Education News

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FOOD ALLERGIES, INTOLERANCES AND SENSITIVITIES: THE HISTAMINE CONNECTION

A naturopathic approach to histamine intolerance

Have you, or maybe someone you know, ever experienced one or more of the following symptoms? Painful digestive cramps, bloating, diarrhoea, acid reflux, flatulence, Irritable Bowel Syndrome (IBS), itchy skin, runny nose, swelling lips, sneezing, coughing, asthma-type symptoms, high blood pressure, heart palpitations, headaches, migraines, dizziness, chronic fatigue, painful periods, nervousness, anxiety, sleep disturbances, brain fog. These symptoms typically appear just after eating certain foods and may persist for hours. However, for some people the symptoms may not manifest for hours after eating making it difficult to pinpoint the offending food.

Maybe beacuse of these symptoms you have personally followed, or suggested, a type of elimination diet, removing common allergenic foods such as gluten and dairy. To confirm this you may have taken, or perhaps recommended, a food allergy or intolerance test, which can reveal positive (reactive) foods. Alternatively, some tests show no reaction to many or even all of the foods tested. However, even with elimination diets or negative food allergy and intolerance tests, symptoms as described above may still persist. For example, it's now known that IBS affects up to 1 in 5 people[1] and up to 25% of the UK population experience food sensitivities and intolerances after consumption of specific foods.[2] So what is the link between these allergy-type symptoms?

HISTAMINE INTOLERANCE – THE MISSING LINK?

Naturopaths are trained to recognise the fundamental importance of an alkalising diet to support healing, health and wellbeing.[5] Foods and drinks are carefully balanced in naturopathic nutrition programmes, alongside other holistic techniques, to provide nutrients to support congestion, stagnation, depletion and deficiency problems, ultimately providing a natural way to address the root causes of dis-ease.[6]

Certain foods or food components, for example gluten, can greatly exacerbate and even cause many states of dis-ease. In fact there has been a rapid rise in the number of health problems linked to consumption of nutrient-poor diets and heavily processed foods, which is now recognised as a greater risk to health than smoking![7,8] Allergies and intolerances are just one of a growing number of health concerns in the UK.[2]

An allergy is the response of the body's immune system to a normally harmless substance, such as pollen (e.g. from grasses or trees), specific food components (e.g. proteins like gluten), moulds, fungal spores, pet dander and house dust mites. In susceptible individuals, the immune system identifies the allergen as a "threat" and mounts specific immune responses mediated by different antibody proteins (e.g. Immunoglobulin E, IgE, or Immunoglobulin G, IgG); levels of which can be detected using skin prick or blood tests. But what causes the symptoms when antibody production is triggered? IgE reactions lead to release of histamine from mast cells, which are ubiquitous in the body especially in mucosal tissues exposed to the external environment including the stomach, digestive tract, lungs, skin, nose, eyes, mouth and throat, as well as the brain. Histamine actions on these tissues leads to the classic allergy symptoms as described.

However, allergy-type symptoms can also occur without a detectable immune-mediated IgE response, commonly referred to as a food sensitivity or intolerance. Elimination diets removing allergenic foods, such as gluten and dairy, may help manage the symptoms to a degree but they do not provide the nutrients, enzymes and bacteria needed to support and heal the affected tissues and pathways, such as those in the gut and immune system that are affected in food allergies and intolerances. So if food intolerances and sensitivities can be immune and non-immune mediated, what is the connection to these irritating and sometimes debilitating symptoms?

According to the National Institute of Allergy and Infectious Diseases based in the USA, a **food intolerance** occurs when:

1. Your body lacks a particular enzyme to digest nutrients.
2. Nutrients are too abundant to be digested completely.
3. A particular nutrient cannot be digested properly.

Histamine is one such nutrient that occurs in high levels in certain foods (Table 1), as well being synthesised in body tissues, and requires specific enzymes, namely histamine N-methyl-transferase (HMT)[9,10] and diamine oxidase (DAO), to degrade it. DAO is mainly present in the small intestines and acts naturally to reduce adverse responses to exposure of dietary (exogenous) sources of histamine.[11,12] Studies suggest that Histamine Intolerance (HIT) occurring from high levels of histamine exposure, coupled with low activity of intestinal DAO is a major cause of non-immune mediated food intolerances and sensitivities (Figure 1) contributing to common symptoms such as gastrointestinal (GI) bloating and/or cramping, diarrhoea, sneezing and runny nose.[13] In fact HIT is becoming increasingly prevalent in the population and could be one of the reasons why allergy-type symptoms persist even in light of no detectable IgE or IgG responses in food allergy skin prick or blood tests.[14,15] High levels of histamine can also contribute to conditions including urticaria (a dis-ease of the skin), asthma, Premenstrual Syndrome panic disorders and schizophrenia. Naturopaths view the origination of many chronic diseases as changes in gastrointestinal (GI) health and function (e.g. food intolerances, dysbiosis and IBS), then reflecting in the skin and other organs including the lungs and brain. This means HIT could be one of the essential factors to consider when investigating the development and progression of chronic, non-infectious dis-ease. Of course, in chronic health conditions no one factor can be singled out as the sole cause, but identifying and removing obstacles, such as high histamine exposure, and providing optimal nutrition via a naturopathic alkalising diet[16] supported with suitable enzymes, nutrients, fatty acids and bacteria can re-establish the pathways for more profound long-term body generated healing.

