

Foods Matter Newsletter

Histamine intolerance

It Feels Like Allergy ... It Looks Like Allergy ... But It's Not An Allergy! Dr Dr Janice Joneja reveals a histamine intolerance case study, and has some advice for sufferers.

Laura is a 37 year old teacher, who came to me with the following problem:

"About two years ago I started to break out in hives, and my face became red and puffy, mostly after I ate in restaurants. Now I am often itchy, and break out in hives for no reason. Sometimes I get hives and a swollen face after eating; sometimes I wake up in the morning with my eyes swollen and my whole body itches. I seem to have heart palpitations, even when I am not particularly active. My heart races and I feel hot and clammy as if I might have a heart attack, or perhaps I'm having a panic attack. I also seem to have headaches more often than before. I thought I was allergic to food so I went for allergy testing, but everything came back negative. I have never had allergies, but I wonder what is happening? – and why now when I am 37 years old and have always been healthy except for a bad infection I had about 3 years ago."

This was my answer:

The symptoms you describe, and the type of pattern of onset, seems to suggest that you are dealing with histamine excess. Excessive histamine, from a variety of different sources, will result in symptoms often indistinguishable from allergy. This is not surprising since the early symptoms of an allergic reaction are mediated by the histamine released during the progress of the allergic response. The question is, of course, why are you experiencing symptoms of histamine excess now?

The key to your problem is possibly the "bad infection" you had about three years ago. I assume you had at least one course of antibiotics, although you do not give details of the infective micro-organism and the treatment you received. It is possible that the infective organism, and/or any antibiotics you may have taken at the time, caused a change in the bacteria that inhabit your large bowel. The bacteria now in your intestines may be the types that make histamine from incompletely digested food materials that pass into the bowel. This can result in more histamine entering your body than previously, and augmenting both your natural histamine (that we require for a various functions in the brain and digestive tract as well as processes in the immune system), and histamine in your diet.

Of course, there may be a number of other reasons why you are suddenly faced with excessive histamine in your body – a situation that we sometimes refer to as "histamine intolerance". It is a complex process, and we are only just beginning to understand the various aspects of the problem, but I'll explain what we know so far, and what you can do to help your symptoms.

Let us start at the begin with the question:

What are **Symptoms of Histamine Excess?**

Whatever the source of histamine, when the total body level exceeds the enzymes' capacity to break it down, symptoms of histamine excess occur. Histamine intolerance manifests itself in a variety of signs and symptoms such as:

- Pruritus (itching especially of the skin, eyes, ears, and nose)
- Urticaria (hives) (sometimes diagnosed as "idiopathic urticaria")
- Tissue swelling (angioedema) especially of facial and oral tissues and sometimes the throat, the latter causing the feeling of "throat tightening" (sometimes diagnosed as "idiopathic angioedema")
- Hypotension (drop in blood pressure)
- Tachycardia (increased pulse rate, "heart racing")
- Symptoms resembling an anxiety or panic attack
- Chest pain
- Nasal congestion and runny nose
- Conjunctivitis (irritated, watery, reddened eyes)
- Some types of headaches that differ from those of migraine
- Fatigue, confusion, irritability
- Very occasionally loss of consciousness usually lasting for only one or two seconds
- Digestive tract upset, especially heartburn, "indigestion", and reflux

Not all of these symptoms occur in any single individual, and the severity of symptoms varies, but the pattern of symptoms seems to be consistent for each person.

Histamine and Eczema

In addition to the symptoms listed above, excess histamine can make some existing conditions worse. Eczema is an example. Eczema is an inflammatory condition in the skin, sometimes called atopic (allergic) dermatitis. When high histamine foods are consumed, people with less than efficient histamine tolerance may experience an increase in the severity of their eczema.

Histamine and Anaphylaxis

There is some evidence to suggest that people who are prone to recurrent anaphylactic (severe allergic) reactions may be experiencing histamine intolerance in addition to their allergies. In such situations the histamine released in the allergic response quickly rises to a dangerously high level, leading to a situation that may be life-threatening.

