An overview of the pharmacological activity of Histamine on acute inflammation

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Abstract- Inflammatory mediators, including cytokines, histamine, bradykinin, prostaglandins, and leukotrienes, impact the immune system, usually as proinflammatory factors. Other mediators act as regulatory components to establish homeostasis after injury or prevent the inflammatory process. Histamine, a biogenic vasoactive amine, causes symptoms such as allergies and has a pleiotropic effect that is dependent on its interaction with its four histamine receptors. In this review, we discuss the dualistic effects of histamine: how histamine affects inflammation of the immune system through the activation of intracellular pathways that induce the production of inflammatory mediators and cytokines in different immune cells and how histamine exerts regulatory functions in innate and adaptive immune responses. We also evaluate the interactions between these effects. Mast cells, basophils, and platelets all store histamine in their granules. Stimuli that cause acute inflammation, anaphylatoxins, and histamine-releasing factors all release histamine from these cells. In the immediate transitory phase of an acute inflammatory reaction, histamine causes vasodilation and increases vascular permeability. In acute inflammation, this acts as a chemical mediator.

Index Terms- Vasoactive amine, vasodilation, chemical mediator, mast cells.

I. INTRODUCTION

Inflammation is a reaction that occurs when living tissues are damaged. The inflammatory response is a defense mechanism that evolved in response to greater levels of inflammation produced by living tissue damage. The inflammatory response is a defense mechanism that evolved to protect higher organisms from infection and harm. Its goal is to find and remove the harmful substance as well as damaged tissue components so that the body can start to mend. Changes in blood flow, an increase in blood vessel permeability, and the migration of fluid, proteins, and white blood cells (leukocytes) from the circulation to the site of tissue damage are all part of the reaction. Acute inflammation refers to an inflammatory response that lasts only a few days, whereas chronic inflammation refers to a response that lasts longer. Through binding to four types of G protein-coupled histamine receptors that are variably expressed in distinct cell types, histamine has been shown to play a pathophysiological regulatory role in cellular events. Histamine [2-(4-imidazolyl)-ethylamine] is an endogenous short-acting biogenic amine made from the basic amino acid histidine by the enzyme histamine synthase. The rate-limiting enzyme histidine decarboxylase has catalytic activity and is broadly distributed throughout the body. Its ability to imitate anaphylaxis was one of the earliest activities reported, and it has since been shown to play a key part in inflammatory processes. Histamine is a physiologically active chemical that can be found in a wide range of living things. It is found in numerous plants, microorganisms, and insect venom, and is widely distributed, if unevenly, throughout the animal kingdom. 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 created by the body during an allergic reaction, which irritates the skin, nose, throat, and lungs. These reactions are a part of the inflammatory response, which is a critical component of the overall immune response. Histamine's primary pleiotropic regulatory nature in cellular events is attributable to its binding to four subtypes of G-protein-coupled receptors (GPCR), designated H1, H2, H3, and H4, which are expressed differently in distinct cell types. [1]

II. HISTAMINE

Many of the symptoms of allergies, such as a runny nose or sneezing, are caused by histamine, a substance contained in certain of the body's cells. When a person is allergic to an item, such as food or dust, the immune system makes the error of thinking that this normally harmless substance is detrimental to the body. The immune system initiates a chain reaction that causes some of the body's cells to release histamine and other substances into the bloodstream in an attempt to defend the body. The histamine then causes allergy symptoms in the eyes, nose, throat, lungs, skin, and gastrointestinal tract. Antihistamine drugs, as you may know, serve to alleviate symptoms caused by the release of histamine during an allergic reaction.[2]

III. SOURCE OF HISTAMINE

Many of the symptoms of allergies, such as a runny nose or sneezing, are caused by histamine, a substance contained in certain of the body's cells. When a person is allergic to an item, such as food or dust, the immune system makes the error of thinking that this normally harmless substance is detrimental to the body. The immune system initiates a chain reaction that causes some of the body's cells to release histamine and other substances into the bloodstream in an attempt to defend the body. The histamine then causes allergy symptoms in the eyes, nose, throat, lungs, skin, and

gastrointestinal tract. Antihistamine drugs, as you may know, serve to alleviate symptoms caused During an allergic reaction, histamine is released. Histamine is a biogenic amine. Smooth muscles, vascular endothelial cells, the heart, and the central nervous system all express it. Phospholipase C and the inositol triphosphate (IP3) signaling pathway are activated.[3]

H1 Receptors

H1 receptor, which is coupled to an intracellular G-protein (G_q). Antihistamines, which work by blocking this receptor, are used to treat allergies. The receptor's crystal structure (shown on the right) was identified and used in structure-based virtual screening tests to find novel histamine H1 receptor ligands.[4]

H2 Receptors

H2 Receptors Adenylate cyclase is favorably linked to H2 receptors via G_s. It is a strong inducer of cAMP synthesis, which results in protein kinase A activation. PKA affects the activity of specific proteins by phosphorylating them. A histamine H2 receptor agonist like borazole is an example.

