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THE CENTRAL ROLE OF HISTAMINE IN ALLERGY, ASTHMA, URTICARIA, AND ANAPHYLAXIS

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ABSTARCT
Histamine, primarily stored in mast cells and basophils, is a key mediator in allergic diseases and anaphylaxis. Elevated plasma and tissue histamine levels are associated with allergic responses in the skin, nose, and airways. Through its receptor subtypes, histamine contributes to multiple pathological features: bronchospasm, edema, and mucus secretion in asthma; pruritus, mucosal edema, and sneezing in allergic rhinitis; vasodilation, vascular permeability, and pruritus in urticaria; and vascular permeability, smooth muscle contraction, tachycardia, and mucus secretion in anaphylaxis. Histamine also functions as a neurotransmitter and regulator of gastric acid secretion. It is synthesized from histidine by histidine decarboxylase (HDC), yet the transcriptional regulation of HDC remains poorly understood. Overall, histamine serves as a central mediator in allergic and inflammatory disorders, with emerging research focusing on the molecular regulation of its synthesis.

KEYWORDS: Histamine Allergic diseases Anaphylaxis Asthma, Allergic rhinitis.

INTRODUCTION

Histamine, a biogenic amine, is an important signalling molecule involved in several physiological and pathological processes in the human body. It exerts its effect by interacting with four distinct receptor subtypes: H1, H2, H3, and H4. The H1 receptor is one of these subtypes that has attracted substantial research due to its role in allergic reactions and its association with a variety of clinical disorders. The H1 receptor is found in various tissues and cell types, such as adrenal medulla, chondrocytes, dendritic cells, endothelial cells, liver cells, lymphocytes, muscle cells, nerve cells, respiratory epithelial cells, and vascular smooth muscle cells.[1,2]

The modulation of H1 receptors is particularly significant, as it directly influences the pathophysiology of allergic responses, inflammation, and other histamine-mediated conditions, making it a critical target for therapeutic intervention.

In general, the H1 receptor is primarily associated with the Gq protein, which activates phospholipase C to raise inositol phosphates and intracellular calcium levels; the H2 receptor interacts with the Gs protein, which stimulates cyclic adenosine monophosphate (cAMP) synthesis; and the H3 receptor and H4 receptor signal through the Gi/o proteins.[3]

Smooth muscle cells, endothelial cells, and immune cells are the most common sites of H1 receptor expression.7 Activation of H1 receptors causes a variety of cellular responses, including increased vascular permeability, vasodilation, bronchoconstriction, pruritus, and the production of pro-inflammatory mediators such as histamine, leukotrienes, and prostaglandins.[3]

Histamine synthesis

Histamine is synthesized primarily by mast cells, basophils, histaminergic neurons in the basal ganglia of the brain and enterochromaffin-like cells (ECL) in the stomach. These cells produce large amounts of histamine and are thought to be the major histamine-producing cells. They continuously synthesize histamine, which is then linked to the carboxyl group of heparin and stored in intracellular granules until the cells receive the appropriate activating stimulus. Upon external stimulation, these cells degranulate, releasing the stored histamine. Stimuli that trigger histamine release by these major histamine- producing cells have been reviewed extensively.[4]

Antigen crosslinking of antigen-specific IgE bound to the high-affinity IgE receptor, FcεRI, on the mast cell and basophil surface is the most robust stimulus that triggers histamine release by these cells (20–23). Substance P and allergy-inducing drugs that bind to G-protein-coupled receptors can also trigger basophils and mast cells to

release histamine *via* different signaling pathway. In addition, complement components, such as the C3a and C5a "anaphylatoxins," have also been shown to induce histamine release by mast cells.[5]

Many cytokines, including IL-3, IL-18, IL-33, GM-CSF, and SCF, promote histamine synthesis. In general, cytokines alone do not induce histamine release although it remains controversial whether IL-33 can have this effect. Some reports describe that IL-33 stimulates histamine release HDC is the primary enzyme that catalyzes histamine synthesis.