Histamine and Hormones

Histamine-intolerant women often suffer from the symptoms listed above, especially headaches and menstrual pain, during certain phases of their menstrual cycle. Histamine levels tend to fluctuate with the level of hormones, especially oestrogen, at ovulation and just prior to the onset of menstruation. In contrast, many women with both allergies and histamine intolerance find significant relief of their symptoms during pregnancy; this is

because the placenta makes a great deal of DAO, the enzyme that breaks down histamine. The result is that the level of histamine no longer exceeds the woman's tolerance threshold, and she remains blissfully free from her symptoms throughout her pregnancy. Unfortunately, the symptoms tend to recur once the DAO from the placenta is no longer available after the birth of her child.

Histamine and Medications

Some medications can release histamine; others can reduce the effectiveness of the enzyme (diamine oxidase) that breaks down histamine. As a result, the level of histamine rises and may cause symptoms, even in a person who has shown no signs of histamine intolerance in the past. Common pain killers such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), some diuretics ("water pills"), antibiotics, and antidepressants are among the medications that can affect the functioning of DAO. A list of medications that either release histamine, or decrease the effectiveness of DAO can be found in Reference 6.ning with the question ...

And now the background questions:

What is Histamine?

Histamine is an extremely important bioactive chemical (a natural chemical that acts in the body) that is indispensable in the efficient functioning of many body systems. It is a neurotransmitter (a chemical that conveys messages between cells of the nervous system) and is involved in the regulation of stomach (gastric) acid, the permeability of blood vessels, muscle contraction, and brain function. Histamine appears in various concentrations in a range of mammalian tissues. In humans, the highest histamine concentrations are found in the skin, lung, and stomach, with smaller amounts in the brain and heart.

Histamine is also essential in defending the body against invasion by potentially disease-causing agents such as bacteria, viruses and other foreign bodies.

Histamine is made and stored within white blood cells (leukocytes) such as mast cells in tissues and basophils that circulate in blood. When the immune system is activated in response to foreign material entering the body, histamine is the first "defense chemical", or more correctly, *inflammatory mediator* released in the process called inflammation. Inflammation is the clinical evidence that the immune system is responding to a potential threat to the body. Histamine is always present when inflammation occurs, and excess histamine will result in symptoms that resemble inflammation.

In addition to its role in controlling vital body processes and defending against foreign invaders, histamine is a key mediator in the symptoms of an allergic reaction. Since allergy is essentially an inflammatory reaction, histamine, together with other protective inflammatory mediators is released in response to the allergen. Allergens are components of living cells that in themselves are harmless, such as plant pollens, animal dander, mould spores, dust particles, dust mites, and foods. An allergic reaction to these "foreign

but harmless" substances occurs when the immune system mistakes these innocuous materials for a potential threat.

How Much Histamine is Excessive?

Histamine levels of 0.3 to 1.0 nanograms per millilitre (ng/mL) in plasma are considered to be normal. Everyone has a level of histamine that they tolerate without symptoms. Exceeding that level (called a person's "limit of tolerance" or "tolerance threshold") can result in symptoms. Even healthy persons may develop severe headache, or flushing as a result of consuming massive amounts of histamine in a meal, but if ingested at lower concentrations only a few sensitive individuals will experience an adverse reaction. It has been speculated that the differences in the level of histamine that people can tolerate may be of genetic origin. In addition, disease, various abnormal physiological conditions, hormone changes, especially in women at various stages in the menstrual cycle and at menopause, and medications, can reduce the tolerance threshold of any individual. People with a low tolerance threshold are designated "histamine intolerant".

What Causes an Individual to be Histamine Intolerant?

Several abnormal physiological conditions may lead to histamine intolerance, in particular a defect in the process of histamine breakdown (called *catabolism*). Under normal physiological conditions excess histamine is degraded by two enzyme systems: histamine N-methyl transferase (HMT), and in the intestine by the mucosal enzyme diamine oxidase (DAO). Of the two systems, it is deficiency in the DAO enzyme system that has received most attention as the probable cause of "histamine intolerance".