H3 Receptors

Receptors for H3 Histamine H3 receptors are found in the central nervous system and, to a lesser extent, the peripheral nervous system, where they function as autoreceptors in presynaptic histaminergic neurons and regulate histamine turnover through feedback regulation of histamine production and release. The H3 receptor has also been demonstrated to presynaptic ally block the release of a variety of other neurotransmitters, including but not limited to dopamine, GABA, acetylcholine, noradrenaline, histamine, and serotonin (i.e., it serves as an inhibitory heteroreceptor).[5]

The H4 Receptors

The Receptors for H4 The substance histamine H4R is expressed on a range of immune cells as well as other cells such as the spleen, intestinal epithelia, lung, synovial tissue, central nervous system, sensory neurons, and cancer cells, and is linked to G proteins. H4R stimulation inhibits forskolin-induced cyclic AMP synthesis, resulting in MAPK activation and increased Ca++ release. In both autocrine and paracrine ways, H4R mediates histamine's pro-inflammatory effects. Histamine increases eosinophil migration via increasing adhesion molecule expression, cell shape modification, and cytoskeletal rearrangement via H4R.[5].

Histamine Receptor	Expression	Activated intracellular signals	G-proteins
HR1	Never cell, airway, and vascular smooth muscles, hepatocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, mono- cites, DC, T, and B cells	Ca+, cGMP, phospholipase D, phospholipase $A_{2'}$ NF_K B	$G_{Q\ 11}$
HR2	Nerves cell, airway, and vascular smooth muscles, hepatocytes, endothelial cells, epithelial cells, neutrophils, eosinophils, mono- cites, DC, T, and B cells	Adenylate cyclase, c-AMP, c-Fos, c-Jun, PKC, $_P$70S6K	$G\alpha_a$
HR3	Histaminergic neurons, eosinophils, DC monocytes, low expression in peripheral tissues	Enhanced MAP-K Kinase, inhibition of cAMP	$G_{i/0}$
HR4	Mast cells, eosinophils, leukocytes, monocytes, CD8+Tcells, basophils, dendritic cells, spleen, bone marrow	Immunomodulation	$G_{i/0}$

[6]

Histamine, also known as 2-[3H-imidazol-4-yl] ethanamide, is a chemical mediator that produces vasodilation and enhanced vascular permeability, as well as contributing to anaphylactic reactions. It also affects cell differentiation, proliferation, hematopoiesis, and cell regeneration, among other physiological activities. Histamine is made by decarboxylating the amino acid histidine with the enzyme L-histidine decarboxylase (HDC), which is found in neurons, parietal cells, stomach mucosal cells, mast cells, and basophils; histamine is broken down by the enzyme diamine oxidase (DAO)Histamine deamination is catalyzed by histamine N-methyltransferase (HNMT). Because HNMT loss is linked to aggressive behavior and irregular sleep-wake cycles in mice, it may serve a vital regulatory role in the central nervous system. Four histamine receptors (HRs), H1R, H2R, H3R, and H4R, are G protein-coupled receptors that mediate histamine's pleiotropic actions. These receptors' active and inactive conformations coexist peacefully. Agonists stabilize the active conformation of these receptors, whereas antagonists stabilize the

inactive conformation. Surprisingly, the aging process reduces the expression or activity of HRs, as well as HDC and DAO enzymes. May play a role in the development of allergic responses and neurological diseases.[6] Chronic itch in the elderly is a common condition caused by physiological changes in aging skin, such as reduced skin barrier function and alterations in immunological, neurological, and psychological systems. H1R is found in neurons, endothelial cells, the adrenal medulla, muscle cells, hepatocytes, chondrocytes, monocytes, neutrophils, eosinophils, DCs, T cells, and B cells, among other cell types. Prostacyclin synthesis, platelet factor activation, nitric oxide, arachidonic acid, and its metabolites, thromboxane synthesis, and smooth muscle cell contraction are all triggered by H1R signaling. Furthermore, H1R activation results in enhanced eosinophil and neutrophil chemotaxis at the site of inflammation, increased antigen-presenting cell (APC) functional capability, activation of Th1 lymphocytes, and decreased humoral immunity but increased IgE synthesis. H1R antagonists, such as pyrilamine, fexofenadine, diphenhydramine, and promethazine, are commonly used to treat allergy symptoms, as would be predicted given their biological activities.[7]

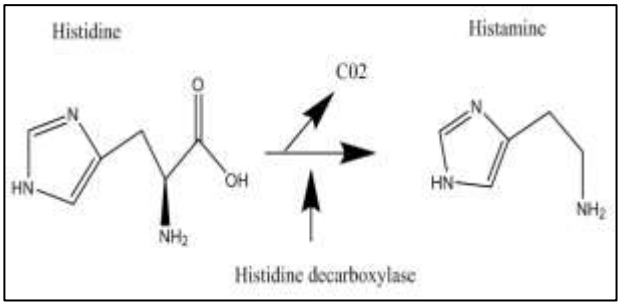
H1R signaling causes intracellular transcription factors like IP3 to become active (inositol triphosphate), Phospholipase C (PLC), protein kinase C (PKC), diacylglycerol (DAG), and calcium (Ca2+). H1R and H4R signaling have recently been linked to MAPK signaling and cAMP build-up, which results in enhanced proinflammatory gene expression. Furthermore, H1R activation is required for the development of Th1 responses, whereas H2R controls Th2 responses. Mice lacking the H1R gene have an increased Th2 profile due to a reduction in Th1 responses. Furthermore, H1R was shown to play a significant role in coordinating the recruitment of Th2 cells to the site of allergic lung inflammation in an experimental allergy paradigm, alongside histamine.[8]

