Specialty - allergy

Histamine

Analyte Information
Histamine

Introduction

Histamine (2-(4-imidazolyl) ethylamine) belongs to the group of biogenic amines. Its molecular weight is 111 Da. Its formula is shown in Fig.1.

Fig.1: Histamine

Histamine is involved in local immune responses as well as in regulating physiological functioning in the gut and acting as a neurotransmitter\(^1\).

In this brochure, emphasis is placed on histamine as a key factor in allergic response.

Biosynthesis

Histamine is synthesized by pyridoxal phosphate (vitamin B-6)–containing L-histidine decarboxylase (HDC) from the amino acid histidine (Fig.2).

Fig.2: Biosynthesis of histamine
It is synthesized by mast cells, basophils, platelets, histaminergic neurons and enterochromaffine cells, where it is stored intracellularly in vesicles and released on stimulation.

**Metabolism**

Histamine can be metabolized in two ways: by oxidative deamination by DAO (diamine oxidase, previously known as histaminase) or by ring methylation by histamine-N-methyltransferase (HNMT)\(^2\) (Fig.3). The method of catabolization is supposed to depend on the localization of histamine.

The DAO protein is stored in plasma membrane–associated vesicular structures in epithelial cells and is secreted into circulation upon stimulation\(^3\), \(^4\). It has been proposed that DAO may be responsible for scavenging extracellular histamine (e.g., after ingestion of histamine-rich food).

Conversely, HNMT, the second-most important enzyme in inactivation of histamine, is a cytosolic protein\(^5\) which can convert histamine only in the intracellular space of cells\(^6\), \(^7\). Thus HNMT and DAO do not seem to compete for the substrate, although they have a similar affinity for histamine and are expressed in some overlapping tissues.

HNMT has a slightly higher affinity for histamine than DAO. In mammals, DAO expression is restricted to specific tissues; the highest levels of activity are in the small bowel and colon ascendens\(^8\), \(^9\), \(^10\) and in the placenta and kidney\(^3\), \(^6\).

Decreased DAO activity has been discussed as a potential indicator of intestinal mucosa damage in inflammatory and neoplastic diseases\(^11\), \(^12\), \(^13\) and in persons undergoing chemotherapy\(^14\).

HNMT is widely expressed in human tissues; the greatest expression is in kidneys and liver, followed by the spleen, colon, prostate, ovary, spinal cord, bronchi and trachea\(^15\). HNMT is regarded as the key enzyme for histamine degradation in the bronchial epithelium\(^16\).
Fig. 3: Histamine and histamine intolerance

Summary of histamine metabolism. Histamine is synthesized via the decarboxylation of the amino acid histidine, catalyzed by L-histidine decarboxylase (HDC) (1). Histamine can be metabolized via extracellular oxidative deamination of the primary amino group by diamine oxidase (DAO) (2) or via intracellular methylation of the imidazole ring by histamine-N-methyltransferase (HNMT) (3). Both enzymes can be inhibited by their respective reaction products in a negative feedback loop (4). N-Methylhistamine is oxidatively deaminated to N-methyl-imidazole acetaldehyde by monoamine oxidase B (MAO B) (5) or by DAO (6). Because the methylation pathway takes place in the cytosolic compartment of cells, MAO B (5) has been suggested to catalyze this reaction in vivo\textsuperscript{14}. The acetylhistamine is a minor metabolite (7).
Histamine and its metabolites are excreted mainly in urine. The total percentage of $^{14}$C-histamine metabolites excreted in urine within the first twelve hours after intradermal injection of $^{14}$C-histamine are as follows:

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>2 – 3</td>
</tr>
<tr>
<td>N-methylhistamine</td>
<td>4 – 8</td>
</tr>
<tr>
<td>N-methylimidazole acetic acid</td>
<td>42 – 47</td>
</tr>
<tr>
<td>Imidazole acetic acid</td>
<td>9 – 11</td>
</tr>
<tr>
<td>Imidazole acetic acid riboside</td>
<td>16 – 23</td>
</tr>
<tr>
<td>Acetylhistamine</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

**Physiological Function**

Histamine is a potent mediator of numerous biological reactions. Besides the well-known triggering of degranulation of mast cells by crosslinking of the FcεRI receptor by specific allergens, several other nonimmunologic stimuli may also activate mast cells. These stimuli include neuropeptides, complement factors (i.e., C3a and C5a), cytokines, hyperosmolarity, lipoproteins, adenosine, superoxidases, hypoxia, chemical and physical factors (e.g., extreme temperatures, traumas), alcohol and certain food and drugs.

