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REVIEW

Histamine, histamine intoxication and intolerance

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Abstract Excessive accumulation of histamine in the body leads to miscellaneous symptoms mediated by its bond to corresponding receptors (H_1–H_4). Increased concentration of histamine in blood can occur in healthy individuals after ingestion of foods with high contents of histamine, leading to histamine intoxication. In individuals with histamine intolerance (HIT) ingestion of food with normal contents of histamine causes histamine-mediated symptoms. HIT is a pathological process, in which the enzymatic activity of histamine-degrading enzymes is decreased or inhibited and they are insufficient to inactivate histamine from food and to prevent its passage to blood-stream. Diagnosis of HIT is difficult. Multi-faced, non-specific clinical symptoms provoked by certain kinds of foods, beverages and drugs are often attributed to different diseases, such as allergy and food intolerance, mastocytosis, psychosomatic diseases, anorexia nervosa or adverse drug reactions. Correct diagnosis of HIT followed by therapy based on histamine-free diet and supplementation of diamine oxidase can improve patient's quality of life.

Introduction

Adverse reactions of the organism to ingested food (Fig. 1) can be divided into toxic and non-toxic, caused by specific individual intolerance of food, which is generally tolerated in healthy individuals. Based on immunological mechanisms the allergic reactions occur. The most common and most severe food allergy is IgE-mediated food allergy, which occurs in predisposed individuals – atopics. Food intolerances occur in non-immune mechanisms. They can be a result of disturbance of enzymes of gastrointestinal system or as a result of pharmacologic effects of vasoactive amines present in food.[1] One of these food intolerances is histamine intolerance, which is analysed in this review article.

Histamine and it's role in organism

Biogenic ammine – histamine (2-[4-imidazolyl]ethylamine) has been known since 1910, when it was isolated for the first time from *Claviceps purpurea* by Sir Henry Dale and his colleagues from Wellcome Laboratories.[2] Today, we know that histamine plays an important role in many physiological and pathological processes. Histamine causes contraction of smooth muscle cells, particularly the bronchi and intestine, dilation of vessels and their increased

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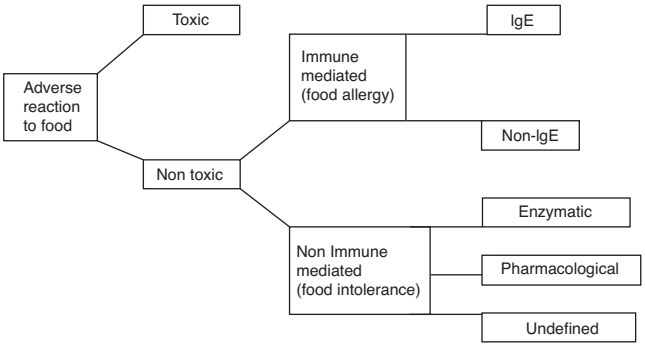

Figure 1 Adverse reactions of organism to food, EAACI classification.
Modified from 1.

permeability, increases mucosal secretion, causes tachycardia and arrhythmias, influences blood pressure, stimulates secretion of gastric juices and irritates nociceptive nerve fibres. Other important processes in which histamine is involved include neurotransmission, immunomodulation (enhanced chemotaxis of eosinophils and neutrophils, production of prostaglandins and thromboxane B, suppressed synthesis of lymphokines, etc.), haemopoiesis, wound healing, intestinal ischaemia, day-night rhythm, the regulation of histamine- and polyamine-induced cell proliferation and angiogenesis in tumour models.[3,4] Pleiotropic effects of histamine are mediated by its bond to membrane receptors of different cell types. Presently, there are four subtypes of histamine receptors described: histamine receptor 1 (H_1R), histamine receptor 2 (H_2R), histamine receptor 3 (H_3R) and histamine receptor 4 (H_4R). All these receptors belong to a family of receptors coupled with G-proteins. They are heptahelical transmembrane molecules, which act as transducers of extracellular signals via G-protein and intracellular system of second messengers.[5]

