

Role of Histamine in Acute Inflammation

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Abstract

Aim:

To enhance the role of histamine in acute inflammatory reaction

Objective:

Histamine is a vasoactive amine that plays an important role in the early acute inflammatory response. This review enhances the activity of histamine in the acute inflammatory reaction.

Background:

Histamine is stored in the granules of mast cells, basophils, platelets. This histamine is released from these cells by the stimuli inducing acute inflammation, anaphylatoxins, and histamine releasing factors. Histamine increases the vasodilatation, and also increases the vascular permeability in the immediate transient phase of the acute inflammatory reaction. This act as a chemical mediator in acute inflammation.

Keywords- Vasoactive amine, vasodilatation, chemical mediator, mast cells.

INTRODUCTION

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 [1]. The response consists of changes in blood flow, an increase in permeability of blood vessels, and the migration of fluid, proteins, and white blood cells (leucocytes) from the circulation to the site of tissue damage. An inflammatory response that lasts only a few days is called acute inflammation, while a response of longer duration is referred to as chronic inflammation [1]. Histamine has been established to play a pathophysiological regulatory role in cellular events through binding to four types of G-protein-coupled histamine receptors that are differentially expressed in various cell types. Histamine [2-(4-imidazolyl)-ethylamine] is an endogenous short-acting 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 [2]. Histamine biologically active substance found in a great variety of living organisms. It is distributed widely, albeit unevenly, throughout the animal kingdom and is present in many plants and bacteria and in insect venom. Histamine is chemically classified as an amine, an organic molecule based on the structure of ammonia (NH₃). It is formed by the decarboxylation (the removal of a carboxyl group) of the amino acid histamine. Histamine is a chemical neurotransmitter produced by the body during an allergic reaction, most noticeably causing skin, nose, and throat and lung irritation. These reactions are part

of the inflammatory response, which is an important part of the overall immune response [2]. The fundamental pleiotropic regulatory character of histamine in cellular events is attributed to its binding to four subtypes of G-protein-coupled receptors (GPCR), designated H₁, H₂, H₃ and H₄ that are differentially expressed in various cell types [2].

SOURCE OF HISTAMINE

The English scientists George Barger and Henry H. Dale first isolated histamine from the plant fungus ergot in 1910. Plants that produce histamine include stinging nettles; the histamine in the hair like structures on nettle leaves is partly responsible for the swelling and itching produced by contact with them [3]. Histamine is also the irritating ingredient present in the venom of many species of wasps and bees. In humans histamine is found in nearly all tissues the body, where it is stored primarily in the granules of tissue mast cell. The blood cells called basophils also harbour histamine-containing granules [3].

STORAGE AND RELEASE OF HISTAMINE

Most histamine in the body is generated in granules in mast cells and in white blood cells called basophils and eosinophils. Mast cells are especially numerous at sites of potential injury — the nose, mouth, and feet, internal body surfaces, and blood vessels. Non-mast cell histamine is found in several tissues, including the brain, where it functions as a neurotransmitter [4]. Another important site of histamine storage and release is the enterochromaffin like cell (ECL) of the stomach. The most important pathophysiologic mechanism of mast cell and basophil histamine release is immunologic. These cells, if sensitized by IgE antibodies are attached to their membranes, degranulate when exposed to the appropriate antigen [4]. Certain amines and alkaloids including such drugs as morphine and curare alkaloids can displace histamine in granules and cause its release. Antibiotics like polymyxin are also found to

stimulate histamine release. Histamine release occurs when allergens bind to mast-cell-bound IgE antibodies. Reduction of IgE overproduction may lower the likelihood of allergens finding sufficient free IgE to trigger a mast-cell-release of histamine [5].

EVENTS IN ACUTE INFLAMMATION

Once acute inflammation has begun, a number of outcomes may follow. These include healing and repair, suppuration and chronic inflammation. The outcome depends on the type of tissue involved and the amount of tissue destruction that has occurred, which are in turn related to the cause of the injury [6].

(a) *Healing And Repair*

During the healing process, damaged cells capable of proliferation regenerate. Different types of cells vary in their ability to regenerate. For regeneration to be successful, it is also necessary that the structure of the tissue be simple enough to reconstruct. For example, uncomplicated structures such as the flat surface of the skin are easy to rebuild, but the complex architecture of a gland is not. In some cases, the failure to replicate the original framework of an organ can lead to disease [6].

Repair, which occurs when tissue damage is substantial or the normal tissue architecture cannot be regenerated successfully, results in the formation of a fibrous scar. Through the repair process, endothelial cells give rise to new blood vessels, and cells called fibroblasts grow to form a loose framework of connective tissue [1]. As repair progresses, new blood vessels establish blood circulation in the healing area, and fibroblasts produce collagen that imparts mechanical strength to the growing tissue. Eventually a scar consisting almost completely of densely packed collagen is formed [1].

