Histamine Intolerance

EMERGING EVIDENCE

ARTICLE BY
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Histamine intolerance (HIT) continues to be a topic of increasing clinical interest with scientific research continuing into its prevalence, aetiology, pathophysiology, clinical presentation, and comorbidities along with the most appropriate therapeutic assessment and management strategies. There is significant complexity associated with each of these - paralleled by the ubiquitous physiological and functional nature of this biogenic amine in relation to the many body systems, organs and tissues it influences, as well as the interindividual variability in its clinical manifestation/ presentation.[2-4]

Histaminosis

Histaminosis (HIT) is reported to affect up to 3% of the population, however, with its clinical heterogeneity and diagnostic challenges, its actual prevalence may be higher.[5-7] **Histaminosis is defined as the impaired capacity to methylate/deaminate histamine via diamine oxidase (DAO) and histamine N-methyltransferase (HNMT) enzymes respectively.** This inability results in the accumulation of endogenous histamine, allowing it to bind to histamine receptors (HR 1-4) producing subsequent effects on tissues and organs[2,7,8,10] (See Table 1 and Histamine Basics).

> **'Histamine' – derived from the Greek word 'histo' translating to 'tissue'.[1]**

Table 1. The role of the varying histamine receptors

Low Affinity receptors		High Affinity receptors	
Allergic inflammation (H1) Alteration of vascular permeability ➔ extravasation ➔ oedema ➔ adhesion molecules ➔ inflammatory cell migration	Histamines	**Neurotransmission (H3)** Regulation of neuronal histamine turnover (autoreceptors) Neuronal functions Cognition (heteroreceptors)	Histamines
Gastric acid secretion (H2) Regulation of gastric acid secretion Immune cell differentiation (?)	Histamines	**Immunomodulation (H4)** Immune cell chemotaxis, immune response, inflammation	Histamines

Cells involved in histamine production
Mast cells | Basophils | Enterochromaffin-like-cells | Neurons | Leukocytes | Platelets | Epithelial cells | Chondrocytes | Tumour cells | Other cells

Histamine Basics

Synthesis

Histamine is synthesised intracellularly in central and peripheraltissues in the Golgi apparatus organelle following decarboxylation of L-histidine by the inducible enzyme histidine decarboxylase.[2,11] This occurs in cells that store histamine including mast cells and basophils, and cells that produce histamine in response to stimuli such as enterochromaffin- like, histaminergic neurons, lymphocytes, monocytes, platelets, neutrophils, gastric and dendritic cells.[1,4,10] Such stimuli can involve both immunological and non-immunological substances.[2]

Function

Histamine is necessary in the body for many functional processes including:

- Inflammation
- Innate and adaptive immunity
- Vasodilation and vascular permeability
- Smooth muscle contraction and relaxation
- Gastric acid secretion
- Neuromodulation (including thermoregulation, appetite and cognition).[1,3,9,11,12]

Metabolism and Inactivation

Endogenous histamine is metabolised intracellularly by histamine N-methyltransferase (HNMT) (expressed in respiratory, small intestinal, liver and kidney cells) via deamination and extracellularly by diamine oxidase (DAO) through methylation.[2,4,11,13] DAO, largely expressed by intestinal epithelial villi cells as well as liver, kidney, placental and skin cells, breaks down 15-30% of histamine by removing an amine group, producing imidazole acetaldehyde, ammonia and hydrogen peroxide. This pathway requires vitamins B6, C and copper to function effectively.[4,8,11,13] Because HNMT is more widely expressed throughout the body it metabolises 50-80% of endogenous histamine by adding a methyl group from S-adenosyl-L-methionine, producing N-methylhistamine and subsequently M-methylimidazole acetic acid. [4,8,9]

Causes of Histamine Intolerance (HIT)

The many endogenous and exogenous aetiological factors associated with HIT pathophysiology are clinically observed to predominantly involve multiple antecedents rather than an individual trigger.