THE HISTAMINE CONNECTION

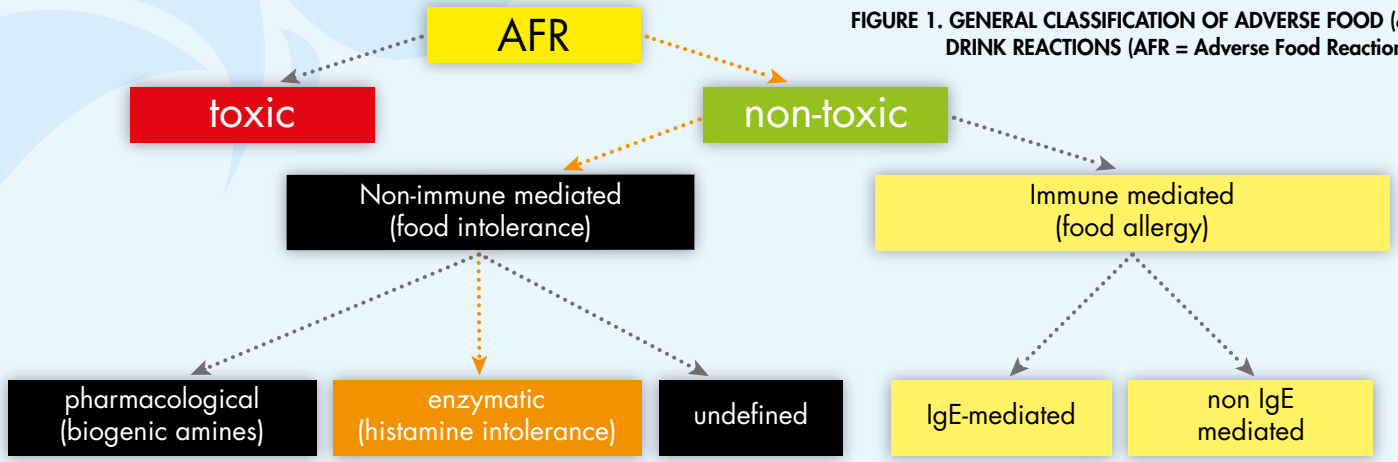


FIGURE 1. GENERAL CLASSIFICATION OF ADVERSE FOOD (& DRINK REACTIONS (AFR = Adverse Food Reaction)

Histamine is a potent mediator of numerous physiological and pathological processes throughout the body.[18,19,20] The name derives from the Greek histos – meaning tissue, because it is present in many tissues, as well as found in high levels in certain foods (Table 1).

Histamine exerts its effects by binding to four specialist receptors throughout different organs and body tissues causing:

- Increased smooth muscle contractions especially in the lung and intestine.
- Dilation and increased permeability of blood vessels.
- Increased mucus secretion especially in the gut, nasal or lung mucosa.
- Alterations in blood pressure and increased heart rate (tachycardia).
- Pain (nociceptive) fibre stimulation.
- Increased gastric juice secretion.
- Chemical signalling within the brain (including circadian rhythms like the sleep-wake cycle)
- Inflammation.

Histamine can be made in the body by specific tissue enzymes converting the amino acid histidine into active histamine.[21] It is produced by a wide variety of cells including mast cells, which store and release large quantities of histamine when stimulated by immune system mediators like IgE and IgG, or non-immunological stimuli like chemical and physical factors (e.g. extreme temperatures and trauma), alcohol, certain foods and drugs (Table 3).[22] Mast cell activation plays a crucial role in the development and progression of many health problems including allergies like hayfever, asthma and food allergies, Irritable Bowel Syndrome (IBS)[23], Inflammatory Bowel Diseases like ulcerative colitis and Crohn's Disease[24] and allergy-type reactions as seen in HIT.

GUT HEALTH & HISTAMINE

Diamine oxidase (DAO) expression is limited to specific tissues with the highest activity in the small intestines, and to some extent in the ascending colon. DAO sits in the plasma membrane of mucosal cells and is responsible for the breakdown of extracellular histamine mainly from dietary sources, but also from intestinal bacterial synthesis.[25] DAO activity is nutrient dependent requiring copper, Vitamin C, B6 cofactors and optimal conditions in the intestinal lumen including a healthy gut mucosa and pH 6.5-6.8.[26] Its currently understood that 99% of exogenous histamine never enters the circulation in the presence of a healthy intestinal mucosa, suggesting a primary role of the gut as a histamine barrier.[27]

Many health conditions, including IBS, are now recognised to have a degree of GI mucosal breakdown (intestinal permeability), which can increase levels of circulating histamine around the body, as well as reduce levels and activity of DAO. Naturopaths also recognise that gut lumen pH is altered in a dysfunctional bowel potentially impacting on the activity of endogenous DAO.[28] Under these conditions non-degraded histamine from the digestive tract can enter the circulation contributing to the wide-ranging allergy-type symptoms seen in HIT (Table 2).[29] This is perhaps one credible explanation why allergy-type symptoms can still be prevalent even with a negative set of IgE and IgG-mediated food allergy and intolerance blood tests (Figure 1).