Gastric mucosa parietal cells, muscular, epithelial, endothelial, neuronal, hepatocyte, and immunological cells all express H2R. H2R counteracts part of the effects of H1R and causes smooth muscle cell relaxation, resulting in vasodilation. Activation of the H2R regulates several histamine-mediated processes, including heart contraction, stomach acid secretion, cell proliferation, and differentiation. In DCs, it also works as a suppressor molecule, boosting the production of IL-10. Histamine works on H2R and inhibits leukotriene production in human neutrophils via cAMP-dependent protein kinase (PKA) signaling, according to a recent study. H2R depletion affects invariant natural killer T (iNKT) cells in a mouse lung inflammation model, exacerbating local inflammation. H2R activation counterbalances the Toll-like receptor (TLR) response in monocyte-derived DCs from healthy adult participants, resulting in suppression of CXCL10, IL-12, and TNF-stimulated IL-10, which is likely related to Th2 polarization. TLR-associated NF-B and AP-1 pathways are inhibited by cAMP activation, [3] which happens downstream of H2R activation. While mast cell and basophil-mediated allergy diseases are mostly caused by H1R and H2R activation, H3R functions to govern the release of histamine and other neurotransmitters have been discovered in the central nervous system, peripheral and presynaptic receptors. The asymmetry of histamine via H3R reduces the release of acetylcholine in the mouse cortex, which inhibits cAMP production and Ca2+ build-up and so controls neurogenic inflammation. H3R knockout mice develop obesity, implying that H3R regulates insulin resistance and leptin release,[6] as well as a reduction in homeostatic energy, the cellular process for coordinating homeostatic regulation of food intake (energy inflow) and energy expenditure (energy outflow), as linked to the UCP1 and UCP3 genes. Bronchoconstriction, pruritus (without mast cell participation), enhanced proinflammatory activity, and antigen-presentation capacity may all be linked to H3R expression. Histaminergic neurons are involved in neuromodulation and the awake state. Constant activation of aminergic maintains the waking state (such as histamine, dopamine, noradrenaline, and acetylcholine). HRs are found in the brain in three subtypes, not just on neurons but also on astrocytes and blood vessels. GABAA receptor positive-allosteric modulators that operate on histamine neurons in the posterior hypothalamus cause natural NREM-like sleep. Targeting the histamine and noradrenergic systems could help researchers develop more accurate sedatives while also revealing more about the normal sleep-wake cycle. Histamine H3R antagonists/inverse agonists could be useful for CNS diseases. An experimental investigation found that when microglia-mediated inflammation is induced by LPS, histamine protects dopaminergic neurons, indicating the down-modulatory capacity of histamine and/or HR agonists.[7] This discovery could aid in the development of novel treatment options for neurodegenerative diseases. The gut, spleen, thymus, bone marrow, peripheral hematopoietic cells, and cells of the innate and adaptive immune systems all express H4R. IFN, TNF-, IL-6, IL-10, and IL-13 stimulate H4R expression, which causes cAMP build-up to be inhibited and MAPK (mitogen-activated protein kinases) to be activated. Chemotaxis occurs when this receptor is activated in mast cells and eosinophils, resulting in an influx of inflammatory cells and DC control of cytokine production.H4R is also implicated in Th2 cells' enhanced production of IL-31. The H4R antagonist reduces pruritus in mice in response to histamine, IgE, and compound 48/80, and its inhibitory impact is stronger than that of H1R antagonists. HRs are found on tumor cells, making them sensitive to fluctuations in histamine. Using this synthetic H4R antagonist in a mouse encephalomyelitis model increased clinical and pathological symptoms of the disease, suggesting a modulatory role [8]. High levels of histamine are linked to bivalent behavior in the regulation of numerous malignancies (including cervical, ovarian, vaginal, uterine, vulvar, colorectal, and melanoma) by stimulating or preventing their growth. The presence of H3R and H4R in human mammary tissue implies that H3R is involved in regulating breast cancer growth and progression, implying that antihistamines could be used as cancer chemotherapy adjuvants. A decrease in H4R expression on iNKT cells is associated with reduced production of IL-4 and IFN- by those cells in HDC-deficient animals, demonstrating that these factors are regulated. Several investigations have revealed that histamine regulates DC activity by potentiating antigen endocytosis,[9] increasing intracellular Ca2+ mobilization, and other mechanisms. Promoting F-actin polymerization and MHC class II molecule production in immature DCs generated from monocytes. H3R/H4R antagonists impede cross-presentation, which is the capacity to push MHC II-associated antigens towards the MHC I pathway. In an H1R/H2R-dependent manner, histamine also affects T cell polarization by blocking IFN- or LPS-driven IL-12 production. H4R acts as a

modulator in APCs (DCs and monocytes) by inhibiting inflammation and lowering the production of IL-12 and CCL2. Males are more likely to get asthma throughout childhood, whereas girls are more likely to develop asthma during adolescence and maturity. In addition, allergy disorders are prevalent among women of childbearing age. During pregnancy, asthma and atopic dermatitis might worsen, improve, or stay the same. Female hormones, such as estrogen, can influence how the body works. Males and females have distinct histamine receptors, which could explain why men and women have varying allergy rates. H2R and H3R, for example, are more heavily expressed in female rats than male rats and are downregulated in ovariectomized females, although H1R is expressed equally in both sexes.[10]