Under normal conditions, when histamine levels from any source rise above a certain level, these enzymes rapidly degrade the excess. However, when the rate of breakdown of excess histamine is insufficient to deal with the excess, the total level of histamine in the body rises. At a certain critical level, signs and symptoms occur that are the result of histamine coupling with histamine receptors on specific cells, producing a clinical picture that is often indistinguishable from allergy.

How Can Histamine Intolerance be Distinguished from Food Allergy?

Food allergy is a hypersensitivity reaction of the immune system that is caused when antibodies of the IgE type are produced against a specific food protein, called an allergen. When the allergenic food is consumed by the person who is sensitised to it (i.e. whose immune system has produced IgE to the food on a previous occasion in an inappropriate attempt to protect the body from a perceived threat), inflammatory mediators (chemicals that cause or mediate inflammation) are immediately released. This results in the onset of symptoms usually within minutes of the food entering the body. So an allergic reaction to a food leads to the immediate appearance of symptoms, and in response to the mere presence of the allergen, however small the dose might be. In contrast, symptoms of histamine intolerance, although they may be the same in type, take time to appear and are not evident immediately after histamine-rich foods and beverages are consumed. This is because the level of histamine needs to reach a certain critical level before the tissues

respond. Thus, a small amount of histamine will not cause a response – it is the total amount of histamine in the body, in excess of the body's requirements, that causes the reaction. It is like filling a bucket with water. Everything is fine until the water level reaches the top of the bucket and overflows. Then your feet get wet! It is the overflowing of histamine that results in the symptoms. For this reason, tests designed to provoke and measure an immediate response, such as the "gold standard for allergy", the double-blind, placebo-controlled food challenge (DBPCFC), will not detect histamine intolerance. Often symptoms will appear several hours after consumption of histamine-rich foods, as the total level of histamine in the body gradually rises and overwhelms the enzymes' capacities to break it down. Thus the association between cause and effect is often difficult to demonstrate in histamine intolerance.

Where Does Histamine Come From?

Body Cells and Systems (*Intrinsic histamine*)

Histamine is a *biogenic amine* (sometimes referred to as a *vasoactive amine*) that, in mammals, including humans, is produced primarily by the action of the enzyme histidine decarboxylase on the amino acid histidine. Histidine is one of the 20 or so amino acids that combine together to make a protein. Histidine decarboxylase is present in large quantities in leukocytes known as granulocytes (granule-containing cells), especially tissue mast cells and blood basophils. In these cells it converts histidine to histamine. The newly formed histamine is then stored in structures within the cell (the intracellular granules) in readiness for release in response to signals from a variety of body systems. In inflammation, whether produced in defending the body from injury or infection, or as a result of an allergic reaction, these signals come from lymphocytes, cytokines and antibodies. However, this is not the only source of histamine in our bodies.

Microorganisms in the Large Bowel

There are a large number of microorganisms that are capable of producing histamine. Many of the bacteria that live in the human large bowel produce histidine decarboxylase and are capable of converting the histidine in any protein that enters the bowel into histamine. Therefore, the more microorganisms that produce histidine decarboxylase that are present in the colon, and the greater the amount of protein material that enters the bowel, the higher the level of histamine in the digestive tract. From here, histamine can be conveyed through the bowel wall to various sites in the body.

Histamine in Natural Foods (*Extrinsic histamine*)

Another source of pre-formed histamine is the food we eat. Microorganisms capable of converting histidine to histamine exist ubiquitously in nature, so histamine can arise from various sources. For example, histidine decarboxylase-producing bacteria colonise the gut of fish. As soon as a fish dies, the gut bacteria start to break down the tissue proteins, releasing histidine, which is then rapidly converted to histamine. Since bacteria multiply rapidly, it is possible that the level of histamine in the ungutted fish can double every twenty minutes. The longer a fish remains ungutted after it dies, the higher the level of

histamine in its tissues. Furthermore, since shellfish are not gutted after harvesting, the bacteria in their gut will produce histamine as long as the fish remain uncooked. Many a reaction to fish or shellfish has been blamed on allergy, when in reality it was a reaction to an exceedingly high level of histamine in an incorrectly processed fish.