(b) *Suppuration*

The process of pus formation, called suppuration, occurs when the agent that provoked the inflammation is difficult to eliminate. Pus is a viscous liquid that consists mostly of dead and dying neutrophils and bacteria, cellular debris, and fluid leaked from blood vessels [6]. Once pus begins to collect in a tissue, it becomes surrounded by a membrane, giving rise to a structure called an abscess. Because an abscess is virtually inaccessible to antibodies and antibiotics, it is very difficult to treat. Sometimes a surgical incision is necessary to drain and eliminate it [6]. Some abscesses, such as boils, can burst of their own accord. The abscess cavity then collapses, and the tissue is replaced through the process of repair [1].

HISTAMINE RECEPTORS

Histamine activity is mediated through the activation of one of four specific histamine receptors, designated H₁, H₂, H₃, or H₄, in target cells [2]. Most histamine-induced vascular effects are mediated by H₁ receptors [2]. H₂ receptors mediate some vascular effects but are more important for their role in histamine-induced gastric secretion. Less is understood about the role of

H₃ receptors, which may be localized to the CNS [21]. H₄ receptors are located on cells of hematopoietic origin, and H₄ antagonists are promising drug candidates to treat inflammatory conditions involving mast cells and eosinophils (allergic conditions). Among this four the H₄ receptors play an important role in inflammatory conditions [21].

EFFECT OF HISTAMINE IN IMMUNE SYSTEM

Histamine H₄ receptor is a pertussis-toxin-sensitive GPCR predominantly expressed on cells of the immune system, including MCs, monocytes, eosinophils, dendritic cells (DCs), T cells and natural killer cells in peripheral tissues such as spleen, thymus, colon, blood leukocytes and bone marrow, its expression being induced or altered in response to inflammatory stimuli [7]. Chemotaxis to sites of inflammation via Gai/o proteins and increases in intracellular Ca²⁺ concentration. Eosinophils chemotaxis Histamine was first described as a selective chemo attractant for eosinophils more than 30 years ago. In a retrospective literature evaluation, the reported histamine effects on eosinophils chemotaxis can now be attributed to the H₄ receptor. The existence of a histamine receptor on the surface of eosinophils that was distinct from H₁, H₂ or H₃ receptors and demonstrated low-affinity binding for R-(a)methyl histamine antagonized by the H₃/H₄ antagonist thioperamide was hypothesized in 1994 [7]. Concrete evidence that H₄ receptors control leukocyte trafficking and pro-inflammatory responses was derived from the H₄ receptor-mediated histamine-induced activation of eosinophils increased expression of adhesion molecules like CD11b/CD18(Mac1) and CD54(ICAM-1) and rearrangement of the actin cytoskeleton leading to eosinophils migration from the bloodstream into the sites of inflammation [8]. Histamine was originally considered to be a mediator involved in the immediate hypersensitivity response. It has also been shown to affect leukocyte function and migration. It is involved in inhibition of lectin- or antigen-induced proliferation of T cells, release of lymphokines from T cells, the induction of cytotoxic T cells, cytolysis by mature cytotoxic T cells, B cell differentiation, lysosomal enzyme release in neutrophils, IgE-mediated histamine release from basophils, and in chemokinetic effects on neutrophils and eosinophils [9]. These actions can be blocked by H₂ antagonists. Many of these effects on leukocyte function are inhibitory and can be seen as anti-inflammatory actions, which can limit antibody hypersensitivity. However, H₁ effects of histamine on blood vessels and skin are proinflammatory and occur during hypersensitivity reactions. It has been proposed that histamine initially promotes and later inhibits immune responses [4].

ACTION OF HISTAMINE IN INFLAMMATION

Histamine produces many of the effects of inflammation and hypersensitivity, including

vasodilation, edema, increased vascular permeability, and smooth muscle contraction [5]. Increased vascular permeability causes fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction – a runny nose and watery eyes [10]. It is thought to be a major mediator of the acute inflammatory response, although histamine H1 antagonists have little effect on acute inflammation [5]. Histamine plays a pivotal role in many types of allergic and inflammatory processes, including both acute and delayed hypersensitivity reactions [5]. The source of histamine in such cases is tissue mast cells. The magnitude of such problems depends on the route of exposure (local versus systemic), sites of exposure (e.g. inhaled versus cutaneous), the dose of allergen, and the degree of previous sensitization to the allergen. Clinical manifestations of histamine release vary from life-threatening anaphylactic reactions, to urticaria (hives), to local wheal and flare reactions. Many of the signs of allergic reaction result from the ability of histamine to affect blood vessels, inducing increased blood flow, vasodilation and increased vascular permeability [10].

