Introduction

Histamine is an organic compound that is involved in many processes in the body. It can be produced within the human body or ingested in foods. In humans, histamine is synthesized in several cells, including mast cells, basophils, platelets, histaminergic neurons, and enterochromaffin cells. It is stored intracellularly in vesicles, and released on stimulation. It can bind to one of its four known receptors, that have actions in the gut, central nervous system, skin, respiratory tract, cardiovascular system, uterus, and bone marrow. While histamine is often thought of as a key player in allergic reactions, it also plays many other important roles in the body. It is a neurotransmitter that mediates attention and arousal, and a stimulant of gastric acid secretion from parietal cells in the stomach.

Regardless of whether it was endogenously produced or ingested in foods, histamine is metabolized by several enzymes; however, in some individuals, the consumption of high-histamine-containing foods as well as alterations in the metabolic pathways can lead to histamine intolerance. Histamine intolerance, also known as histaminosis, is defined as a disequilibrium between accumulated histamine and the capacity for histamine degradation. The prevalence of histamine intolerance in the general population is estimated to be 1% by some authors.

Metabolism

The two main enzymes that metabolize histamine are diamine oxidase (DAO, previously known as histaminase) and histamine N-methyltransferase (HNMT). Studies have shown that DAO is important for inactivation and scavenging of extracellular histamine, whereas HNMT is a cytosolic enzyme that is responsible for inactivation of intracellular histamine. Both enzymes are expressed in a number of tissues, with DAO being...
expressed predominately in the gut,[5] while HNMT is expressed almost ubiquitously.[4] DAO plays a key role in the metabolism of ingested histamine,[6] likely due to its presence in the gut.

Histamine in Food
As mentioned, histamine and several other biogenic amines have been found to occur naturally in many foods. They can also be produced in food by bacteria as part of the production process, or during storage or decay.[7] Foods that contain considerable amounts of histamine are typically fermented foods such as certain cheeses, meats, beer, and wine.[8][9] However, some vegetables also naturally contain histamine, as well as a number of fish.[9] It has been suggested that some foods, such as citrus, increase the release of histamine from the body, even though the foods themselves contain very little histamine.[1]

Histamine Intolerance
Symptoms of histamine intolerance vary widely, which is not surprising, since histamine has actions at many sites in the body. The main symptoms are diarrhea, sneezing, rhinorrhea and congestion of the nose, headache, pruritus, flushing, asthma, hypotension,[10] urticaria,[11] and arrhythmias.[12]

Many of the symptoms of histamine intolerance mimic those of an IgE-mediated allergic response; therefore, skin-prick tests are often conducted, but no triggers found.[9] The mechanism of IgE-mediated allergy is different in that in IgE-mediated allergy, the reaction is due to cross-linking of antibodies and only a small amount of the allergen is needed, whereas histamine intolerance is based on an imbalance between the buildup and breakdown of histamine. The cumulative amount of histamine in the body is a key factor in histamine intolerance.[1]

Mechanism
Ingesting large quantities of foods high in histamine is one way to precipitate the symptoms of histamine intolerance, although researchers have noted that it may be hard to clearly blame histamine, as foods containing histamine often contain other biogenic amines or additives.[13] However, consuming a diet low in histamine has been shown to help with a reduction of symptoms.[9]

Insufficient degradation of histamine in the body, due to impaired activity or inhibition of the enzymes, is the other causative factor of histamine intolerance. Alcohol, aside from
possible histamine content of certain types, can also affect histamine accumulation by altering the metabolism. It was found that alcohol inhibits DAO,[14] which would lead to decreased metabolism of histamine. Certain drugs have also been found to alter the metabolism of histamine, including a number of medications used in an intensive-care setting, such as cephalosporin antibiotics.[15][16]

Low production of DAO in the gut due to intestinal damage has been found.[17] In a study conducted by Raithel et al, individuals with food allergy (other GI diseases ruled out by colonoscopy) were found to have diminished DAO activity in certain parts of the intestines.[17] In individuals suffering from inflammatory bowel diseases, tissue samples from diseased mucosa revealed significantly lower DAO activity when compared to healthy tissue.[18][19] Plasma levels of DAO have been positively correlated with the maturity and integrity of the intestinal mucosa,[20] suggesting that a compromised gut could precipitate histamine intolerance.