Histamine in Manufactured Foods

There are a number of food manufacturing processes that depend on the production of amines and similar chemicals for the flavour and nature of the food. Any process that requires microbial fermentation will result in the production of relatively high levels of amines, especially histamine. Cheese of all types, alcoholic beverages, vinegar, fermented vegetables such as sauerkraut, fermented soy products such as soy sauce, and processed meats such as pepperoni, bologna, salami, and frankfurters that are produced by a process of fermentation, all contain substantial levels of histamine.

Other Food Sources of Histamine

Certain foods seem to contain high levels of histamine in conditions where microbial fermentation is an unlikely event. Histamine has been consistently detected in fruits such as citrus fruits, berries such as strawberry and raspberry, tomatoes, several types of tree fruits such as apricot, cherry and plums, and some vegetables, particularly aubergine, and pumpkin. Some preliminary research studies have indicated that histamine may be produced during ripening in tomatoes, and it may be that some, if not all fruits that go through a similar process produce histamine in the course of ripening. It remains for future research to explain this phenomenon.

Histamine derived from foods by unknown mechanisms

Traditionally, certain foods have been said to have "histamine-releasing" properties because ingestion of the food tends to result in symptoms of histamine. For example, egg white is a food that is frequently referred to as "histamine-releasing", separate and distinct from its activity as an allergen. Strawberries, raspberries and shellfish were previously similarly designated, but more recent research has uncovered evidence of physiological and biochemical processes as the origin of histamine from these foods (see above). However, a non-allergic mechanism of histamine release by egg white remains to be determined.

Another mode of histamine release associated with food materials is suggested by research into the mechanisms of intolerance associated with food additives. Azo (nitrogen-containing) food dyes such as tartrazine, and preservatives such as benzoates, sorbates, and possibly sulphites have been suggested to release histamine by as yet undisclosed processes. Clinical experiments have demonstrated that persons sensitive to these chemicals experience an increase in plasma histamine that remains elevated long after histamine levels in the non-reactive person have returned to normal. Again, an understanding of the way in which histamine is released in such reactions will depend on future research.

How Can Diet Help in Reducing Excess Histamine?

The degree of improvement or resolution of the symptoms of histamine excess that can be achieved by diet alone will depend on whether the food sources of histamine can be reduced below a person's limit of tolerance. The histamine-restricted diet detailed below is designed to exclude all known food sources of histamine. However, some people will not achieve relief by diet alone because even by excluding all of the histamine-rich foods their total level of histamine still exceeds their enzymes' capacity to break it down. In these cases taking antihistamines often helps.

A person with histamine intolerance will typically experience a constant fluctuation in the signs and symptoms of histamine excess in response to changing conditions. For example, when a person is experiencing allergy to air-borne allergens such as seasonal pollens, the histamine released in the allergic response alone might put them into the symptom range. In such a case, avoiding histamine-associated foods will no longer relieve their symptoms because their total level of histamine will remain above their limit of tolerance. This explains the observation that during their "pollen allergy season" many people find themselves reacting to foods (usually histamine-rich foods) that they could normally eat with impunity.

As a result of the multiple factors contributing to excess histamine, combined with each individual's capacity to deal with histamine excess, symptoms of histamine intolerance are constantly changing in incidence and severity. Unlike an allergy in which the presence of the antigen results in an immediate immunological response and development of typical symptoms, histamine intolerance is frequently baffling because a specific food does not always result in clinical symptoms. Therefore, it is not possible to eliminate just those foods that cause a reaction. It is necessary to restrict a person's intake of histamine-associated foods to a total that remains below their personal limit of tolerance. This usually requires following the histamine-restricted diet for the long term if a histamine-intolerant person wishes to remain symptom-free.

The guidelines for the histamine-restricted diet are provided in the Table. It is important for anyone following a diet that restricts important nutrients to obtain complete balanced nutrition by substituting foods of equal nutritional value to those restricted. It is a good idea to enlist the help of a registered dietitian in this process. Full details of the histamine-restricted diet with suggestions for substitutions can be found in Reference 4.