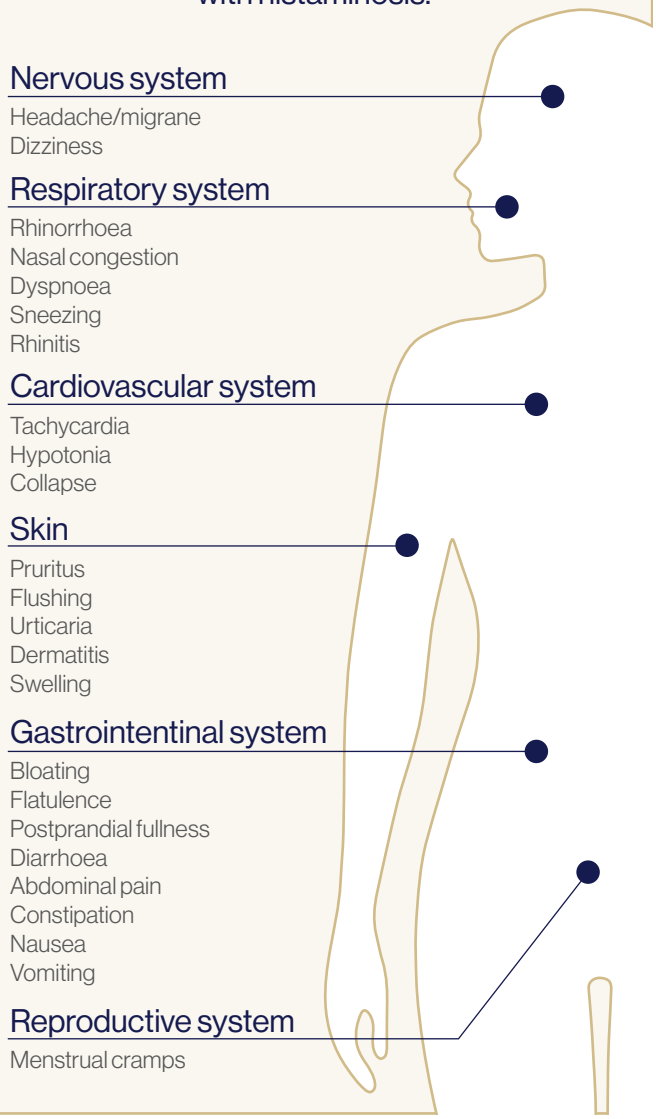
Endogenous aetiologies of histamine intolerance include:

- Genetic (DAO rs10156191, rs1049742, rs2268999, and rs104979 polymorphisms)
- Acquired (functional) impairment of DAO or HNMT enzymes
- Gastrointestinal dysfunction or pathology (damaged intestinal enterocytes, bleeding, inflammation, dysbiosis and infections)
- Nutrient deficiencies (copper, vitamins C and B6).[1-3,6,8,10,11,13,15,16]

Exogenous aetiologies of histamine intolerance include:

- Diet (considered to be a significant exogenous trigger specifically the ingestion of foods with high levels of histamine (sauerkraut, processed meat, dried anchovies, fish sauce, spinach, tomatoes, cocoa, eggplant, fish, chicken, yoghurt, soy, red wine); those promoting mast cell histamine release (citrus foods, pineapple, bananas, strawberries, papaya, tomatoes, additives); or containing other biogenic amines that interfere with the binding of histamine to mucosal mucine resulting in more histamine in circulation.[10,11,13,18]
- Other exogenous factors include stress, alcohol, medications and xenobiotics that decrease DAO activity (or interfere with histamine metabolism and distribution).[3,8,15,20]

Fig. 1. Symptoms associated with histaminosis.