Still experiencing allergy-type symptoms despite negative IgE food allergy tests? Histamine Intolerance (HIT) may be the answer.

IBS patients commonly have higher levels of intestinal histamine compared to healthy volunteers.[30] Endogenous histamine, released from intestinal mast cells, has also been implicated in symptom severity in IBS, in part by excess intestinal histamine triggering nerves within the colon exacerbating symptoms like GI pain.[31,32] This is one reason why a low histamine, alkalising diet may support some people with intractable IBS.[33]

Specific bacteria within the gut can also synthesise and release histamine contributing to the histamine levels in the digestive tract.[34] However, the biological consequence of this is still largely unknown. More research is required to show whether histamine secretion by gut bacteria is altered during, or contributes to, GI disorders like IBS. The implications are that gut bacteria modulation (i.e. restoration of eubiosis), alongside other factors including histamine exposure and DAO enzyme activity, should be addressed in people with food intolerances and those with allergy-type symptoms (see Nutritional Therapy Support section and Table 4 at the end of this newsletter). Addressing imbalances in gut bacteria is important as triggers from certain pathogenic species have also been shown to stimulate mast cells leading to HIT-induced inflammation manifesting as conditions like autoimmune rheumatoid arthritis.[35,36,37] This may be yet another mechanism when drawing naturopathic parallels to the origination of many chronic diseases starting within the bowel.

ADRENAL HEALTH & HISTAMINE

The adrenal glands are heavily implicated in allergy-type symptoms and allergic conditions, in part due to the anti-inflammatory adrenal hormone cortisol. The amount of cortisol circulating in the blood is a key factor in controlling the level of inflammatory reactions in the body. For this reason, healthy adrenal function plays an important role in modulating histamine release and inflammatory reactions that produce the symptoms experienced with allergies and food intolerances (Table 2).

People experiencing adrenal fatigue, where normal adrenal responses are altered (as seen in conditions like Chronic Fatigue Syndrome[38] and during chronic and profound stress), may notice that they have more allergy-type symptoms or existing allergies/intolerances seem to get worse. This may in part be due to less cortisol produced by under-functioning adrenal glands, as well as the effect of adrenal imbalances on gut health and function.[39] Conversely, the more histamine released and circulating in the body, as seen in HIT, the harder the adrenals have to work to produce enough cortisol so the more compromised they may become. It is therefore not surprising that people with food and environmental allergies, intolerances and sensitivities commonly tend to have a strong requirement for adrenal support within their naturopathic nutrition programme. If adrenal support is ignored then this can set up a vicious cycle of reduced cortisol output allowing excess histamine to inflame the tissues further, leading to pronounced adrenal fatigue and potentially developing more adverse allergy and allergy-type reactions. For this reason, therapeutic interventions for addressing HIT should also combine adrenal, as well as intestinal support.[40] See the Nutritional Therapy Support section at the end of this newsletter for more information and the Adrenal Health Nutrigold newsletter (www.updates.nutrigold.co.uk/nutritional_newsletters).

HISTAMINE & THE DIET

TABLE 1: HISTAMINE IN THE DIET

High Histamine Foods or Foods That Release Histamine (HR foods)	Low Histamine Foods
• **Alcohol** – champagne, wine, beer, cider and other fermented drinks and spirits • **Pickled or canned foods** – e.g. sauerkraut • **Matured cheeses** – e.g. parmesan, mature cheddar • **Mushrooms and Quorn** • **Smoked meat products** – salami, ham, sausages, bacon • **Fish** – tinned and smoked fish and shellfish • **Beans and pulses** – chickpeas, soy beans, peanuts • **Dried fruit, seeds and nuts** • **Chocolates and other cocoa based products** • **Vinegar** including salad dressings, pickles, mayonnaise, ketchup, mustard • **Ready meals** • **Yeast extract, yeast** • **Additives** – benzoate, sulphites, nitrites, glutamate, food dyes • **Fruit**[HR] – bananas, strawberries, tomatoes, pineapple, mango, raspberry, grapefruit, avocado, tangerines • **Vegetables**[HR]- spinach, pumpkin, aubergines, tomatoes • **Green and black tea** (block DAO enzyme)	• **Fresh meat** (cooled, frozen or fresh) including chicken • **Freshly caught fish** • **Egg yolk** • **Fresh fruits** – with the exception of strawberries, and other fruits listed in the HR column, most fresh fruits are considered to have a low histamine level • **Fresh vegetables** – with the exception of tomatoes, pumpkin and aubergine most fresh vegetables are considered to have a low histamine level • **Grains** – short grain brown rice, rice noodles, yeast free rye bread, rice crisp bread, oats, puffed rice crackers, millet flour, pasta (spelt and corn based) • **Dairy alternatives** – coconut milk, rice milk, oat milk • **Cooking oils** – especially organic virgin coconut oil • **Organic flaxseed oil** • **Leafy herbs** • **Herbal teas** – including peppermint, ginger or fennel

Histamine is naturally present in high concentrations in certain foods and drinks especially fermented products, cocoa and chocolate, tomatoes, spinach, alcohol and mature cheeses (Table 1). In one study of 517 people the main HIT trigger foods were red wine/alcohol (48%), mature cheese (42%) and chocolate (33%) with symptoms including gastrointestinal disturbance and pain (76%), headaches/ migraines (47%) flushing/sweating (42%), as well as aching, itching, urticaria and asthma.[41] Symptoms varied in length with nearly 59% of people experiencing symptoms of 1 day or longer, and 22% suffering from more than 2 days.