IV. SYNTHESIS AND METABOLISM OF HISTAMINE

L-histidine decarboxylase (HDC), which requires the cofactor pyridoxal-5′-phosphate, produces histamine by decarboxylating histidine. Mast cells and basophils are the primary sources of granule stored histamine, which is tightly linked to anionic proteoglycans and chondroitin-4-sulfate. When these cells degranulate in response to numerous immunologic and nonimmunologic stimuli, histamine is produced. Furthermore, certain myeloid and lymphoid cell types (dendritic cells [DCs] and T cells) that do not retain histamine have high HDC activity and can produce large amounts of histamine.[11] In vitro, cytokines such as IL-1, IL-3, IL-12, IL18, GM-CSF, macrophage colony-stimulating factor, TNF-, and calcium ionophore affect HDC function. LPS stimulation, for example, has been used to demonstrate HDC activity in vivo. HDC-deficient mice provided histamine-free platforms for researchers to investigate the role of endogenous histamine in a variety of normal and pathological processes. These mice have fewer mast cells and have much lower granule content, suggesting that histamine may impact mast cell granule protein production. The production of HDC is induced by IgE binding to the FCRI on IL3–dependent murine bone marrow-derived mast cells via a signaling route separate from that used during antigen-stimulated FCRI activation. Before excretion, about 97 percent of histamine is digested in two primary routes. 10 Histamine The majority of histamine is converted to Methylhistamine by N methyltransferase, which is then converted to the principal urinary metabolite M-methylimidazole acetic acid by monoamine oxidase. 15% to 30% of diamines are metabolized by diamine oxidase.[12]



[6]

V. STORAGE AND RELEASE OF HISTAMINE

The majority of histamine in the body is produced in mast cell granules and white blood cells known as basophils and eosinophils. Mast cells are abundant in possible damage locations such as the nose, mouth, and foot, as well as internal body surfaces and blood arteries. Histamine from non-mast cells can be detected in a variety of tissues, including the brain, where it acts as a neurotransmitter. The enterochromaffin-like cell (ECL) in the stomach is another significant site for histamine storage and release. The immunologic mechanism is the most important pathophysiologic mechanism of mast cell and basophil histamine release. If IgE antibodies have sensitized these cells, they are linked to their membranes. It degranulates when exposed to the right antigen. Histamine can be displaced from granules and released by certain amines and alkaloids, such as morphine and curare alkaloids. Antibiotics like polymyxin have also been shown to raise histamine levels. Histamine is released when allergens attach to mast-cell-bound IgE antibodies. Reduced IgE overproduction may lower the chances of allergens finding enough free IgE to cause mast cell histamine release.[13]

VI. ACUTE INFLAMMATION

Acute inflammation normally lasts a few minutes to a few days, depending on the severity of the injury. The arrival of leukocytes, initially neutrophils and later macrophages, is indicated by the release of fluid and blood plasma proteins. The influx of various blood and tissue proteins such as cytokines and growth factors occurs as a result of increased blood flow into the injury site due to vascular dilatation. The infiltration and accumulation of leukocytes from blood arteries into the injury site, which is the most essential characteristic of the inflammatory process, is triggered by these. During the first several days after an injury, neutrophils are the most common cell type.[14] They arrive in vast numbers and are largely responsible for phagocytosing germs and foreign materials, as well as cleaning up injury-related debris. Neutrophils have a short lifespan, disintegrating and disappearing after 24–48 hours. The neutrophils are replaced by monocytes that specialize in macrophages during the next several days to weeks. These cells have a long lifespan and can last for months. Microorganisms are phagocytosed by macrophages, which also clean up dead tissue cells and neutrophils. Acute inflammation normally goes away within a week, but a longer period indicates infection.[15]

VII. CHRONIC INFLAMMATION

Chronic inflammation, on the other hand, can be caused by other undesired elements in the body, such as toxins from cigarette smoke or an overabundance of fat cells (especially fat in the belly area). Inflammation inside arteries contributes to atherosclerosis, the build-up of fatty, cholesterol-rich plaque. Because this plaque is aberrant and foreign to your body, it tries to isolate it from the flowing blood. However, if that wall fails, the plaque may rupture. The contents then mix with blood and form a clot, which prevents blood flow. The majority of heart attacks and strokes are caused by blood clots.[16]

