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REVIEW

Histamine intolerance and dietary management: A complete review

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Abstract
Background: Present in several types of food, bioactive amines are described as organic bases of low molecular weight, which constitute a potential health risk. An awareness of amine levels in foods today is therefore important in relation to food safety and patient care. This review aims to emphasise the need to unify the information on the content of biogenic amines in foods and prevent patients' misunderstanding.
Methods: Selective literature search for relevant publications in PubMed and other scientific data bases combined with further data from the World Wide Web on histamine and other amines content in foods.
Results: Available reference sources do not reflect a homogeneous consensus, and the variation between foods makes it impossible for dieticians to accurately estimate amines content to correctly advise patients.
Conclusions: To achieve the goal of collecting reliable information, all methods and tools used in analytical studies should be standardised and information exposed to patients should be verified.

Introduction

Bioactive amines are described as organic bases of low molecular weight produced by the metabolism of plants, animals and microorganisms. They have vasoactive, psychoactive and toxicological characteristics and constitute a potential health risk. The concentration of amines formed in foods depends on the type of microorganisms present, the action of decarboxylase enzymes produced by microorganisms on specific amino acids and favourable conditions for enzymatic activity. The presence of these chemical metabolites has been suggested as a quality indicator in routine analyses for food production and marketing monitoring.[1]

Biogenic amines are present in low concentrations or are not detected in fresh food (below 10 μg/g); however, in food of animal origin such as fish, meat, eggs, cheese and fermented foods, they can be present in high concentration (above 50 μg/g) able to induce chemical poisoning.[2]

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The most important biogenic amines found in food are: histamine, tyramine, tryptamine, phenethylamine and cadaverine, the synthesis of which occurs by decarboxylation of the precursor amino acids histidine, tyrosine, tryptophan, phenylalanine and lysine, respectively.[3]

Based on the mean content of the most toxic biogenic amines (histamine and tyramine), the food safety relevance of the considered food categories can be ranked in the following decreasing order – for histamine: 'dried anchovies', 'fish sauce', 'fermented vegetables', 'cheese', 'other fish and fish products' and 'fermented sausages'; and for tyramine: 'fermented sausages', 'fish sauce', 'cheese', 'fermented fish' and 'fermented vegetables'. Based on the consumer exposure to the most toxic biogenic amines, the food safety relevance of the considered food categories can be ranked in the following decreasing order – for histamine: 'other fish and fish products', 'fermented sausages', 'cheese', 'fish sauces' and 'fermented vegetables'; and for tyramine: 'beer', 'cheese', 'fermented sausages', 'fermented fish meat' and 'preserved meat'.[4]

Histamine is also contained in mast cells and basophils, and its biological effects are usually seen only when it is released in large amounts in the course of allergic and other reactions.[5]

Amines can be formed by transamination of aldehydes and ketones, hydrolysis of nitrogen compounds, thermal decomposition or by decarboxylation of amino acids.[6] The decarboxylation process can proceed through two biochemical pathways: decarboxylation through endogenous (naturally occurring) decarboxylase enzymes or by exogenous decomposition through enzymes released by microflora. The production of amines by the exogenous process is considered far more significant.[7]

According to their biosynthetic pathway, bioactive amines are classified into[1]:

1) Biogenic: they are formed by bacterial enzymatic decarboxylation of amino acids (histamine, serotonin, tyramine, phenethylamine, tryptamine, putrescine, cadaverine and agmatine).
2) Natural: spermine and spermidine are formed ''*in situ*'' in the cells as they are required.

It is noteworthy that since histamine is stored in mast cells, it could be classified as biogenic and natural.

There is a natural mechanism for bioactive amine catabolism. They are oxidised by amine oxidades (monoamine oxidases (MAO) and diamine oxidases (DAO)).[8] Amine oxidases are enzymes which catalyse the oxidative deamination of mono-, di- and polyamines with the formation of an aldehyde, ammonia and hydrogen peroxide: $RCH_2NH_2 + O_2 + H_2O$ $RCHO + H_2O2 + NH3$.[7]

The metabolic function of these enzymes is the breakdown of a number of biologically active amines. The enzymes are divided into two separate groups:

The first group is the flavin co-factor dependent enzymes known as monoamine oxidases (MAO).[7]

The so-called 'trace amines' are synthesised in humans from their corresponding amino acids (tyrosine, phenylalanine and tryptophan, respectively) by decarboxylation. Their catabolism is mainly mediated by monoamine oxidase (MAO). Two MAO isozymes exist, A and B, with different locations and substrate specificity. MAO-A predominates in the stomach, intestine and placenta and has polar aromatic amines (as noradrenalin and octopamine) as preferred substrates. MAO-B predominates in the brain and selectively deaminates non-polar aromatic amines (as phenethylamine and dopamine).[4]

Tyramine is a substrate for either form of MAO, MAO-A is responsible for intestinal metabolism of tyramine, thereby preventing its systemic absorption. Tyramine and phenethylamine are also subjected to N-methylation by N-methyltransferases, generating the sympathetic neurotransmitter, noradrenaline. Tyramine can be further converted into octopamine.[9]

The second group is the copper amine oxidases or diamine oxidases (DAO), which are found in animal tissue and plasma, plants, yeasts, fungi and bacteria.[7]

Humans metabolise histidine to urocanic acid through the activity of L-histidine ammonium lyase, to form glutamate and then α-ketoglutarate, which enters the citric acid cycle, or to histamine through the activity of histidine decarboxylase. There are two ways of histamine metabolism in the human body. Nitrogen in the imidazole cycle is methylated by histamine N-methyltransferase at the formation of N-methylhistamine, which is further oxidised by monoamino oxidase to N-methylimidazolylacetic acid. This enzyme is very selective for histamine detoxification and involves S-adenosylmethionine as donor of methyl group. Histamine is oxidised by diamino oxidase to imidazolylacetic acid, which is bound to ribose.[5]

The biogenic amine content of some foods has been widely studied because of their potential toxicity. Histamine has been implicated as the causative agent in outbreaks of food poisoning where intoxication results from the ingestion of foods containing excessive amounts of histamine. Tyramine and phenethylamine have been identified as the initiators of hypertension during treatment with monoamino oxidase inhibitor drugs and of dietary-induced migraine in susceptible individuals.[4]

The accumulation of biogenic amines in food depends on the availability of free amino acids and the presence of microorganisms with decarboxylase activity on amino acids.[10] Amine formation also depends on food intrinsic and extrinsic parameters such as: temperature and pH, oxygen tension, availability of carbon sources, presence of vitamins, co-enzymes, concentration of free amino acids and fermentable carbohydrates.[11]

Individual differences in enzyme activities besides varying amine concentrations in food may account for different tolerance levels.[12]

In general, increased sensitivity against biogenic amines is due to a weakened enzymatic amine degradation caused by genetic or acquired impairment of MAO, DAO, histamine-N methyltransferase (HNMT) function.[4]

Impairment of DAO activity either due to genetic predisposition, gastrointestinal diseases, or due to medication with DAO inhibitors results in high histamine blood levels, which consequently overload the internal hepatic inactivation system of histamine-N methyltransferase,[12] and leads to histamine intolerance causing numerous symptoms mimicking an allergic reaction even after the ingestion of small amounts of histamine tolerated by healthy individuals.[13]