These mast cell activation-induced increases in *Hdc* mRNA expression and histamine synthesis are also induced by phorbol 12-myristate 13-acetate.[6]

Steps for synthesis of histamine

Step 1: Histamine release

Mast cells and basophils store histamine, which is released in response to immunological or allergic stimulation.

Step 2: Receptor binding

H1 Receptor → Smooth muscle contraction, vascular permeability, and allergy.

H2 Receptor → Heart stimulation, gastric acid secretion

H3 Receptor → CNS neurotransmitter modulation

H4 Receptor → Inflammation, immune cell chemotaxis p.158). H4 Receptor → Inflammation, immune cell chemotaxis

Step: 3 – Physiological / Pathological effect

Physiological/pathological effects include inflammation, neurotransmission, gastric secretion, and allergy.

Storage of histamine

The storage of histamine: In mammalian tissues, histamine is primarily stored in mast cells and basophils. There, it is found in cytoplasmic granules and complexed with heparin and acidic proteins to maintain stability until release.

Histamine Mechanism of Action

Step 1: Following allergen–IgE binding, mast cells and basophils release histamine.

Step 2: Binding of Receptors H1 receptor: Vascular permeability, smooth muscle contraction

Step 3: H2 receptor: stimulation of the heart and secretion of gastric acid

Step 4: Histamine release is decreased by the H3 receptor, a presynaptic autoreceptor

Step 5: Immune cell chemotaxis via the H4 receptor

Step 6: Signalling Within Cells H1 → Gq–PLC–IP3/DAG → ↑Ca^{2+}

Step 7: H2 → Gs–↑cGMP

Step 8: Physiological Outcome: immunological modulation, neurotransmission, gastric secretion, and allergy

ROLE OF HISTAMINE IN VARIOUS DISEASE

Asthma

The cardinal features of asthma include smooth muscle spasm, mucosal edema, inflammation, and mucus secretion, which can be the result of both glandular secretion of mucus glycoproteins and increased movement of interstitial fluid into the airway lumen. Examination of the mediators potentially responsible for causing these pathologic features of asthma reveals that bronchospasm and mucosal edema can be caused by H~-receptor stimulation, whereas H2 and possibly H1 activation may be minor causes of mucus secretion.

It has been elucidated that four types of histamine receptors such as H1, H2, H3, and H4 exist in the airway and pulmonary tissue. The bronchoconstriction of smooth muscle mediated via H1 receptors is one of the most well-known biological actions of histamine in the respiratory system. It was reported long before that histamine evoked a contraction of human bronchi, and bronchoconstriction was recognized first as one of the biological actions of histamine while histamine contracts bronchial smooth muscles as strongly as muscarinic M1 receptor agonists, histamine contracts pulmonary peripheral tissue samples more strongly than M1 receptor agonists. This result seemed to suggest the higher sensitivity of peripheral airways to histamine, although it was possible that the contraction of vascular smooth muscles was involved in the contraction of the pulmonary peripheral tissue samples because the sample contained vessels.[7]

Rhinitis

Rhinitis is broadly defined as inflammation of the nasal mucosa. It is a common disorder that affects up to 40% of the population. Allergic rhinitis is the most common type of chronic rhinitis, affecting 10–20% of the population, and evidence suggests that the prevalence of the disorder is increasing. Severe allergic rhinitis has been associated with significant impairments in quality of life, sleep and work performance. In the past, allergic rhinitis was considered to be a disorder localized to the nose and nasal passages, but current evidence indicates that it may represent a component of a systemic airway disease involving the entire respiratory tract. There are a number of physiological, functional and immunological relationships between the upper (nose, nasal cavity, paranasal sinuses, Eustachian tube, pharynx and larynx) and lower (trachea, bronchial tubes, bronchioles and lungs) respiratory tracts.[8]

Examination of the putative mediators reveals that histamine can cause all the pathologic features of allergic rhinitis, with the exception of late-phase inflammatory reaction. Pruritus, which is responsible for the palatal clicking so characteristic of allergic rhinitis, is caused by stimulation of HI receptors on sensory nerve endings; prostaglandins may also contribute. Mucosal edema, which manifests as nasal obstruction, can be caused by H~ stimulation as well as eicosanoids and kinins.