VIII. HISTAMINE AND INFLAMMATION

Histamine's interaction with the HR1 mediates several anaphylactic symptom-related actions. However, there is growing evidence that it affects a variety of immune/inflammatory and effector activities. Histamine promotes the course of allergic inflammatory reactions by increasing the secretion of proinflammatory cytokines such as IL-1, IL-1, and IL-6, as well as chemokines such as RANTES and IL-8, in a variety of cell types and tissues. In explant cultures of the human nasal mucosa, histamine activates the CC chemokines, monocyte chemotactic protein 1 and 3, RANTES, and eutaxon via HR1, implying a longer inflammatory cycle in allergic rhinitis between the cells that produce histamine and their accelerated migration to the nasal mucosa. Endothelial cells have functioning HR1 and HR2, as well as enhanced production of adhesion molecules such as ICAM-1 and VCAM-1. Histamine impacts the overall inflammatory response by regulating the expression of its receptors on endothelial cells.[17] In many mechanisms, histamine governs granulocyte accumulation in tissues. H1-antihistamines effectively suppress allergen-induced eosinophil accumulation in the skin, nose, and airways. Histamine's effect on eosinophil migration varies depending on the dose. High concentrations limit eosinophil chemotaxis via HR2, whereas low amounts promote chemotaxis via HR1. HR4, the histamine receptor responsible for the selective recruitment of eosinophils, was recently discovered. Histamine has all of the features of a traditional leukocyte chemoattractant (agonist-induced actin polymerization, intracellular calcium mobilization, etc.) Upregulation of adhesion molecule expression and changes in cell structure). When compared to the powerful CCR3-active ß-chemokines eotaxin and eotaxin-2, histamine's chemo attractive capacity to eosinophils is limited. However, when the HR4 is activated, histamine causes eosinophils to migrate further towards eotaxin and eotaxin-2. Other variables, such as growth factors or cytokines like IL-5, the cytokine specialized for eosinophil development, activity, and survival, may enhance the ability of histamine alone to operate as an eosinophil chemoattractant in vivo. Mast cell chemotaxis is also induced when HR4 is triggered. Mast cells from wild-type and HR3 receptor-deficient animals moved in response to histamine, whereas mast cells from HR4 receptor-deficient mice did not thus, the HR4 is primarily responsible for eosinophil and mast cell chemotaxis induced by histamine.[18] HR4 antagonists can stop histamine's persistent inflammatory effects, and combination therapy with HR1 antagonists are a potential method. Due to HR2 triggering, histamine inhibits neutrophil chemotaxis, which is mimicked by impromidine (HR2 agonist), but not by betahistine (HR1 agonist). Histamine also suppresses neutrophil activation, superoxide production, and degranulation through HR2. Downregulation of NF-B, a potent transcription factor involved in the initiation of inflammation, could be one way by which H1-antihistamines reduce inflammatory cell accumulation. Low dosages of H1 antihistamines, cetirizine, and azelastine have been shown to decrease pro-inflammatory cytokines while also inhibiting NFB expression. Histamine primarily produced from non-mast cells has a crucial role in angiogenesis and the formation of inflammatory granulation, according to a recent study using HDC deficient and mast cell-deficient animals.[19]

IX. ACTION OF HISTAMINE IN INFLAMMATION

Vasodilation, edema, increased vascular permeability, and smooth muscle contraction is all impacts of histamine, which causes inflammation and hypersensitivity. Fluid escapes from capillaries into tissues when vascular permeability rises, resulting in the classic symptoms of an allergic reaction: a runny nose and watery eyes. Although histamine H1 antagonists have a limited effect on acute inflammation, it is regarded to be a significant modulator of the acute inflammatory response. Histamine is involved in a variety of allergic and inflammatory reactions, including acute and delayed hypersensitivity reactions. Tissue mast cells are the source of histamine in such circumstances. The severity of such issues is determined by the route of exposure (local versus systemic), as well as the exposure sites (e.g. inhaled versus cutaneous), the allergen dosage, and the degree of previous allergy sensitization Histamine release can cause life-threatening anaphylactic reactions, urticaria (hives), and local wheal and flare reactions, among other symptoms. Many symptoms of an allergic reaction are caused by histamine's capacity to influence blood vessels, causing increased blood flow, vasodilation, and vascular permeability.[20]

X. VASCULAR CHANGES

When tissue is wounded, the small blood arteries in the afflicted area tighten for a brief period, a process known as vasoconstriction. The blood vessels widen (vasodilation) in reaction to this brief event, which is thought to have little impact on the inflammatory response. This increases blood flow into the location. Vasodilation might last anywhere from 15 to several hours. The walls of the blood arteries then become more permeable, allowing just water and salts to pass through easily. Exudate, a protein-rich fluid, can now leave the body and enter the tissues. Clotting factors, which assist restrict the transmission of infectious pathogens throughout the body, are found in the exudate. Antibodies, for example, aid in the destruction of invading bacteria. Blood flow becomes increasingly sluggish as fluid and other chemicals leak out of the blood vessels, and white blood cells begin to fall out of the axial stream in the vessel's center and flow closer to the vessel wall. The white blood cells then cling to the blood vessel wall, marking the start of their emigration into the tissue's extravascular region.[15]

XI. CELLULAR EVENTS

The accumulation of white blood cells at the site of injury is the most critical aspect of inflammation. The majority of these cells are phagocytes, which are leukocytes that devour bacteria and other foreign particles as well as clean up cellular debris left behind by the injury. Neutrophils, a type of white blood cell that carries granules of cell-destroying enzymes and proteins, are the predominant phagocytes engaged in acute inflammation. When tissue damage is minor, these cells can be acquired in sufficient quantities from those already circulating in the circulation. When the damage is severe, however, some immature neutrophils are discharged from the bone marrow, where they are produced. Neutrophils must not only exit through the blood vessel wall to

complete their job, but they must also actively migrate from the blood vessel to the location of tissue damage[10]. Chemical compounds that diffuse from the location of tissue damage and produce a concentration gradient followed by neutrophils enable this migration. Chemotactic factors are the molecules that form the gradient, and chemotaxis is the one-way migration of cells along the gradient. Large numbers of neutrophils arrive immediately at the site of damage or infection, sometimes within an hour. After the neutrophils, which arrive 24 to 28 hours after the inflammation starts, another type of white blood cell, monocytes, arrive, which eventually mature into cell-eating macrophages. Macrophages, a cellular characteristic of persistent inflammation, become more abundant at the site of injury only after days or weeks [12].