Endogenous sources of histamine in organism

Histamine originates in decarboxylation of amino acid histidine mediated by enzyme L-histidine decarboxylase, which contains pyridoxal phosphate (vitamin B6).[6] The name histamine comes from Greek *histos* – tissue, because it is present in many tissues of organism. It was isolated from liver and lung samples in 1927 by Best et al.[7] Classical sources of histamine in the organism are gastric enterochromaffin cells, histaminergic neurons, mast cells and basophils, which store histamine in intracellular vesicles, from where it is released upon stimulation. It is known that degranulation of mast cells and histamine release is a result of bonding of specific antigen to FcεRI receptor, which can be inhibited by luteolin (flavonoid with antioxidant properties).[60] Activation of mast cells can also occur in non-immune stimuli, such as neuropeptides (substance P), parts of complement system (e.g. C3a and C5a), cytokines (IL-1, IL-3, IL-8, and GM-CSF), platelet activating factor (PAF), hyperosmolarity, lipoproteins, adenosine, superoxidases and hypoxia. Many chemical and physical factors can be responsible for histamine release as well, for example extreme temperatures, trauma, vibrations or alcohol and some certain types of food and medication.[8] Mast cell activation plays a crucial role in the pathogenesis of many diseases – not only allergic, but autoimmune as well, such as rheumatoid arthritis.[61] Ability of de novo synthesis of histamine is also present in other cell types, e.g. platelets, monocytes/macrophages, dendritic cells, neutrophils and lymphocytes.[9]

Exogenous sources of histamine

Apart from endogenous production, histamine is introduced to the organism from exogenous sources by ingestion of some types of food, where histamine is naturally present in a high concentration. Histamine in exogenous sources can be synthesised by microbial decarboxylation of histidine by different fermenting bacteria, including natural human flora in the gut. Some bacteria are able to decarboxylate histidine in temperatures around +4 °C. To prevent histamine contamination of food the cooling is insufficient, freezing and early liquidation of viable bacteria is necessary. Due to thermostability, histamine which is present in food is almost irremovable. Some types of food contain naturally high amount of histamine (cocoa, spinach, tomatoes, ...). A high content of histamine is present in foods which originate by fermentation, either spontaneous or targeted (fermentation of alcoholic beverages – beer, wine; fermented vegetables, cheeses, meat, soy, yoghurt, ...). It is also important not to forget bacterial contamination of food when stored improperly.[10] The ability to produce histamine is present in Gram-positive, as well as Gram-negative bacteria. Many Gram-negative bacteria with this ability are common contaminants of food. From fish, ingestion of which caused histamine intoxication, the strains of *Hafnia alvei, Morganella morganii, Klebsiella pneumoniae, Morganella psychrotolerans, Photobacterium phosphoreum* and *Photobacterium psychrotolerans* were isolated. In fermented foods, the strains of *Oenococcus oeni, Pediococcus parvalus, Pediococcus damnosus, Tetragenococcus species, Leuconostoc species, Lactobacillus saerimneri 30a, Lactobacillus hilgardii, Lactobacillus buchnerii* and *Lactobacillus curvatus* are responsible for histamine production. Furthermore, it was discovered that for the contamination of ingredients in manufacturing process of wine and histamine production the strains of *Lactobacillus parabuchneri*, or *Lactobacillus rossiae* are responsible.[11] Enzymatic activity of histidine decarboxylase can last even after bacterial autolysis.[12]

Histamine degradation

Based on localisation, histamine can be inactivated by two processes – oxidative deamination of primary aminogroup to imidazolacetaldehyde, catalysed by enzyme diaminooxidase (DAO, histaminase)[13] or methylation of imidazole core to N4-methylhistamine catalysed by enzyme histamine N-methyltransferase (HNMT).[14] For proper function of DAO enzyme its cofactors are important – vitamins B6 and C and copper. DAO protein, stored in vesicular structures, bonds to plasma membrane of cells and is released in circulation after stimulation and is responsible for degradation of extracellu-