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Histamine

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Summary

Histamine has at least twenty-three known physiological functions, including playing a prominent role in immunologically mediated inflammation. The structure and metabolism of histamine is discussed, together with the various types of histamine receptors. Histamine plays a role in anaphylaxis, mast cell activation syndromes and mastocytosis and these conditions are relevant to anaesthetic practice. The antihistamine drugs and the H2 receptors agonists are discussed with regard to their role in anaesthesia.

Keywords: histamine structure, function, role in anaphylaxis, anti-histamine drugs

Introduction

Histamine is known to be involved in twenty-three different physiological functions and plays a major role in immunologically mediated inflammation, with multiple pro- and anti-inflammatory effects.

Structure and metabolism[1]

Histamine is a monoamine with the chemical formula $C_5H_9N_3$. It is water soluble with two basic centres, so acts as a singly charged cation. Other similar biological mono- and diamines include adrenalin ($C_9H_{13}NO_3$), noradrenalin ($C_8H_{11}NO_3$) and serotonin ($C_{10}H_{12}N_2O$).

Histamine is synthesised from histidine via the catalytic enzyme *l*-histidine decarboxylase. Histamine is either stored in granules or rapidly metabolised in three ways: via diamine oxidase, (DAO); via histamine -N- methyltransferase or via monoamine oxidase (MAO). The gut and placenta have high levels of DAO.

Most histamine is generated and stored in mast cells and basophils, which collect and reside at sites of potential injury or infection – such as the nose, mouth, feet and the lining surfaces of the gut, lungs and blood vessels. Mast cells have vast arrays of receptors on their surfaces and are able to be activated by a large number of molecules, including complement. Non-mast cell histamine occurs in enterochromaffin-like cells (ECL cells) found in the stomach and gut. In the brain, histamine acts as a neurotransmitter.

Mechanism of action of histamine[2,3]

There are two types of histamine receptors.

1. G-protein coupled receptors

Histamine binds to four sub-types of G-protein coupled histamine receptors, named H_1R to H_4R, and activates two second messenger systems within cells, namely adenylate cyclase (H_2 receptors) and inositol phosphate (H_1 receptors). These result in increased phospholipase levels and the accumulation of intracellular Calcium (Ca^{2+}).

2. Ligand gated chloride channels

Histamine binds to ligand gated chloride channels in the gut and brain and causes inhibition of post-synaptic potentials (the cause of secretions, e.g. secretory diarrhoea). The histamine receptors and their actions are noted in Table I.

Clinical significance of histamine for anaesthesiology

1. Allergic diseases involving histamine[4]

Anaphylaxis

Allergic asthma

Atopic dermatitis

Allergic rhinitis

Food allergies

Allergic drug reactions

2. Gastric acid secretion

3. Histamine intolerance, mast cell activation disease, mastocytosis.

Anaphylaxis[5-8]

Anaphylaxis is a severe, systemic, potentially life-threatening hypersensitivity reaction.

Clinical signs of anaphylaxis

Cutaneous symptoms occur in 80% of cases, with flushing, urticaria, pruritis, angio-oedema.

Table I

Histamine receptor	Actions
H_1R • ubiquitously expressed in many organs, including lungs, blood vessels and mast cells, hepatic cells, epithelium	Regulates the maturation and activation of leucocytes and directs their migration to target sites, where they cause inflammation. Mediates many other types of immune functions – modulates the effect of monocytes, T cells, B cells, macrophages, dendritic cells and eosinophils. Causes Type 1 hypersensitivity reactions with • bronchoconstriction. • vasodilation with decreased blood pressure. • increased blood vessel permeability and local oedema – causes the initial, rapid onset of hypersensitivity symptoms. Mediates the cutaneous "triple response" and allergic skin reactions. Is involved in hyper-nociception of visceral and cutaneous pain; is especially associated with itch perception (sneezing-sensory stimulation mediated by histamine). Hypersecretion from glandular tissue.
H_2R • on ECL cells, lymphocytes also found on blood vessels, lungs and urinary bladder • widely present in the central nervous system – function uncertain	H_2Rs are the final common pathway for gastric acid secretion. Stimulates the production of cytokines from lymphocytes. Provokes the later and sustained drop in blood pressure associated with hypersensitivity reactions. Mediates chronotropic response of heart.
H_3R • exclusively in central nervous system	Important in maintaining the normal blood–brain barrier. Involved in regulation of • sleep-wakefulness cycle, • appetite and feeding, and • memory. Implicated in migraine and headaches. Acts as a neurotransmitter, modulating release of dopamine, acetylcholine, noradrenaline, GABA. Involved in modulation of nociception, itch sensation. Protects against convulsions, stress, dementia.
H_4R • preferentially expressed on various cells of the immune system and on mast cells, also present in epithelia, central nervous system	Involved in the activation of chemotaxis of eosinophils, mast cells, basophils and lymphocyte T cells; controls the release of IL-16 from lymphocytes. Implicated with H_1R in the progression and modulation of histamine mediated allergic diseases.