Certain types of fermenting bacteria found in foods like live yoghurts and kefir, and also bacteria that naturally reside in the intestinal tract, can synthesise histamine from histidine, increasing the histamine levels in the gut. For this reason, individuals with compromised intestinal mucosa and HIT symptoms may find that initially avoiding fermented foods, including those which have long been associated with naturopathic diets for increasing levels of beneficial bacteria such as kefir, may help to reduce allergy-type symptoms. Scientifically proven bacteria supplements, alongside dietary approaches to support the levels of beneficial gut bacteria may help manage allergy-type symptoms better and prevent symptom flare-ups.[42] Fermented foods can be introduced later in the naturopathic nutrition programme and enjoyed long term when gut structure, the microbiota within and GI function is stabilised.

Food that has been incorrectly stored can also have high levels of histamine produced from contaminating strains of bacteria. This is particularly true of less-than-fresh fish like mackerel, tuna, marlin and swordfish, which contain naturally high levels of histidine that is converted into histamine. In fact, histamine intoxication resulting in symptoms such as rashes, sweating, nausea, vomiting and headaches, has been recorded in people who have normal levels and activity of histamine degrading enzymes but have eaten fish that has been improperly stored - also known as scombroid fish poisoning. This has resulted in the EU setting maximum regulatory limits of 200mg/kg histamine in fresh fish and 400mg/kg in fishery products in brine.[43]

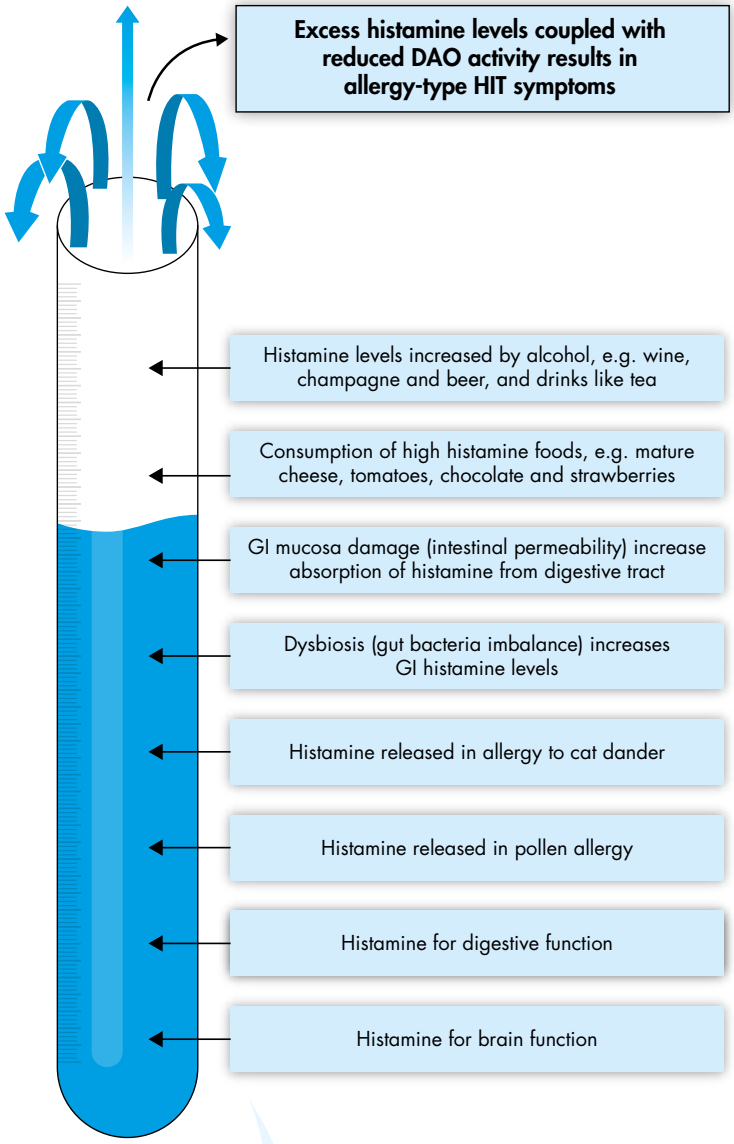
However, clinical investigations show that the symptoms in scombroid fish poisoning are not solely due to high histamine levels but also because of the potentiation of histamine effects by other substances present in decomposing fish tissue, as well as the individual's natural levels of intestinal DAO enzymes (cadaverine and putrescine in the fish compete for the DAO enzyme active site so reduce histamine degradation and raise intestinal histamine levels).[44] What this condition serves to demonstrate is that exposure to dietary histamine in excessive levels can lead to allergy-type symptoms if the mechanisms to degrade histamine, namely DAO, are defective and the histamine levels become too great (Figure 2). Nutritional therapists quite rightly espouse the many health benefits of including fresh fish in the diet but the lesson is to make sure it's as fresh as possible!

