 and TA1535 and then used TA98 and TA100 with R-factor plasmid in a metabolic activation system from the liver of rats treated with cytochrome P-450 inducers. Most typical carcinogens such as azo dyes, dialkyl nitrosamines, aflatoxin B₁, and benzo[a]pyrene were shown to be mutagenic. By use of the Ames test, a series of HCAs was isolated from pyrolysates of amino acids and proteins as well as from grilled sardines, fried beef, and beef extract, substances that have been shown to have mutagenic activity (4-9). Organic solvent extraction, acid/base partition, blue cotton treatment, various column chromatographies, and high-performance liquid chromatography were used for the purification of the HCAs by monitoring the mutagenicity in S. typhimurium TA98. The structures of the HCAs were determined by mass spectroscopy, UV and nuclear magnetic resonance spectra, and also by X-ray crystallography. Finally, the structures were confirmed by chemical synthesis. A surprising finding was that humans are continually exposed to strong mutagenic compounds that are produced under ordinary cooking conditions.

Fig. 1 illustrates the structures of representative HCAs. These HCAs are metabolized by cytochrome P450IA2 and result in hydroxyamino derivatives that are further activated into their ultimate reactive forms through O-acetylation and O-sulfation. These reactive forms then bind at the C-8 position of DNA guanine residues.

In rodents, HCAs produce cancers in various organs, including the liver, small and large intestines, forestomach, Zymbal glands, skin, oral cavity, clitoral gland, lung, blood vessels, urinary bladder, lymphoid tissue, and mammary glands (2,7). HCA-induced tumors of Zymbal glands often bear ras mutations. The mutational spectrum comprises changes from G to T and G to A. In 96% of cases, the G:C pair is involved, reflecting the formation of HCA adducts with the guanine base of DNA. In contrast to Zymbal gland tumors, HCA-induced colon cancers have not frequently been observed to bear ras mutations. However, human colon cancers are associated with Ki-ras activation, but not in all cases. Thus, a mechanism involving other oncogenes in rat colon cancers induced by HCAs may correspond to human cases of colon cancer in which Ki-ras was not detected. The urine of patients receiving parenteral alimentation lacks HCAs, but healthy volunteers eating a normal diet excrete HCAs into urine. One of the HCAs, IQ, was shown to be carcinogenic in nonhuman primates (10).

Multiple-Step Carcinogenesis and Significance of Environmental Carcinogens

HCAs provide examples of newly identified carcinogenic substances encountered in our daily life. However, the concentrations of HCAs in foods might not be high enough to produce tumors by themselves. Nevertheless, it should be emphasized that because of lifestyle and occupation, humans are continuously exposed to many other carcinogenic agents and are confronted with many different carcinogenic conditions including chronic viral and bacterial infections, as well as UV radiation, which may induce chronic regenerative lesions and the overproduction of endogenous oxidants such as active oxygen and nitric oxide.

It is extremely important that we consider the multiple-step carcinogenesis involved in multiple genetic alterations. There are many cells that may have a number of genetic alterations that are still insufficiently numerous to convert to malignant cells. Those cells are likely to be more sensitive to the effects of further exposure to carcinogenic factors (8,9). It has been documented that second primary cancers, which are neither metastases nor recurrences of the first cancer, are newly produced in patients who once overcame cancers through surgical treatment without additional...
Fig. 1. Structures of mutagenic and carcinogenic heterocyclic amines.

chemotherapy or radiation therapy. The term ‘‘field cancerization’’ was mentioned many years ago (11).

The extension of carcinogenic risk demonstrated in animal models to humans has often been a subject of debate. ‘‘Quantum toxicology,’’ a field of study in carcinogenic toxicology developed 20 years ago (12), is different from other systemic toxicology. For example, the dose producing a single cancer cell among 250 rats can kill only one rat. However, a corresponding dose can kill a human, the body weight of whom corresponds to the collective body weight of the 250 rats, as illustrated in Fig. 2.

The need to avoid exposure to carcinogens or, at least, to minimize exposure without greatly affecting daily life should be emphasized. Avoiding the formation of char on food and the overcooking of food as well as minimizing the contact of meat and fish with the naked flame is certainly desirable. Skillful handling of eating utensils in the removal of char on food can adequately eliminate a major source of food that contains HCAs. The use of the microwave oven is also recommended.

Studies of carcinogenesis were historically initiated by the observation of a high frequency of cancers seen in association with particular lifestyles. Most of those cancers were ‘‘occupational cancers.’’ In principle, such cancers are preventable by improvement of occupational conditions and by advancement in technology. Also in such cases, the causative agent can usually be clearly identified if the degree of exposure is substantial. However, most common cancers that develop in individuals who maintain an ordinary lifestyle are difficult to characterize in regard to causative agents, except those related to cigarette smoking and alcohol.

Perhaps it is time to shift to a strategy of cancer prevention and accept that human carcinogenesis is largely due to an accumulation of many kinds of carcinogenic factors, each of which in itself may have little impact. For instance, among common foods, sodium chloride and fat may be responsible, if taken in excess, for stomach and colon carcinogenesis, respectively. HCAs offer another example of carcinogenic factors to which people are being continuously and unconsciously exposed. Therefore, improvements in our surroundings and lifestyle should be encouraged to minimize exposure to HCAs as much as possible without interfering with our taste, tradition, and economics. Research on HCAs also indicates the possibility of future identification of other series of carcinogenic factors present in food, the environment, or in the human body.

References


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Fig. 2. Concept of quantum toxicology.


Notes

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