The Histamine Restricted Diet

DO NOT EAT THE FOLLOWING FOODS

Meat, Poultry, Fish

Fish and shellfish whether fresh, frozen, smoked, or canned, if processing is unknown

- If the fish is freshly caught, gutted and cooked within ½ hour, it may be eaten

Egg

- a small quantity of cooked egg in a baked product such as pancakes, muffins, cakes is allowed

Meat

- Processed, smoked and fermented meats such as luncheon meat, sausage, wiener, bologna, salami, pepperoni, smoked ham, cured bacon
- Avoid left-overs: freeze any uneaten protein-based food. Bacteria will quickly act on protein at room and refrigerator temperatures, resulting in histamine production

Milk and Milk Products

All *fermented* milk products, including:

- Cheese: any kind of fermented cheese such as Cheddar, Cheshire, Colby, Blue cheese, Brie, Camembert, Feta, Romano, etc.
- Cheese products such as processed cheese, cheese slices, cheese spreads
- Cottage cheese
- Ricotta cheese
- Yoghurt
- Buttermilk
- Kefir

Fruit

- Orange, grapefruit, lemon, lime, cherries, grapes, strawberries, apricots
- Raspberries, pineapple
- Cranberries, prunes
- Loganberries, Dates
- Raisins, currants (fresh or dried)
-

Vegetables

- Tomatoes, tomato sauces, ketchup, soy and soy products
- Spinach, red beans
- Eggplant, olives in vinegar or brine
- Pumpkin, avocado
- Pickles, relishes and other foods containing vinegar

Food Additives

- Tartrazine and other artificial food colours
- Preservatives, especially Benzoates and Sulphites

Note: Many medications and vitamin pills contain these additives; ask your physician or chemist to recommend additive-free supplements and medications

Seasonings

- Cinnamon, cloves, vinegar
- Chilli powder, anise
- Curry powder, nutmeg

Miscellaneous

- Fermented soy products (such as soy sauce, miso)
- Fermented foods (such as sauerkraut)
- Tea (regular or green)
- Chocolate, cocoa, and cola drinks
- Alcoholic beverages of all types
- "Dealcoholised" beverages (e.g. beer, ale, wine, etc)

References

1. Dyer J, Warren K, Merlin S, Metcalfe DD, Kaliner M. Measurement of plasma histamine: description of an improved method and normal values. *J Allergy Clin Immunol* 1982;70:82-87
2. Hershko AY, Dranitzki Z, Ulmanski R, Levi-Schaffer F, Naparstek Y. Constitutive hyperhistaminaemia: a possible mechanism for recurrent anaphylaxis. *Scand J Clin Lab Invest* 2001;61:449-452

3. Jarisch R, Wantke F. Wine and headache. *Int Arch Allergy Immunol* 1996;110:7-12
4. Joneja, J.M.Vickerstaff Biogenic Amines Intolerance; Histamine. In: *Dealing with Food Allergies: A Practical Guide to Detecting Culprit Foods and Eating a Healthy, Enjoyable Diet* Bull Publishing Company, Boulder, Colorado. May 2003 ISBN 0-923521-64-X Pages 233-246
5. Joneja JMV and Carmona Silva C. Outcome of a histamine-restricted diet based on chart audit. *Journal of Nutritional and Environmental Medicine* 2001;11(4):249-262
6. Maintz L, Novak N. Histamine and histamine intolerance. *Am J Clin Nutr* 2007;85:1185-1196
7. Wohrl S, Hemmer W, Focke M, Rappersberger K, Jarisch R. Histamine intolerance-like symptoms in healthy volunteers after oral provocation with liquid histamine. *Allergy and Asthma Proc* 2004;25(5):305-311
8. Worm M, Fiedler EM, Dolle S, Schink T, Hemmer W, Jarisch R, Zuberbier T. Exogenous histamine aggravates eczema in a subgroup of patients with atopic dermatitis. *Acta Derm Venereol* 2009;89(1):52-56

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