Herbal teas including peppermint, ginger or fennel are low in histamine

HISTAMINE INTOLERANCE SYMPTOMS

Histamine Intolerance is due to the accumulation of histamine arising from the imbalance between excessive histamine exposure and the ability to eliminate it (Figure 2). HIT is more common in middle age with prevalence estimated to be around 1% of the population.[45] Symptoms are varied and wide-ranging (Table 2) with secondary symptoms resulting from release of chemical messengers like adrenaline, which can increase heart rate (tachycardia), heart palpitations, nervousness, sensations of inner tremor and sleep disturbances.

FIGURE 2. CUMULATIVE EFFECTS OF HISTAMINE EXPOSURE CONTRIBUTING TO HIT



Think of it like filling a bucket; HIT is one of the major factors in contributing to allergy-type symptoms (Table 2) and is also linked to conditions like PMS.[46] Gut health also plays an important role, including levels of DAO activity and gut bacteria, as does adrenal health where stress greatly impacts on adrenal function as well as gut health.[47] If we continually fill the bucket up with anti-health factors like high histamine foods, stress and nutritionally poor diets (Figure 2) then eventually the bucket will overflow creating a potential cascade of symptoms, as seen in many allergy-type conditions including IBS and chronic fatigue. For this reason, reducing HIT via a low histamine diet is a crucial part for many people when managing allergy-type symptoms, but is just one component in a complete naturopathic programme.

TABLE 2: SYMPTOMS OF HISTAMINE INTOLERANCE (HIT)

ACUTE SYMPTOMS	
Skin	Itching, redness, hives, rash, swelling
Gastrointestinal (GI) Tract	Pain – cramps, bloating, diarrhoea, gastro-oesophageal reflux, flatulence
Oral cavity/ upper airways	Itching and swelling of lips, tongue and eustachian tube (inner ear), glottis, sneezing, watery discharge, swelling of nasal lining, phlegm, cough
Lower airways	Cough, respiratory distress asthmatic symptoms
Cardiovascular system	Changes in blood pressure, palpitations, heart rhythm disorders
Nervous system	Headache (migraine), dizziness, loss of consciousness
CHRONC SYMPTOMS	
Chronic fatigue	
Dysmenorrhoea (painful periods)	
Nervousness, sleep disturbances (insomnia)	
Anxiety, panic disorder, depression	

HIT, IBS & IBDS

One of the primary tissues affected in HIT involves the GI tract with common symptoms including diffuse gastric and colonic pain, bloating, flatulence and diarrhoea. Increased concentration of histamine and decreased DAO activity are also reported in GI inflammatory diseases including Crohn's disease, ulcerative colitis, food allergy and colorectal cancer.[48] This is not surprising as DAO is located in the GI mucosa so any intestinal damage, such as intestinal permeability, and atrophy will affect the level of GI DAO activity, as well as raise levels of circulating histamine.

HIT & ATOPIC DISEASE

Ingestion of high histamine foods and drinks in people with HIT often results in immediate effects on the respiratory tract including sneezing, phlegm, coughing and in extreme cases even bronchial asthma.[49] This is in part due to increased levels of histamine and also reduced activity of the Histamine N-methyl transferase (HMT) enzyme, which deactivates circulating histamine, in the bronchial epithelium.[50,51] The skin is also affected with decreased levels of serum DAO observed in patients with atopic dermatitis[52] and decreased activity in patients with urticaria.[53] A low histamine diet suppressed and stopped symptoms including skin flushing, chronic headaches and GI discomfort in these patients.[54]

HIT & PMS

Women with HIT often suffer symptoms linked to the menstrual cycle including dysmenorrhea (painful periods) and headaches.[55] Endogenous histamine has an essential role in uterine contractions including at the onset of menstruation. Histamine also dose-dependently stimulates the synthesis of the female sex hormones oestradiol and progesterone. When levels of these hormones are too high, such as with HIT, then they can also contribute to painful uterine contractions experienced in primary dysmenorrhea.[56] One study showed that reducing histamine activity on the first day of menstruation prevented cramping-type pain leading to a suggestion that a low histamine diet may help, in part, to manage symptoms of PMS.[57] DAO levels are also influenced by the menstrual cycle with the highest levels expressed during the luteal phase corresponding to reduced levels of HIT symptoms.[58] This means that HIT will often manifest during the follicular phase (i.e. menstruation + 1 week), and show some improvement at other times.

