



## **Histamine**

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#### **Introduction**

Histamine, an imidamine synthesised metabolically from the decarboxylation of histidine, is a vasoactive amine of the gut and the immune system. It also acts as a neurotransmitter in the central nervous system and as a chemotactic agent for leucocytes. After synthesis, histamine may be broken down or stored in an inactive protein-bound form, primarily in the blood basophils or the pulmonary mast cells. Histamine exerts its actions by combining with one of four specific cell receptors, designated H1, H2, H3 and H4 [1].

Studies of allergic disease have shown that histamine release plays a central role in the pathogenesis of the early-phase allergic response. High histamine production and release is associated with allergic responses, particularly type I (immediate hypersensitivity) reactions [2], which are mediated by IgE antibodies. Excess histamine may also be responsible for immediate hypersensitivity reactions that are not associated with IgE antibodies, such as the symptoms of scombroid fish poisoning [3]. Gastric enterochromaffin-like cells and histaminergic nerves in the brain are also sources of histamine.

#### **Histamine receptors**

Histamine receptors are members of the 7-transmembrane-spanning family of receptors that couple ligand binding to intracellular reactions through interactions with guanosine triphosphate-binding heterotrimeric proteins [1]. The significance of histamine release is essentially defined by the cell types that express histamine receptors. There are four classes of histamine receptor.

The H1 histamine receptor is widely distributed throughout smooth muscle, the vascular endothelium and the nervous system, as well as endothelial cells, neutrophils, eosinophils, monocytes and dendritic cells. Activation of the H1 receptor causes symptoms such as vasodilation, bronchoconstriction, smooth muscle activation and itching, as well as intracellular events characterized by changes in free cytosolic calcium concentration and by elevations in cyclic adenosine monophosphate (cAMP). H1 receptor activation is also associated with increased production of prostaglandins. The H1 histamine receptor is thus the primary receptor involved in the symptoms of, for example, allergic rhinitis and motion sickness.

The H2 histamine receptor is expressed on many of the same cells as the H1 receptor, but is also found on the gastric parietal cells, where its activation causes release of gastric acid (hence the use of H2 receptor antagonists to reduce gastric acid secretion). Activation of the H2 receptor also leads to an increase in mucus secretion, increased intracellular synthesis of cyclic AMP, stimulation of suppressor lymphocyte function and bronchodilation.

The H3 histamine receptor is located on histaminergic neurons in the brain. Its activation decreases the rate of release of brain neurotransmitters – histamine, acetylcholine, noradrenalin and serotonin.

H4 histamine receptors are immune modulators, highly expressed on bone marrow and peripheral hematopoietic cells, eosinophils, neutrophils, T cells, basophils and mast cells. They are most abundant in the spleen, lung, and thymus [1].

## **Histamine in allergic disease**

Allergic diseases are characterized by activation and subsequent release of inflammatory mediators by immune cells (mast cells, basophils and T cells). Histamine is usually the most abundant mediator produced during an allergic response, but is only partially responsible for the symptoms associated with this condition. The allergic cascade involves a number of inflammatory mediators in a response that is composed of three distinct phases: a) sensitization, b) the early-phase allergic reaction, and c) the late-phase allergic reaction [4].

- a) The sensitization phase begins with exposure to an allergen and ends with the binding of antigen-specific IgE antibodies on target mast cells.
- b) The early-phase allergic reaction begins when IgE-bound mast cells are re-exposed to the allergen in sensitized patients [5]. Repeat allergen exposure initiates antigen cross-linking of mast cell-IgE antibodies, causing rapid degranulation of the mast cells and release of histamine, interleukins, prostaglandins, kinins and leukotrienes. These inflammatory mediators are collectively responsible for increasing local blood flow and vascular permeability, stimulating excessive secretion of mucus, and reducing airway patency in the respiratory tract. The clinical outcome in affected patients is the rapid onset of sneezing, itching, rhinorrhoea and nasal obstruction.
- c) Basophil-mediated histamine release is thought to play a subordinate role during the late-phase reaction allergic reaction [4].

## **Histamine intolerance**

Histamine is present in some food and drink; consumption of histamine from these sources, such as spoiled tuna and mackerel, may precipitate an allergic-type response without the subject actually having a true allergy. This is known as histamine intolerance. If diamine oxidase activity is deficient or inhibited (e.g. by alcohol) histamine intolerance may develop - gastro-intestinal disturbance, migraine and the symptoms of an allergic response.

## **Histamine in psychiatric disease**

Interest in the role of histamine in psychiatric disease, especially schizophrenia, dates from the work of Carl Pfeiffer, who suggested that schizophrenics can be classified into three subtypes [6,7]:

- a) Patients with histopenia (low blood histamine - about 50% of patients). These were described as paranoid and hallucinatory patients with low serum folic acid levels and elevated serum copper, some of whom also had gluten sensitivity.
- b) Patients with histadelia (high blood histamine - about 20% of patients). These were described as patients with suicidal depression, high basophil counts (possibly the source of the excess histamine) and low to normal serum copper.
- c) 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 in the urine.

Pfeiffer suggested that the schizophrenia associated with these conditions may be amenable to dietary treatment. But in spite of its known function as a regulator of CNS neurotransmitters, histamine has since received relatively little attention in peer-reviewed clinical studies of psychiatric disorders. The availability of long-acting histamine receptor antagonists has prompted some clinicians to re-examine the role of histamine in schizophrenia. It has been reported that patients with schizophrenia have histamine receptor abnormalities and current trials are examining the possible antipsychotic properties of histamine receptor antagonists [8].

## Specimen requirements and patient preparation

Blood for histamine analysis should be collected into a BDH EDTA venoject tube (purple top 4.0 mL). For urine histamine determinations, a random sample (10 mL) should be submitted. No special preservatives are required. For analysis of serum diamine oxidase activity, blood specimens should be collected into a clotted SST (serum separator, yellow top) tube. Freshly collected samples for diamine oxidase analysis may be stored at room temperature or at 2 - 8°C for up to 24 hours.

A postal sample kit can be supplied.

## Methodology

Histamine determinations in plasma and urine are carried out by enzyme immunoassay (ELISA) using reagents supplied by IBL International GMBH [9]. Serum diamine oxidase activity is determined by a radioenzymatic method using radiolabelled putrescine dihydrochloride as a substrate [10] with reagents supplied by Immundiagnostik AG [11].

## Interpretation of results

The reference interval for plasma histamine is 1.8 – 9.0 nmol/L.

Urine histamine is reported in micrograms per mL of urine, with the reference interval expressed as the ratio to creatinine. A normal histamine/creatinine ratio is between 8 – 53 ug of histamine per gram of creatinine.

Diamine oxidase activity is reported in U/ml of plasma. The interpretation of the results is:

- < 3 : histamine intolerance indicated,
- 3 - 10 : histamine intolerance probable,
- > 10 : histamine intolerance improbable.

The measurement of histamine together with the analysis of the enzyme diamine oxidase provides a method for the detection of histamine intolerance and the monitoring of a histamine-free diet in affected subjects. Histamine intolerance cannot be diagnosed in cases of anaphylactic shock or during pregnancy.

## References

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