XII. HISTAMINE'S OTHER ACTIONS

Secretion from the stomach:
Histamine stimulates stomach acid secretion via acting on H2-receptors, which is its most important therapeutic activity. It has been linked to the development of peptic ulcers.
Effects on Smooth Muscle:
Histamine acts on the smooth muscle in the ileum, bronchi and bronchioles, and uterus to produce a contraction. It could have a role in the increased peristalsis that comes with food allergies. The earliest stage of bronchial asthma has been linked to histamine-induced bronchiolar constriction. Histamine was discovered to raise airway smooth muscle tone and produce mucosal edema and glandular secretion in asthmatics, resulting in airway constriction and reduced airflow. Bronchial activity to histamine was reduced in non-asthmatics, most likely due to fewer H1-receptors in airway smooth muscle.[8]
Cardiovascular system:
Histamine produces blood vessel dilatation by inducing endothelial cells to produce vascular smooth muscle relaxants such as prostacyclin and nitric oxide, which cause vasodilation. It raises heart rate and cardiac output by acting on H2-receptors. Histamine causes reddening of the skin, wheal, and flare when injected intradermally. The reddening is caused by vasodilation of tiny arterioles and precapillary sphincters, while the wheal is caused by increased permeability of postcapillary venules; both of these effects are linked to H1-receptor activation. Capillary permeability is not increased by histamine. Histamine also generates an "axon reflex," which causes sensory nerve fiber stimulation and the release of a vasodilator mediator, resulting in the flare. Itching is caused by the activation of sensory nerve endings when histamine is injected into the skin.[3]
Nasal Mucosa Effects:
Allergens can bind to IgE-loaded mast cells in the nasal mucosa, resulting in three clinical responses. Sneezing occurs as a result of histamine-induced sensory neuronal stimulation; glandular tissue hypersecretion occurs; nasal mucosal congestion ensues as a result of vascular engorgement caused by vasodilation and increased capillary permeability.[7]

Immunoregulatory effects of Histamine:
properties Cells that present antigens Dendritic cells (DCs) are antigen-presenting cells that evolve from monocytic and lymphoid precursors to become the DC1 and DC2 phenotypes, which aid in the development of Th1 and Th2 cells, respectively. During cytokine-induced DC differentiation, endogenous histamine is actively produced, acting in an autocrine and paracrine manner to modify DC markers. histamine is involved in the functions and activities of DC precursors, both immature and adult versions. Both immature and mature DCs express all four HR, although their levels of expression have not been compared. HR1 and HR3 operate as positive stimulants in the differentiation of DC1 from monocytes, increasing antigen presentation capacity, proinflammatory cytokine secretion, and TH1 priming activity. HR2, on the other hand, suppresses antigen-presenting capacity, increases IL-10 synthesis, and promotes IL-10-producing T cells or TH2 cells.[15] Histamine reduces the production of pro-inflammatory IL-1-like activity, TNF, IL-12, and IL-18 in monocytes activated with Toll-like receptor triggering bacterial products, but increases IL-10 secretion through HR2 activation. CD14 expression is also suppressed by histamine via H2 receptors. Histamine's inhibitory impact on the H2-receptor is mediated by the control of ICAM-1 and B7.1 expression, resulting in a decrease in the innate immune response elicited by LPS. Due to the activation of HR1 and HR3 subtypes, histamine causes intracellular Ca++ flow, actin polymerization, and chemotaxis in immature DCs. The loss of these reactions occurs as DCs mature. Histamine, on the other hand, increases intracellular cAMP levels and boosts IL-10 secretion in developing DCs while blocking IL-12 synthesis via HR2. Interestingly, while human monocyte-derived dendritic cells (MODC) have both H1 and H2 receptors and can trigger histamine production, human epidermal Langerhans cells do not, owing to TGF.G [15]

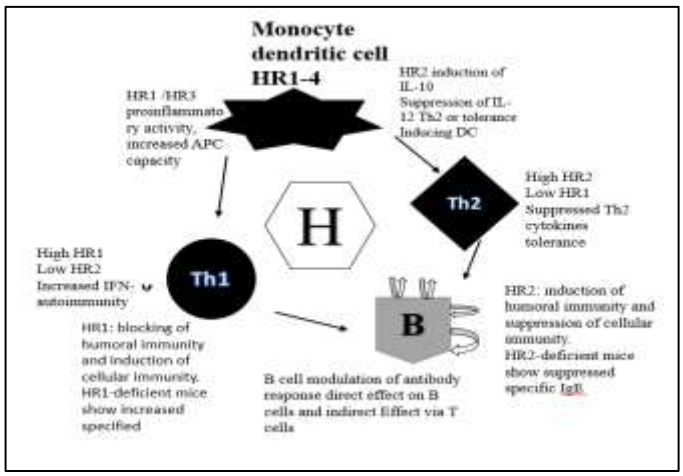


Figure - Immunoregulatory effects of Histamine [6]