HIT & PREGNANCY

The mutual interaction between histamine and female sex hormones, histamine's effects on blood vessels and its ability to stimulate cell growth and proliferation means the placenta produces a remarkable increase in DAO of up to 500 times. This prevents excessive amounts of maternal histamine entering the foetal circulation, reducing the risk of pregnancy complications.[59] Interestingly, women who are prone to HIT symptoms but produce high levels of DAO during pregnancy find that their symptoms may temporarily cease for the gestation duration.[60] Conversely, women who do not produce enough placental DAO during pregnancy may incur complications including miscarriage, diabetes, premature rupture of foetal membranes and premature births.[61]

HIT & MIGRAINES

Along with gastrointestinal problems in HIT, other significant symptoms include headaches and migraines. Histamine levels are raised in people diagnosed with migraines, both during and outside of migraine attack. Studies have confirmed reduced levels of DAO activity in people suffering from migraines.[62] Reducing histamine rich foods (e.g. cheese and wine) may alleviate migraine symptoms.[63] The mechanism for histamine triggering migraine attacks is not well understood especially as histamine circulating in the blood does not cross the blood brain barrier (BBB) and reach different brain regions. Current research speculates that circulating histamine may influence areas of the brain that lack BBB, such as the hypothalamus, triggering specific histamine receptors and activating pain pathways involved in the underlying pathophysiology of migraine headaches.[64,65,66]

HIT & SCHIZOPHRENIA

Interest in the role of histamine and psychiatric disease, especially schizophrenia, dates from the work of Carl Pfeiffer (1908-1988), who suggested schizophrenics could be classified into 3 subtypes:[67]

1. Patients with histapenia (low blood histamine – about 50%). These were described as paranoid and hallucinatory patients with low serum folic acid levels and elevated serum copper, with some degree of gluten sensitivity.
2. Patients with histadelia (high blood histamine - about 20%). These were described as patients with suicidal depression, high basophil counts (possibly the source of the excess histamine) and low to normal serum copper.
3. Patients with pyroluria (normal blood histamine – about 30% of patients). These were described as patients with normal serum trace element levels, except for low serum zinc, vitamin B6 deficiency and the presence of kryptopyrrolles i.e. blood haemoglobin by-products elevated in the urine people.

It has been reported that patients with schizophrenia have histamine receptor abnormalities and clinical trials have examined the possible antipsychotic properties of specific histamine receptor antagonists.[68] Pfeiffer also suggested that the schizophrenia associated with these histamine-linked conditions may be amenable to dietary treatment. We know that changes in diet are intimately linked to the development, and also support, of behavioural issues, by the pioneering work of Dr Alex Schauss and a landmark set of studies set out in Diet, Crime and Delinquency.[69] One of his studies described up to 90% of criminals in the US with abnormal and altered body chemistry, often as a result of impaired nutrition and environmental insult. This suggests that diets low in highly allergenic foods and balancing histamine exposure may be part of the therapeutic intervention to support underlying brain chemistry.

Of course, HIT symptoms (Table 2) and conditions described in this section are not exclusive to issues with histamine exposure and inability to degrade histamine such as through reduced DAO activity. There are many interconnecting reasons that can be attributed to these conditions. However as one reads through the research discussing conditions with a HIT element, it brings to mind the naturopathic understanding of Dr Constantine Hering's Law of Cure that fundamentally states:

"All healing occurs from within out, from the head down, and in the reverse order in which the symptoms have appeared."

We see that HIT can manifest within the bowel as IBS-type symptoms and on the skin as rashes and atopic dermatitis. One could then draw naturopathic parallels that HIT may then affect other systems such as the lung and brain. Understanding the causes of HIT and management through an appropriately designed alkalising diet low in histamine coupled with suitable enzymes and nutrient supplement support and other naturopathic approaches may be one approach to help to manage HIT and other chronic diseases. See Nutritional Therapy Support section and Table 4 at the end of this newsletter.

CAUSES OF HISTAMINE INTOLERANCE

Intestinal DAO enzyme provides part of the gut barrier function in preventing excess absorption of histamine into the circulation. HIT is therefore partly caused when the amount or activity of this protective enzyme is insufficient or inhibited.[70] One study of 316 people demonstrated low levels of serum DAO activity in people with suspected HIT compared to healthy controls.[71] Almost 40% of the HIT patients in the study with significantly reduced DAO activity saw their symptom profile (including gastrointestinal, skin, eye and respiratory symptoms) improve on a low-histamine diet.

DAO gene polymorphism can significantly influence the expression and activity of DAO, but this is currently not thought to be sufficient to cause development of HIT in its own right.[72] Other cofactors contributing to HIT include:

- Decreased levels of DAO by damaged enterocytes in inflammatory bowel disease, infections, parasites, metabolic malabsorption and dysbiosis.
- Inhibition of DAO activity by other biogenic amines, lack of cofactors (Vitamin B6, C copper and zinc), alcohol or medications (Table 3).
- Reduced tolerance of endogenous histamine.
- Endogenous histamine liberators increasing levels of systemic histamine including hormone activation of mast cells.
- Increased histamine synthesis from hydrolysis of tissue-based L-carnosine during physical activity and increased levels of stress, which also has negative effects on the epithelium of the small intestines increasing permeability of the gut barrier and potentiating input of histamine and its liberation from mast cells.[73]
- Medications that increase histamine or limit DAO release.
- Genetic polymorphisms, like MTHFR (methylene tetrahydrofolate reductase) and others that lower DAO.
- Coeliac disease and possible non coeliac gluten sensitivity.