Symptoms of Histamine Intolerance

Histamine Intolerance results in the onset of a broad range of symptoms across different body systems. The more commonly observed symptoms in clinical and research settings are:

- Gastrointestinal (abdominal distension, constipation, postprandial fullness, nausea, vomiting, diarrhoea, abdominal pain and constipation)
- Nervous (dizziness, headaches and migraines)
- Respiratory (sneezing, rhinorrhoea, nasal congestion, swelling, phlegm, cough and asthma)
- Integumentary (eczema, dermatitis, urticaria, pruritis, flushing and oedema)
- Muscular (pain)
- Cardiovascular (tachycardia and hypotension)[3,5-7,10,13-17]

In addition to these more commonly observed clinical presentations of HIT, correlations between the condition and other clinical pathologies are emerging (See Fig. 1 and Table 2).

Table 2: Histamine Intolerance - Comorbidities and Pathologies

Comorbidities	Clinical Consideration
Gastroinestinal	
Intolerance/Malabsorption issues • Fructose • Sorbitol • Lactose • Non-coeliac gluten sensitivity (NCGS)	• Lower serum DAO levels trigger elevated histamine producing clinical symptoms. Each of these comorbidities can individually or combined co-exist with HIT with a cross over in clinical symptoms commonly observed between HIT and these conditions.[7,15,17,19,20,22]
Functional/Structural • Impaired intestinal permeability (increased zonulin) • Intestinal dysbiosis (elevated histaminogenic bacteria, lower beneficial bacteria)	• Increased intestinal translocation of exogenous histamine. • Increased bacterial synthesis and impaired histamine catabolism. • Mucosal inflammation. • Reduced DAO activity. Can be primary aetiology or secondary exacerbating factor in HIT onset and severity. [3,7,15,16,19,21,23]
Pathologies • Crohn's disease and ulcerative colitis • Coeliac disease (HIT found in >50% of non-responding patients) • Irritable Bowel Syndrome (IBS) • Food allergies • Gastroenteritis • Small Intestinal Bacterial Overgrowth (SIBO)	• Increased mucosal histamine synthesis and impaired catabolism. • Increased tryptase secretion. • Mucosal inflammation and damage. • Impaired mucosal immunity. • Reduced DAO activity. Cross over in pathophysiology and clinical symptoms commonly observed between HIT and these conditions.[7,8,15-17,19,20]
Reproductive	
Oestrogen excess	• Histamine promotes oestradiol (E2) synthesis. E2 stimulates mast cell histamine release. • Can co-exist with HIT.[27]
Dysmenorrhoea/premenstrual cramps	• Histamine promotes E2 synthesis stimulating mucosal prostaglandins and uterine contractions. • Associated with increased sensitivity to histamine.[3,25,27,28]
Menstrual migraines/headaches	• Histamine stimulates nitric oxide (NO) secretion in brain arteries.[27]
Ovarian endometriomas	• Increased mast cell concentration leads to degranulation induced by local E2.[26]
Endometriosis	• Elevated blood and endometrial lesion histamine levels activates local nerves increasing pelvic pain intensity.[26,30]
Pelvic adhesions	• Elevated follicular fluid histamine produces local inflammation and impaired ovulation.[29]
Implantation failure	• Excessive histamine promotes Th1/Th2 imbalance.[26]

Thyroid	
Subclinical and overt hypothyroidism	• Increased thyroid tissue mast cell concentrations modulates thyroid function and hormone (T3, T4) synthesis. • Excessive histamine inhibits TRH release increasing TSH synthesis. • Thyroid hormone metabolites (T1AM, TA1) triggers MC histamine release leading to a bidirectional relationship between histamine, thyroid function and pathology[12,34]
Autoimmune hypothyroidism	• Mast cell degranulation increases thyroid histamine levels promoting thyroiditis progression.[12]
Metabolic	
Insulin resistance	• Histamine (HR1, HR2) involved in glucose and lipid metabolism. • Histamine dysregulation may be involved in impaired glucose and lipid metabolism[27,36]
Excess adiposity	• Increased mast cell accumulation and activation in adipose tissue (exacerbated by high fat diet) promotes inflammation. • Histamine involved in regulation of energy intake and expenditure. • Histamine dysregulation may affect endogenous energy balance and adipose associated inflammation. [1,27,35]
Genitourinary	
Interstitial cystitis / bladder pain syndrome	• Increased bladder mast cell counts and faecal histamine levels. • Histamine promotes hypersensitisation of nociceptive neurons to bladder distension[24,31,32]
CNS	
Migraine	• Blood DAO enzymatic deficiency more common in subjects vs controls.[33]