Sneezing, like prutitus, is an Hi-mediated neural reflex and can also be mediatedby eicosanoids. Nasal mucus secretion can be mediated by histamine both directly and indirectly through muscarinic discharge and by eicosanoids.

Atropic dermatitis (AD)

Atopic dermatitis (AD) is an allergic inflammatory disease characterized by intense pruritus, chronic eczematous plaques, and relapsing inflammation induced by repeated exposure to an antigen.1 The prevalence of AD was reported to be approximately 3% in adults and 25% in children, and has increased by 2- to 3-fold during the last century in industrial countries.

By activating the H1 receptor on sensory nerves and immune cells, histamine plays a role in the inflammation and itching of the skin in AD. Additionally, it encourages inflammatory cell recruitment and vascular permeability in skin lesions. Although antihistamines reduce itching, complex histamine-mediated immune dysregulation is frequently a part of chronic AD.

(H2R) is involved in the release of gastric acid.15 H1R and H2R are expressed on many cell types including inflammatory and immune cells and modulate their functions. Histamine H3 receptor (H3R), which is primarily expressed in the nervous system, acts as a presynaptic autoreceptor in central and peripheral neurotransmission.16 Histamine H4 receptor (H4R), which was cloned in 2000, is mainly expressed on several hematopoietic cells and plays important roles in the histamineinduced activation of mast cells, eosinophils, monocytes, DC, and T cells.

Vigorous pruritus is the most important issue requiring a therapeutic strategy in AD, more so than allergic inflammation. However, pruritus associated with AD is poorly controlled clinically. The mediators of pruritus have been extensively studied, and histamine has been shown to be a potent pruritogen when applied to both normal skin in healthy individuals26 and the lesional skin of AD patients.27 However, although the itching associated with a nettle rash is potently alleviated by H1R antagonists, whether histamine is involved in the pruritus of AD has yet to be confirmed.[9]

Urticaria

The hallmark of urticaria is a pruritic, erythematous raised lesion that blanches with pressure; this sign is indicative of venous dilation and edema. Therefore the three cardinal features of urticaria are pruritus, vasodilation, and increased vascular permeability involvingthe superficial dermis. Histamine, acting through its H1 receptor, can mediate all three pathologiccomponents of urticaria: it is the only proved mediator of pruritus and can mediate vascular permeability and vasodilation. Other vasoactive mediators that might contribute to vasodilation and edema include prostaglandin D2, leukotrienes C4 and D4, platelet-activating factor, and bradykinin. Prostaglandin D2 is a vasodilator, whereas leukotrienes C4 and C4 mediate increased vascular permeability. These eicosanoids may act synergistically in the skin." Release of platelet-activating factor, which can mediate increased vascular permeability, has been measured during experimentally induced cold urticaria. Bradykinin, which is generated in the tissues after mast cell degranulation, is also a potent vasoactive substance that induces a burning pain. Bradykinin may be a more prominent mediator in angioedema, which is characterized by deep dermal vasodilation and edema concomitant with burning pain.[9]

Anaphylaxis

Inflammation is a response triggered by damage to living tissues. The inflammatory response is a defense mechanism that evolved in higher inflammation response triggered by damage to living tissues. The inflammatory response is a defense mechanism that evolved in higher organisms to protect them from infection and injury .Its purpose is to localize and eliminate the injurious agent and to remove damaged tissue components so that the body can begin to heal. Histamine has been established to play a pathophysiological regulatory role in cellular events through binding to four types of G-proteincoupled histamine receptors that are differentially expressed in various cell types. Histamine [2-(4- imidazolyl)-ethylamine] is an endogenous shortacting biogenic amine synthesized from the basic amino acid histidine through the catalytic activity of the rate-limiting enzyme histidine decarboxylase and widely distributed throughout the body. One of the first described functions was its ability to mimic anaphylaxis and has since been demonstrated to play a major role in inflammatory processes.[10]

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