XIII. EVENTS IN ACUTE INFLAMMATION

Several consequences may occur once acute inflammation has commenced. Healing and repair, suppuration, and persistent inflammation are among them. The outcome is determined by the type of tissue implicated and the extent of tissue loss, both of which are related to the injury's source. [14]
(a) Regeneration and healing Damaged cells that are capable of proliferation renew throughout the healing process. The ability of different types of cells to regenerate varies. The structure of the tissue must also be simple enough to recreate for regeneration to be successful. Simple structures like the flat surface of the skin,

for example, are simple to reconstruct, but the complex design of a gland is difficult. Failure to duplicate an organ's original framework can result in illness in specific situations. The creation of a fibrous scar occurs when tissue damage is significant or when the normal tissue architecture cannot be properly repaired. Endothelial cells give rise to new blood vessels throughout the repair process, while fibroblasts develop to build a loose connective tissue framework. As the healing process continues, new blood vessels form in the healing area, and fibroblasts generate collagen, which gives the growing tissue mechanical strength. Eventually, a scar is produced that is virtually entirely made up of densely packed collagen.[12]

(b) Suppuration, or the production of pus, occurs when the agent that caused the inflammation is difficult to remove. Pus is a viscous liquid made up largely of dead and dying neutrophils and bacteria, as well as cellular debris and blood vessel fluid. When pus collects in a tissue, it forms an abscess, which is enclosed by a membrane. It is extremely difficult to treat an abscess because antibodies and antibiotics are almost inaccessible to it. To drain and eradicate it, a surgical incision may be required. Some abscesses, such as boils, might spontaneously explode. The abscess cavity closes, and the tissue is replaced as part of the healing process. Inflammation is triggered by histamine. Activated cells create inflammatory mediators, which enhance and extend the inflammatory response. Histamine is a powerful inflammatory mediator that promotes vascular and tissue alterations while also acting as a chemoattractant. It is usually connected with allergy reactions. In addition to stimulating actin filament rearrangement, histamine binding to eosinophil H4R causes enhanced production of macrophage-1 antigen (Mac1) and ICAM-1 adhesion molecules.[10] These circumstances encourage eosinophils to migrate from the circulation to the site of inflammation. Histamine binding to this same receptor stimulates intracellular calcium release and mast cell migration into tissues in mast cells. H4R-knockout mice's mast cells lose their capacity to move against a histamine gradient. The recruitment of these cells to inflammatory sites increases histamine-mediated inflammatory reactions and may favor the creation of a persistent inflammatory response. Histamine promotes granulocyte infiltration into the intestinal mucosa in experimental animals, which causes colitis. The binding of histamine to H1R stimulates the synthesis of the proinflammatory cytokine IL-6 and -glucuronidase, a hallmark of exocytosis, in human lung macrophages, and the release These findings imply that histamine may have a role in maintaining inflammatory conditions in the lungs. When activated with LPS, activation of H2R in rat peritoneal macrophages suppresses the generation of TNF- and IL-12.

XIV. HISTAMINE STIMULATES INFLAMMATION

Histamine appears to have a key role in allergic inflammation, according to new research. When patients with allergies are exposed to certain antigens, histamine levels rise locally or systemically. Human lung parenchyma and skin tissues include histamine-containing cells, which can be activated in response to a variety of immunologic and nonimmunologic events, epithelial damage and basement membrane rupture are linked to lysosomal enzymes. These findings imply that histamine may have a role in maintaining inflammatory conditions in the lungs. When activated with LPS, activation of H2R in rat peritoneal macrophages suppresses the generation of TNF- and IL-12. [9]

ROLE OF HISTAMINE IN ALLERGIC DISORDERS

Histamine appears to have a key role in allergic inflammation, according to new research. When patients with allergies are exposed to certain antigens, histamine levels rise locally or systemically. Human lung parenchyma and skin tissues include histamine-containing cells, which can be activated in response to a variety of immunologic and nonimmunologic events. Several chemokines from peripheral blood recruit peripheral blood basophils to allergic inflammatory sites. Basophils, for example, can be seen at the site of inflammation in human skin during late-phase reactions and in the lung parenchyma in bronchial asthma. This shows that histamine is an endogenous mediator in allergic inflammation, as it is secreted locally by tissue mast cells and invading basophils. The rationale for employing H1-receptor antagonists to treat allergic rhinoconjunctivitis, urticaria, and atopic dermatitis stems from these discoveries.[13]

XV. RELEVANCE OF HISTAMINE IN THE CYTOKINE NETWORK IN ALLERGIC INFLAMMATION

Histamine has been found to stimulate and/or modify cytokine production in allergic inflammation. Direct effects of histamine on cytokine production and modification of cytokine synthesis produced by immunologic stimuli have both been demonstrated. Histamine, for example, differentially modulates IL-4 and IFN- release from T cells; inhibits TNF- and IL-12 production by human monocytes; directly induces IL-1026 and IL-18 synthesis from human monocytes; inhibits IFN-, TNF-, and IL-12 production while increasing IL-10 production in LPS- or mitogen-activated peripheral blood mononuclear cells; and enhances IL-1–induced IL-6 production by monocyte 30 The activation of H1 H2 and H3 receptors mediates histamine's complicated effects on immune cell cytokine production. The fourth type of histamine receptor (H4) has just been cloned and functionally and pharmacologically identified. The H4-receptor shares several properties with the histamine receptors previously discovered in human eosinophils. These surprising findings show that histamine, long assumed to be a chemical mediator of acute inflammation, may play a more nuanced function in the control of the cytokine network than previously thought. Low amounts of histamine, such as those detected in the bronchoalveolar lavage fluid of individuals with bronchial asthma or at other sites of allergic inflammation, have lately been investigated as a potential activator of human lung macrophages. The significant abundance of macrophages in the human lung parenchyma and BAL fluid prompted researchers to investigate this cell. Furthermore, macrophages are typically present in human airways close to histamine-containing cells. Macrophages purified (>98%) from the lung parenchyma of thoracic surgery patients were treated with low doses of histamine for 1 to 18 hours, which mimicked those released in vivo in various pathophysiologic situations. Histamine increased the basal release of -glucuronidase, a hallmark of exocytosis in macrophages, in a concentration-dependent manner, as previously demonstrated. Histamine, interestingly, caused macrophages to produce IL-6 from scratch. The H1-agonist 6-[2-(4-imidazolyl) ethylamine]