TABLE 3: EXOGENOUS SOURCES OF HISTAMINE AND CONTRIBUTING FACTORS TO HIT

Naturally occurring histamine	See Table1
Natural histamine liberators	See Table1
Bacteria and yeast contributing to histamine production	Foods with viable yeasts – sour dough and fresh bread
Dietary factors that decrease DAO activity	Alcohol
Medicines that decrease DAO activity	• Antiarrhythmics (verapamil, propafenone) • Antibiotics (cefuroxime, cefotiame,acidum clavulanicum, doxycyclinum, isoniazid, framycetin) • Painkillers (metamizole) • Antidepressants • Psychiatric medications (amitriptyline, diazepam, MAOI-1, haloperidol) • Pancuronium, d-tubocurarin) • Antiemetics (metoclopramide) • Antihistamines (promethazine, cimetidine) • Antihypertensive drugs (dihydralazine) • Antimalarials (chloroquin) • Bronchodilators (aminophylline, theophylline) • Diuretics (furosemide) • Mucolytics (N-acetylcysteine, ambroxol) • Muscle relaxant (alcuronium, pancuronium, d-tubocurarin) • Antiseptics
Histamine liberators in medication	• Painkillers (morphine, pethidine, codeine, metamizole • Anti-inflammatory painkillers (acetylsalicylic acid) • Antibiotics (d-cycloserine, chloroquin, pentamidine) • Anti-hypotensives (dobutamine) • Antihypertensive drugs (verapamil, alprenolol) • Antitussives (codeine) • Cytostatics (cyclophosphamide) • Diuretics (amilorid) • Iodine-containing contrast medium • Local anaesthetics (mesocaine, procaine, marcaine, prilocaine) • Muscle relaxant (d-tubocurarin) • Narcotics • Anaesthetics (barbiturates, thiopental)
Pyridoxine (Vitamin B6) inactivating drugs	• Antihypertensives (hydralazine) • Antibiotics (d-cyclosporine, isoniazid) • Hormonal contraception containing oestrogens
Medications potentiating IgE-mediated histamine release	• Painkillers (acetylsalicyclic acid, diclofenac, indomethacin, keoprofen, mefenamin, naproxen)
Allergic reactions	• Allergens that stimulate a IgE-mediated histamine release from mast cells including pollen and animal dander
Substances potentiating allergic IgE-mediated histamine releases	• Painkillers (acetylsalicylic acid, diclofenac, flurbiprofen, indomethacin, ketoprofen, mefenamin, naproxen)
Infection, trauma, shock	

IDENTIFYING HIT

Due to the manifestation of multi-clinical symptoms, HIT is often left undiagnosed, misinterpreted or overlooked.[74] The crossover of HIT symptoms with other conditions such as IgE–mediated food allergies, IgG related food intolerances and adverse drug reactions (Table 3) can complicate the diagnosis. However, teasing out the causative factors contributing to allergy-type symptoms is essential to optimise the naturopathic nutrition programme.

Clinical studies have investigated using oral histamine provocation but the test is expensive, unreliable and as one might expect, rather unpleasant.[75,76] Therefore a practical approach to identifying HIT includes:

1. **Diet diary and food elimination** – association of food consumption and symptoms, especially sneezing, coughing and GI disturbances, to identify offending foods (remember that HIT develops from cumulative histamine exposure – Figure 2).
2. **Exclusion of other causes** – allergies (IgE and IgG skin prick and blood tests for food allergies and intolerances), metabolic, toxic (Figure 1) .
3. **Determination of DAO levels and activity.**

DAO TESTING

As we've discussed, HIT is a combination of overexposure to dietary and endogenous histamine coupled with the under activity and/or levels of DAO, the enzyme responsible for degrading histamine within the small intestines (Figure 2). Histamine response can be measured in a skin prick test[77] but a simple blood test can be used in nutritional programmes to measure the level of DAO activity in the serum as a marker of histamine degradation ability.[78]

From a specific DAO blood test kit, serum DAO activity is determined by a radio-enzymatic assay (REA) measuring the degree of degradation of 3[H]-labelled putrescine – another substrate for the DAO enzyme with similar affinity to histamine.[79,80] DAO levels are measured in units (U) per milliliter (ml) of serum (U/ml) where 1 Unit refers to the amount of enzyme that catalyses the conversion of 1 micromole of substrate per minute. Low U/ml results therefore signify a reduced activity of DAO to degrade 3[H]-labelled putrescine. This provides a clear understanding of degree of HIT, in which the frequency of symptoms and DAO activity are inversely correlated [81]:

DAO < 3 U/ml = histamine intolerance indicated
3U/ml < DAO < 10U/ml = histamine intolerance probable
DAO > 10U/ml = histamine intolerance improbable

This functional test can be used as part of a naturopathic nutrition programme to give directional information about supplementing with DAO enzyme alongside a low-histamine diet and other approaches for managing allergies, intolerances and sensitivities (see Table 4). [82,83] **DAO-REA test kits are provided by functional testing companies like Regenerus Laboratories (www.regeneruslabs.com).**