Histamine exerts its effects by binding to target cells of various tissues via its four receptors (H1R, H2R, H3R, and H4R) (Fig.4). It causes smooth muscle cell contraction, vasodilatation, increased vascular permeability and mucus secretion, tachycardia, alterations of blood pressure and arrhythmias; and it stimulates gastric acid secretion and nociceptive nerve fibers. In addition, histamine has been known to play various roles in neurotransmission, immunomodulation, hematopoiesis, wound healing, day-night rhythm, and the regulation of histamine- and polyamine-induced cell proliferation and angiogenesis in tumor models and intestinal ischemia.
Fig. 4: Summary of histamine mediated symptoms

Histamine affects various systems and organs, including:

- **Central nervous system**
  - Vertigo
  - Headache
  - Nausea, Vomitus
  - Circadian rhythm, arousal

- **Cardiovascular system**
  - Hypotonia, Hypertension
  - Anaphylaxis
  - Arrhythmia
  - Pruritus
  - Flush
  - Urticaria
  - Congestion of the nose, rhinorhea, sneezing

- **Bone marrow**
  - Contribution to the regulation of body temperature, food intake, locomotion, learning, memory

- **Mast cell secretion**

- **Gastrointestinal system**
  - Leukocytes
  - Diarrhea
  - Gastrointestinal
  - Uterus
  - Uterus
  - Meteorism
  - Stomach ache, cramps

- **Respiratory tract**
  - Bronchoconstriction, dyspnea

- **Skin**
  - H1/2
  - H1
  - H2
  - H4

- **HISTAMINE**
  - Vasodilation
  - Neuropeptide release
  - Regulation of hematopoiesis
  - CGMP
  - CAMP
  - Gastric acid secretion
  - Smooth muscle constriction
  - Mucus secretion
  - Estrogen
  - Endothelial permeability

- **Other effects**
  - Smooth muscle constriction
  - Mucus secretion
  - Estrogen
  - Endothelial permeability
**Allergic response**

Histamine is a central mediator of allergic response.

Allergens are usually proteins, processed and presented to T cells through antigen-processing cells such as dendritic cells. T helper cells (Th2 type), mast cells, basophils or eosinophils produce proinflammatory cytokines that may induce an allergic response. Many inhalant allergens have enzymatic activities that enhance the allergic response. Exposure of sensitized individuals to the allergen then triggers histamine release in basophil or mast cells by IgE/FceRI crosslinking. Histamine binds to specific receptors on smooth muscle cells and provokes potent adverse effects (Fig.5).

**Fig.5: Summary of allergic response**

[Diagram of allergic response process]
Levels

Basal plasma histamine concentrations of 0.3 to 1.0 ng/mL are considered normal\textsuperscript{23}. Concentrations in excess of the individual histamine tolerance give rise to concentration-dependent histamine-mediated symptoms\textsuperscript{24, 25, 26, 27} (Table 2).

Table 2 - Histamine effects according to plasma histamine concentration (ng/mL)

<table>
<thead>
<tr>
<th>Histamine (ng/mL)</th>
<th>Clinical effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>None</td>
</tr>
<tr>
<td>1 – 2</td>
<td>Increase in gastric acid secretion</td>
</tr>
<tr>
<td></td>
<td>Increase in cardiac heart rate</td>
</tr>
<tr>
<td>3 – 5</td>
<td>Tachycardia, headache, flush, urticaria, pruritus</td>
</tr>
<tr>
<td>6 – 8</td>
<td>Decrease in arterial pressure</td>
</tr>
<tr>
<td>7 – 12</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>~ 100</td>
<td>Cardiac arrest</td>
</tr>
</tbody>
</table>

Diagnostic utility – Possibilities

Allergy testing

Histamine is released from basophils and mast cells as the result of an allergic reaction. Its level increases transiently in the blood as well as in tissue and it exerts a variety of pathological effects which may lead to cardiac arrest. The release of histamine may occur \textit{in vivo} as the result of immediate hypersensitive reaction or may be induced by provocation. This release may be evidenced by plasma or urine measurement.