Respiratory symptoms include nasal congestion, coryza, sneezing, stridor, upper airway respiratory obstruction and wheezing.

Cardiovascular symptoms are related to the hypotension and arrythmias provoked by histamine release and include a metallic taste, feeling of impending doom, headache, blurred vision, dizziness, syncope, chest pain and palpitations.

Diarrhoea, nausea, vomiting and cramps may occur.

Pathophysiology of anaphylaxis

Anaphylaxis is caused by release of chemical mediators, including histamine, leukotriene B_4, interleukins 4 and 13, prostaglandin D_2 and platelet activating factor (PAF) from mast cells and basophils. Histamine release alone is sufficient to produce most of the symptoms of anaphylaxis.

The previously named "classic" form of anaphylaxis requires presensitisation with an allergen and subsequent exposure and is immunoglobulin E (IgE) mediated. The commonest causes of anaphylaxis are drugs, foods, and insect stings. IgE binds to high affinity receptors on mast cells, basophils, neutrophils, eosinophils, monocytes, platelets and dendritic cells, with immediate release of the preformed mediators noted above.

Administration of the anti-IgE antibody omalizumab can reduce the severity of these reactions, but not consistently. Severe reactions can occur with low levels of IgE and conversely, patients with IgE antibodies do not always respond with anaphylactic reactions in the presence of antigens.

The term "anaphylactoid" is no longer used but referred to those anaphylactic reactions mediated by other antibodies such as IgG, or by non-immunological means such as activation by complement C3a, C4a and C5a.

Certain amines, morphine, polymyxin and curare-like compounds can displace histamine from granules in mast cells in a non-allergic manner and cause histamine release. Radiographic contrast agents are also known to release histamine, an effect often wrongly attributed to iodine allergy.

The physiological purpose of histamine release in response to antigens is not clear; in mice these reactions appear to improve survival in response to envenomation with snake venom. Mast cells also appear to secrete anti-anaphylaxis mediators which may help limit the anaphylaxis reaction.

Diagnosis

The diagnosis of anaphylaxis is generally made clinically. National Institute for Health and Clinical Excellence (NICE) guidelines recommend that blood for serum tryptase should be taken within four hours of suspected drug anaphylaxis as confirmation of the diagnosis. β tryptase is stored in basophils and mast cell

granules and is released during anaphylactic reactions, although its function in the condition is unknown.

Anaphylaxis and anaesthesia

Multiple agents used in anaesthesia can cause life-threatening anaphylaxis by acting as haptens to stimulate the formation of antibodies. The incidence of anaphylactic reactions to anaesthesia is recorded as between 1:10 000 and 1:20 000, with a mortality of 3–5%. Common agents include suxamethonium, rocuronium, penicillins, cephalosporins, aspirin, nonsteroidal anti-inflammatories, colloids and latex.

Histamine intolerance[9]

Bacteria, fungi and yeast can also produce histamine from histidine, giving rise to the presence of histamine in various foodstuffs, such as alcohol, matured cheeses, shellfish, smoked meat products, beans, nuts and chocolate. Ingestion of histamine rich foodstuffs, or decreased activity in DAO or MAO can result in symptoms similar, although generally less severe, to anaphylaxis, such as hot flashes, urticaria, itching, dermatographism, hypotension, syncope and "brain fog".

Scombroid food poisoning occurs when food, usually fish, is contaminated by histamine producing bacteria, resulting in high levels of ingested histamine.

Mast cell activation syndrome

Mast cell activation syndrome is an immunological disorder in which mast cells inappropriately and excessively release histamine and other chemical mediators, resulting in both chronic symptoms (cardiovascular, neurological, dermatological) and episodes of anaphylactic type reactions.

Mastocytosis

Mastocytosis is a rare clonal bone marrow disorder that results in accumulation of excessive, functionally deficient mast cells and mast cell precursors. Clinical symptoms include itching, hives and anaphylactic shock.

Both mast cell activation syndrome and mastocytosis may be associated with the occurrence of peri-operative hypersensitivity reactions that may be delayed for up to one hour.[10] Triggers for these reactions are non-specific, and include psychological, pharmacological, mechanical and changes in temperature. There are no current guidelines for anaesthetising patients with these conditions. Avoidance of known triggers, including drugs that release histamine is prudent. Treatment of reactions require adrenalin and fluids. Corticosteroids and histamine blocking drugs are often recommended, although the efficacy of these drugs has not been properly trialled.

Pharmacology of drugs related to histamine[11]

Drugs antagonising the effects of histamine at H_1R and H_2R are commonly used. At present, there are no clinically available antagonists for H_3R and H_4R.

First-generation H_1 antihistamines

H_1R antagonists actually act as inverse agonists at the receptor and are therefore known as antihistamines rather than antagonists. They have been used since the 1950s to treat allergic disorders, psychosis, insomnia and nausea and vomiting.