VASCULAR CHANGES

When tissue is first injured, the small blood vessels in the damaged area constrict momentarily, a process called vasoconstriction. Following this transient event, which is believed to be of little importance to the inflammatory response, the blood vessels dilate (vasodilation) increasing blood flow into the area. Vasodilation may last from 15 minutes to several hours. Next, the walls of the blood vessels, which normally allow only water and salts to pass through easily, become more permeable. Protein-rich fluid, called exudate, is now able to exit into the tissues [11]. Substances in the exudate include clotting factors, which help prevent the spread of infectious agents throughout the body. Other proteins include antibodies that help destroy invading microorganisms. As fluid and other substances leak out of the blood vessels, blood flow becomes more sluggish and white blood cells begin to fall out of the axial stream in the centre of the vessel to flow nearer the vessel wall [10]. The white blood cells then adhere the blood vessel wall, the first step in their emigration into the extravascular space of the tissue [10].

CELLULAR EVENTS

The most important feature of inflammation is the accumulation of white blood cells at the site of injury. Most of these cells are phagocytes, certain “cell-eating” leukocytes that ingest bacteria and other foreign particles and also clean up cellular debris caused by the injury [11]. The main phagocytes involved in acute inflammation are the neutrophils, a type of white blood cell that contains granules of cell-destroying enzymes and proteins. When tissue damage is slight, an adequate supply of these cells can be obtained from those already circulating in the

blood. But, when damage is extensive, stores of neutrophils some in immature form are released from the bone marrow, where they are generated.

To perform their tasks, not only must neutrophils exit through the blood vessel wall but they must actively move from the blood vessel toward the area of tissue damage. This movement is made possible by chemical substances that diffuse from the area of tissue damage and create a concentration gradient followed by the neutrophils [12]. The substances that create the gradient are called chemotactic factors, and the one-way migration of cells along the gradient is called chemotaxis [11]. Large numbers of neutrophils reach the site of injury first, sometimes within an hour after injury or infection. After the neutrophils, often 24 to 28 hours after inflammation begins, there comes another group of white blood cells, the monocytes, which eventually mature into cell-eating macrophages. Macrophages usually become more prevalent at the site of injury only after days or weeks and are a cellular hallmark of chronic inflammation [13].

OTHER ACTIONS OF HISTAMINE

Gastric Secretion: The most important action of histamine, in a clinical sense, is its stimulation of gastric acid secretion by acting on H2-receptors. It is implicated in the formation of peptic ulcers [5].

Smooth Muscle Effects: Histamine causes contraction of the smooth muscle of the ileum, bronchi and bronchioles, and uterus by acting on H1-receptors. It may be involved in increased peristalsis associated with food allergies [3]. Histamine-induced bronchiolar constriction has been implicated in the first phase of bronchial asthma [5]. In asthmatics, histamine was found to increase airway smooth muscle tone and cause mucosal edema and glandular secretion, resulting in the narrowing of the airways and limited air flow. In nonasthmatics, bronchial activity to histamine was limited, most likely due to fewer H1-receptors in airway smooth muscle [19].

Cardiovascular Effects: Acting on H1-receptors, histamine causes the dilation of blood vessels; it induces endothelial cells to synthesize vascular smooth muscle relaxants, including prostacyclin and nitric oxide, which cause vasodilation [3]. Acting on H2-receptors, it increases heart rate and cardiac output. When injected intradermally, histamine leads to reddening of the skin, wheal, and flare, called the “triple response”. Vasodilation of small arterioles and precapillary sphincters causes reddening, while increased permeability of postcapillary venules causes the wheal; both these effects are implicated in activation of H1-receptors. Histamine does not increase capillary permeability. Histamine also induces an “axon reflex”, which leads to stimulation of sensory nerve fibers and the release of a vasodilator mediator; this causes the flare [5].

Itching: If histamine is injected into the skin, it causes itching, due to stimulation of sensory nerve endings [5].

Effects on Nasal Mucosa: Allergens can bind to IgE-loaded mast cells in the nasal mucosa, which leads to three clinical responses: sneezing results from histamine-associated sensory neural stimulation; hypersecretion from glandular tissue occurs; nasal mucosal congestion results due to vascular engorgement associated with vasodilation and increased capillary permeability [20].

CONCLUSION

Acute phase response is generated during inflammation. Histamine is a vasoactive amine that plays an important role in the early acute inflammatory response. Histamine is stored in the granules of mast cells, basophils, platelets. This histamine is released from these cells by the stimuli inducing acute inflammation, anaphylatoxins, and histamine releasing factors. Histamine increases the vasodilatation, and also increases the vascular permeability in the immediate transient phase of the acute inflammatory reaction. This histamine also acts as a chemical mediator in acute inflammation. The receptors of histamine is also involved in acute inflammatory reaction. This review enhances the role of histamine in acute inflammation. Apart from its action in inflammatory reaction, it also performs other functions like gastric secretion, smooth muscle effects, cardiovascular effects, itching and effects on nasal mucosa. This review article elaborately deals with the events occurring in acute inflammation, the pathogenesis of acute inflammation, the action of histamine in acute inflammation and the role of their receptors in the process of acute inflammation.

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