NUTRITIONAL THERAPY SUPPORT FOR HIT & ALLERGY-TYPE SYMPTOMS

One of the main ways to reduce HIT is to manage exposure to exogenous histamine is through the diet.[85] Total avoidance of histamine is not achievable since histamine exists beyond the diet,[86] but the improvement of symptoms following the introduction of an alkalising low histamine diet can help aid diagnosis of HIT, and of course help the patient! People usually respond to a low histamine diet in just a few days[87] and are recommended to keep to a low-histamine diet for around 4-6 weeks. Eliminated foods may then be reintroduced individually and on separate days monitoring any symptoms such as abdominal pain, sneezing, runny nose or headache. As many symptoms of HIT are due to cumulative exposure to histamine (Figure 1) many people find they can eventually tolerate 1-2 high histamine containing foods during one meal per day but avoid combining several high histamine foods and drinks together in one sitting. **Continuing with an alkalising diet and other naturopathic support, once histamine-containing foods have been reintroduced is believed to support long-term optimal health.**[88]

One study demonstrated that a low-histamine diet alone reduced the non-allergy mediated symptoms including those in the GI tract, respiratory system and skin in only around 40% of people with HIT and measurably reduced levels of DAO activity.[89] Taking DAO supplements, coupled with low histamine diet, therefore provides additional cover for helping to manage histamine exposure and intestinal levels.[90]

DAO SUPPLEMENTS

DAO enzyme supplements are available to compliment a low-histamine diet and naturopathic nutrition approach. One study has shown that taking porcine-derived DAO enzyme supplements with a meal reduces HIT symptoms; 48% people reported improved stomach ache/cramps, 30-33% people stated improved flatulence/rumbling and diarrhoea, 33% people reported improvement in headaches/migraines and improvement of skin rashes/wheals, itching and rhinitis was experienced in 12-21% people taking DAO supplements.[84] This suggests that DAO supplements may be part of an effective supplement programme in combination with dietary approaches to managing HIT and non-immune mediated allergy-symptoms, as seen in many conditions including IBS.

DAO enzyme supplements work in combination with other digestive nutritional supplement formulations including mixed strain probiotics, broad spectrum digestive enzymes, aloe vera whole leaf juice, gut supporting botanicals including garlic, turmeric and L-glutamine and high potency phosphatidyl lecithin powder. DAO supplements can also be successfully used as part of other naturopathic alkalising programmes including detox nutritional support programmes, as well as adrenal support outlined in Table 4. DAO enzyme supplements are fast-acting and can be used either as needed if there is periodic exposure to histamine such as eating a meal rich in histamine-containing foods (Table 1) or daily long-term use if other histamine increasing lifestyle factors are present like medications (Table 3).

As we have discussed throughout this newsletter, HIT produces a variety of allergy-type symptoms as a result of low levels of intestinal DAO activity and high dietary histamine exposure. This can result in a number of different symptoms that may be recognised as IBS, migraines, asthma-type conditions or skin problems like rashes and itching and more. For many people these collection of symptoms are undiagnosed and they live with them for years untreated.[91] However, naturopaths understand that an imbalance in one system/pathway, such as DAO activity, is as a result of, and also impacts on, other systems and pathways. For this reason, HIT management is best taken in a wider context of investigating the other key elements involved in allergy-type symptoms including addressing intestinal health by supporting the integrity of the intestinal mucosa lining and balance of gut microbiota.[92]

This makes successful management of allergy-type symptoms a multifactorial approach. There are some specific stages outlined in Table 4 for addressing HIT, which can be applied as part of a wider naturopathic nutrition programme, such as the 5R programme for Irritable Bowel Syndrome (IBS), which addresses intestinal permeability and dysbiosis, as well as HIT.[93] Please refer to the Nutrigold newsletter on Irritable Bowel Syndrome: The 5Rs for more information on a holistic approach to healing the gut (www.updates.nutrigold.co.uk/nutritional_newsletters).

TABLE 4: HIT MANAGEMENT PROGRAMME

Stage	Step	Guidance
1	**Reduce exogenous histamine exposure through low histamine diet (Table 1)**	• Enjoy freshly prepared, low histamine foods and avoid processed foods • Histamine is not easily broken down by heat so storage of food is imperative, as cooking foods will not significantly reduce the histamine levels
2	**Manage substances that inhibit DAO (Table 3)**	• Address medications • Eliminate alcohol
3	**Reduce exposure to histamine releasing substances (Table 3)**	• Reduce exposure to allergens including pollen, gluten etc.
4	**Support adrenal glands and raise levels of natural anti-histamines**	• Reduce stress • Adrenal support with Vitamin C and B5 (pantothenic acid) supplements • Natural anti-histamine supplements Vitamin B6 (P5P) and quercetin
5	**Enhance intestinal DAO activity**	• Supplement with DAO enzyme along with DAO cofactors zinc, copper (as citrate), Vitamin C and B6 • Cofactors can be part of a multivitamin and mineral supplement with additional Vitamin C

For more information please see Nutrigold CPD accredited webinars at www.updates.nutrigold.co.uk/educational_webinars

Should you need a more detailed approach, or should you have any questions or concerns that are not addressed in this article, you are always welcome to contact our nutritional advice team on 0845 603 5675 (9.00am – 5.00pm Monday – Friday).

Alternatively if you would like a more personalised approach, addressing dietary recommendations, lifestyle changes etc., we would suggest you consider consulting a qualified nutrition adviser or therapist, which you can do by either asking us for details of your local practitioners, or contacting the Federation of Nutritional Therapy Practitioners on 0870 312 0042 or by emailing them at admin@fntp.org.uk.

For more information visit the website at: www.fntp.org.uk

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