Another cause of suboptimal DAO and HNMT functioning could be due to genetics. Studies have shown genetic polymorphisms of DAO and HNMT play a role in the expression and activity of the enzymes.[21][22] These polymorphisms have been found in individuals that suffer from a variety of inflammatory intestinal diseases, further suggesting a link between intestinal damage and suboptimal DAO production.[23]

**Diagnosis**

The diagnosis of histamine intolerance remains difficult. Schwelberger et al suggested that diagnosis should start with careful recording of symptoms after food consumption, identification of causative foodstuffs, and determination of their histamine content.[30] They also suggested that a definitive diagnosis necessitates double-blind, placebo-controlled oral histamine provocation with determination of plasma histamine concentrations and objective physical parameters, such as heart rate, blood pressure, and erythema.[6] A recent study by Music et al analyzed serum DAO levels from 316 individuals with clinical signs of histamine intolerance.[24] They found that DAO activity in patients was much lower than in healthy controls, and the patients with highly reduced DAO activity had severe typical symptoms of histamine intolerance after the intake of histamine-rich food. The main symptoms involved the skin, gastrointestinal tract, respiratory system, and eyes. Results of this study suggest that determining DAO activity in serum is a useful tool in diagnosing histamine intolerance.[24] Komericki et al failed to reproduce single symptoms after challenge with oral histamine ingestion in preselected histamine sensitive patients.[13] Knowing that symptoms of histamine intolerance vary widely, along with evidence from the previously mentioned study, suggests that single symptoms alone are not appropriate to diagnose histamine intolerance, whereas a global symptom score would be more appropriate.[13]
Recent Research
While randomized controlled trials are limited, a few more recent studies have investigated the relationship between histamine intolerance and dermatologic concerns. Worm et al evaluated the role ingested histamine plays in the severity of atopic dermatitis. They concluded that high amounts of ingested histamine may aggravate eczema in approximately 30% of patients with atopic dermatitis. Maintz et al reported that symptoms of histamine intolerance were significantly more common in patients with atopic eczema than in controls. They found that a histamine-free diet could reduce symptoms of histamine intolerance and severity of atopic eczema in this population. Similarly, Chung et al have shown that a low-histamine diet may be beneficial in the treatment of atopic dermatitis.

Treatment
Treatment options for suspected histamine intolerance could include a histamine-free or histamine-reduced diet as previously mentioned. Jarisch et al suggest a minimum of four weeks of elimination, along with 14 days of taking an H1 antihistamine medication. There is some concern, as it was found that some antihistamine medications further inhibit DAO activity, specifically cimetidine, a histamine H2-receptor antagonist. Avoiding substances that inhibit DAO or HNMT should be part of treatment. Studies have shown that taking an oral supplement of DAO (extracted from pig kidneys), compared to placebo, led to a statistically significant reduction of total symptom scores. Supporting the activity of DAO by supplementing with pyridoxal phosphate (vitamin B₆) may also be useful.

Conclusion
While the concept of ingested histamine playing a role in the development of an array of symptoms has been noted since the 1980s, sound research has been sparse. In patients with a variety of seemingly unrelated symptoms, initiated by foods that are typically high in histamine content (most notably fermented foods), histamine intolerance should be suspected. Other
factors such as alcohol consumption, drug use, and possible intestinal damage could be impacting DAO levels, therefore should also be considered. Further research investigating the pathophysiology as well as treatment options, specifically those related to improved DAO enzyme production and function, would be useful.

References