Abbreviations: NCGS: non-celiac gluten sensitivity; IBS: irritable bowel syndrome; T1AM: 3-iodothyroanamine; TA1: 3-iodothyroacetic acid; NO: nitric oxide; E2: oestradiol; SIBO: small intestinal bowel overgrowth; Th1/Th2: T-helper 1 / T-helper 2.

Clinical Assessment of Histamine Intolerance

The heterogenous nature of the aetiology, pathophysiology and clinical presentation of HIT and the variability of the validity and clinical information provided by commonly utilised assessment strategies are essential considerations in the accurate clinical diagnosis and effective clinical management of HIT. (See Table 3.)

Table 3: Histamine Intolerance - Clinical Assessment Considerations

Assessment Strategies	Clinical Relevance
STAGE 1 & 2: Initial Clinical Assessment	
Thorough clinical case-taking assessment	Health history, presence, type, severity and duration of clinical presentation, aetiological factors and comorbidities.[15,37]
Low histamine diet for 4-8 weeks	Assess clinical response to lower histamine load (improvements and changes).[3,7,8,17,22]
STAGE 3: Laboratory Pathology Assessments	
Histamine skin prick test	Determines presence of IgE-mediated 'histamine wheal' 50 minutes after exposure and IgE-sensitisation caused by food allergy.[3,7,15,19,37]
Whole blood histamine	Measures serum histamine and 1-methylhistamine levels.[3,15,37,38]
Serum tryptase	Presence of systemic mastocytosis.[7,39]
Urine methylhistamine	Indicates general dietary intake levels of histamine (and protein).[15,19,37]
DAO enzyme activity	Serum = measures blood DAO activity. Intestinal biopsy = measures local DAO activity. Genetic = measures genetic DAO deficiency polymorphisms.[3,7,15,19,22,37,38]
MCAS markers	Determine presence of inflammatory mediators released by mast cells (tryptase, histamine, prostaglandins, leukotrienes, DAO, and IgE).[15,19]

Systemic Assessment of Causes & Comorbidities

Gastrointestinal assessment of functional markers, microbiome population (beneficial, commensal, infections, yeasts), permeability and clinical review of pathologies and surgery	Assess presence of gastrointestinal functional, structural or pathological issues.[7,15,19,20,37]
Central nervous system	Clinical assessment of neurological manifestations of HIT and serum cortisol measurement.[3,7,19,27,37]
Thyroid hormones	Assess clinical response to lower histamine load (improvements and changes).[3,7,8,17,22]
Blood glucose hormones	Insulin resistance index to assess blood glucose and insulin status.[36]
Skeletal	Bone density assessment.[40,41]
Biochemistry	Clinical assessment of blood components (electrolytes, organic acids, fats and proteins).[42]
Dermatological	Clinical assessment of skin manifestations of HIT.[3,7]
Vitamins C, B6 and copper levels	Assess status of histamine metabolising nutrient cofactors.[3,19]

Environmental

Environmental (dust, pollen, heavy metals, pesticides, glyphosate, mould, xenobiotics and alcohol)	Clinical assessment of potential environmental drivers.[3,7,19,43,44-48]

NB: The use and timing of additional assessments to determine potential systemic causes and comorbidities and specific timing of conducting such tests is based on individual case requirements. It is recommended to use multiple assessment tools based on clinical information provided and the limitations of each test as appropriate for the individual case.

Summary

This review emphasises that the basis of effective clinical management of HIT is through the thorough assessment of the systemic clinical presentation and consideration of all potential aetiological and pathophysiological factors in the individual case, as well as the importance of ongoing research to improve the diagnosis and treatment of this condition.

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