\textit{In vitro}, histamine release may be induced by the addition of an allergen to whole blood or to a preparation of leucocytes or mast cells.

Pharmaceutical Industry

Histamine release may be inhibited by drugs. \textit{In vitro} and \textit{in vivo} modulation of histamine release is useful for anti-allergic drug screening and drug efficiency testing.

Histamine is released during adverse hypersensitivity to drugs. The measurement of histamine release during the clinical evaluation of a drug is useful parameter of establishing its harmlessness.
Cosmetology/Dermatology

Histamine and cytokines are crucial in allergenicity testing of cosmetic/dermatologic products. *In vivo* models are progressively transposed into *in vitro* models (mixed skin cell culture).

Research and Clinical Investigations

Significant amounts of histamine and its receptors are found in the mucosa of the stomach. It plays a role in gastric secretions. Histamine and its specific receptors also occur in the central nervous system. Their role in neurological abnormalities is under investigation. Varying levels of histamine have been found in various experimental and pathological conditions in spinal fluid, tears, saliva, nasal secretions, urine, bronchoalveolar lavages and tissues, demonstrating the extensive interest of this molecule in current research.

Veterinary

Histamine is ubiquitous. The use of the histamine release test in isolated cells or in the whole animal permits rapid quantitative exploration of the allergenic potential of a novel substance. Histamine determination is also useful for exploring therapeutic inhibitors of histamine release. All animal models are suitable.

Pets or race horses may also be sensitive to various allergens. The measurement of *in vitro* histamine release in whole blood samples allows the identification of incriminated allergens.

Histamine intolerance^{28, 29, 30, 31}

Histamine intolerance results from a disequilibrium between accumulated histamine and capacity for histamine degradation. Histamine is a biogenic amine that occurs to various degrees in many foods. In healthy persons, dietary histamine can be rapidly detoxified by amine oxidases, whereas persons with low amine oxidase activity are at risk of histamine toxicity (Fig.6).

The ingestion of histamine-rich food, alcohol or drugs that release histamine or block DAO may provoke diarrhea, headache, rhinoconjunctival symptoms, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing and other conditions in patients with histamine intolerance. Symptoms can be mitigated by a histamine-free diet and/or antihistaminics.
Fig. 6: Histamine intolerance

Source: www.alles-essen.at

Food quality – histamine fish poisoning

Histamine fish poisoning (HFP) is a foodborne chemical intoxication caused by the consumption of spoiled or bacterially contaminated fish. Histamine is the main toxin involved in HFP. Although HFP is not uncomplicated histamine poisoning, the disease is generally associated with high levels of histamine (more than 50 mg per 100g of food) in spoiled fish.

Testing food for histamine levels can help to prevent undesirable events connected with HFP.

More information can be found in the brochure “Histamine and Histamine Fish Poisoning”.
Diagnostic utility – Main applications

In vitro histamine release
This test is most useful in the investigation of *in vitro* release of histamine caused by allergens. The allergen, when added to diluted blood, induces the degranulation of basophils, provided that the basophils carry the IgE specific for the allergen on their surface. The test allows the specific and safe identification of allergens to which the blood donor is sensitive.

Plasma histamine
Histamine is a key factor in allergy. *In vivo* allergic reactions are usually associated with increase in plasma histamine levels. Kinetics of *in vivo* histamine release may be followed by measurement of plasma histamine level increase after introduction of the suspected allergen[33, 34].

Urine histamine
Urine histamine excretion may be a good indicator of *in vivo* mast cell activation and indicates anaphylactic reactions which may have occurred in the context of allergies to a medication. Urine histamine levels may also depend on histamine intake originating in the stomach.

Tissue histamine
Intracellular histamine is closely related to the regulation of cell proliferation. It plays a role in tissue repair as well as in cancer. Histamine present in tissues is measured after acid extraction.
References

32. www.alles-essen.at