Many varying chemical substances are known to have H_1 antihistamine effects. They have poor receptor selectivity and so interact with acetylcholine ($C_7H_{16}NO_2$) receptors to produce anti-muscarinic effects as well with α-adrenergic receptors to produce anti α-adrenergic effects.

The 'first' generation antihistamines were lipophilic and crossed the blood–brain barrier easily, producing side effects related to the central nervous system. These included drowsiness, sedation, seizures, extra-pyramidal symptoms, tardive dyskinesia, akathisia and neuroleptic malignant syndrome.

Promethazine ('*Phenergan*') is a phenothiazine that was initially indicated for treatment of psychosis. However, it has only approximately 1/10th of the anti-psychotic effect of chlorpromazine. Indications for use now are to treat allergies, as a sedative and for nausea. Promethazine can cause respiratory depression and is therefore not recommended in children under two years or in the elderly population.

Diphenhydramine ('*Benadryl*') is a first-generation antihistamine commonly used topically and orally for allergies and for insomnia. As with promethazine, anti-cholinergic effects can be prominent (dry mouth, increased heart rate, urinary retention, pupillary dilation). Diphenhydramine acts as a sodium channel blocker, so it has local anaesthetic properties (and has been used as such in patients allergic to the usual local anaesthetics.)

Second-generation H_1 antihistamines[12]

Second-generation antihistamines were developed to reduce the sedative and anti-cholinergic side effects of older drugs. They are used to treat allergic rhinitis, allergic conjunctivitis, urticaria, pruritis caused by atopic eczema, insect bites and angio-oedema. Earlier H_1R antihistamines were associated with QT prolongation but have been discontinued.[13]

H_1R antihistamines can be used as pretreatment together with H_2R antagonists, in cases where anaphylaxis is anticipated.

Ketotifen ('*Zaditor*'), loratadine ('*Claritin*') and cetirizine ('*Zyrtec*') have the advantage of being more lipophobic and therefore less likely to cross the blood–brain barrier.

Use of H_1R antihistamines in anaphylaxis

Adrenalin is recommended universally as first-line treatment for anaphylaxis but is commonly under-utilised, with data indicating that antihistamines are more commonly given.

Antihistamines do not block all the mediators or symptoms of anaphylaxis (including the most serious ones, such as airway

obstruction and hypotensive shock) and they do not act as rapidly as adrenalin, needing 1–3 hours to achieve an effect.

However, there is some evidence to suggest that administration of H_1R antihistamines reduces progression to full blown anaphylaxis amongst emergency department patients with allergic reactions.

H_2R receptor antagonists[14-16]

H_2R antagonists are reversible, highly selective, competitive blockers of histamine at H_2 receptors. They act on gastric parietal cells to reduce the basal and nocturnal hydrochloric acid secretion as well as the secretion after stimulation by ingestion of food.

There are four drugs currently available: cimetidine, ranitidine, famotidine and nizatidine. They have similar efficacy profiles and side effects.

Uses

1. To promote the healing of oesophageal ulceration caused by gastric reflux.
2. As part of a regime to eradicate *H. Pylori* infection, which causes gastric and duodenal ulcers and as part of treatment for Zollinger–Ellison syndrome.
3. Prophylaxis of acid aspiration pneumonitis during anaesthesia and surgery (they decrease the pH of gastric fluid but do not change the volume of gastric fluid).
4. Prevention of stress induced gastric and duodenal ulcers in critical illness.
5. In the treatment of urticaria – both H_1 and H_2 receptors are implicated in the cutaneous response in allergic urticaria.

Of interest

H_2 receptors promote cardiac fibrosis and apoptosis in mice. In a limited observational trial in human heart failure patients, their use was associated with a 15–20% lower mortality over five years as compared to similar patients treated with proton pump inhibitors.

Adverse effects

1. All H_2R antagonists can cause bradycardia and atrio-ventricular blocks by suppressing the positive chronotropic effects of histamine on the heart.
2. Malaise, insomnia, vertigo and confusion can occur.
3. Decreased absorption of vitamin B12 can cause anaemia, and therapy is associated with an increased incidence of clostridium difficile colitis.
4. Cholestatic hepatitis.
5. There is an increased risk of acute gastro-enteritis and community acquired pneumonia in children.
6. All H_2R antagonists are excreted renally but cimetidine in particular is a non-selective inhibitor of cytochrome p-450 enzymes (CYP1A2, CYP2C9 and CYP2D6). Serious interactions have been noted with 143 different drugs and moderate interactions with 193 drugs. Of importance to anaesthesia are interactions with codeine and tramadol, where they inhibit the conversion of the prodrug to the active form, and with warfarin, diazepam, lignocaine, selective serotonin re-uptake inhibitors (SSRIs), carbamazepine, where metabolism is reduced.

Conclusion

Histamine is a monoamine significantly implicated in normal and pathological immunologically mediated inflammation and anaphylaxis; in neurological functions including memory and wakefulness, and is the transmitter involved in gastric acid secretion. H_1R and H_2R antihistamines are used to treat medical conditions such as allergic dermatitis and gastro-oesophageal reflux.

Conflict of interest

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