replicated these results. - N-(4-trifluoromethylphenyl) heptane carboxamide, but not the H2-agonist dimaprit, indicating that they were H1- receptors. Furthermore, histamine increased intracellular Ca2+ concentrations in macrophages in a concentration-dependent manner. These findings support the notion that H1-receptor activation is linked to intracellular Ca2+ influx, and they suggest that this signaling pathway is also active in human macrophages. The H1-mediated activation of macrophages was validated by showing that increasing concentrations of the selective H1-receptor antagonist fexofenadine suppressed histamine-induced IL-6 production in a concentration-dependent manner. The administration of histamine (10–7 mol/L) to human lung macrophages after preincubation with fexofenadine (10–5 mol/L) prevented intracellular Ca2+ concentration rises. The H2-antagonist ranitidine did not affect histamine-induced IL-6 production or Ca2+ signaling (data not shown). Low amounts of histamine enhance exocytosis and IL-6 production in macrophages via activating H1-receptors and increasing intracellular Ca2+ signaling, according to our findings. This finding presents the fascinating notion that histamine is involved in the long-term management of inflammation and tissue remodeling through altering macrophage activities. The finding that fexofenadine inhibits IL-6 production in macrophages could have clinical implications. Indeed, it appears that prolonged fexofenadine treatment for patients with allergic diseases may avoid not just acute symptoms, but also some of the mechanisms involved in chronic inflammation and tissue damage and remodeling associated with macrophage activation.[20]

XVI. IN VITRO ANTI-INFLAMMATORY EFFECTS OF THE H1-RECEPTOR ANTAGONISTS

It has been known that high concentrations of first-generation antihistamines inhibit in vitro histamine release from human basophils. Moreover, certain H1-antagonists prevent not only the release of histamine but also that of other pro-inflammatory mediators such as cysteinyl leukotrienes and platelet-activating factors. It is important to emphasize that not all H1-receptor antagonists have such anti-inflammatory activities in vitro. Indirect evidence suggests that some H1-receptor antagonists inhibit the release of pro-inflammatory mediators from human skin and nasal mucosa in vivo. These effects are probably not related to H1-receptor antagonism but rather to interference with the cell membrane or to inhibition of the metabolic steps required for cell activation. Although these inhibitory effects are concentration-dependent in vitro, they generally require higher doses than those recommended for symptom relief in allergic rhinoconjunctivitis or urticaria. Thus, their clinical relevance is still uncertain.[17]

XVII. IN VIVO BRONCHOPROTECTIVE EFFECTS OF H1-RECEPTOR ANTAGONISTS

It is well known that histamine inhalation causes bronchoconstriction in asthmatic patients. This effect of histamine inhalation is used as a tool to evaluate airway hyperreactivity in patients with allergic disorders. Histamine levels are higher in BAL fluid from asthmatic patients than in normal individuals, and a correlation has been found between the concentration of BAL histamine and bronchial hyperreactivity. Herxheimer54 was the first to propose antihistamines be used to treat bronchial asthma. However, early antihistamines could not be given in high doses because of their sedative effects. Several studies have looked at the effects of antihistamines on histamine and methacholine challenges. For example, it has been shown that terfenadine causes a small but significant improvement in FEV1 and a shift to the right of the dose-response curve of histamine challenge in asthmatic patients. It should be noted, however, that high doses of antihistamines were used in these studies and that the continuous use of such doses to treat bronchial asthma might expose some patients to unwanted side effects.[1]

XVIII. H1-RECEPTOR ANTAGONISTS IN PATIENTS WITH ALLERGIC DISORDERS OF UPPER AND LOWER AIRWAYS

H1-receptor antagonists are effective in the treatment of allergic rhinitis. The effects of H1-receptor antagonists in bronchial asthma were studied in several early investigations. Even high dosages of H1-receptor antagonists failed to establish a positive impact on persistent asthma in these early studies,60, and these drugs may or may not have a glucocorticoid-sparing effect in asthma. Allergy rhinitis and bronchial asthma, on the other hand, frequently coexist, and the two disorders are anatomically and immune pathologically linked. In patients with mild to severe bronchial asthma and allergic rhinitis, typical dosages of H1-receptor antagonists have been linked to a reduction in concomitant asthma symptoms and an improvement in pulmonary function in recent trials. The results of these studies suggest that there might be a potential role for some antihistamines in the treatment of patients with mild to moderate asthma associated with allergic rhinitis.[3]

XIX. OTHER ANTI-INFLAMMATORY EFFECTS

Now, we'll go through the effects of H1 antihistamines on eosinophils and superoxide production briefly. Eosinophils and their mediators appear to play a major role in the etiology of allergy diseases such as seasonal allergic rhinitis (SAR) and asthma, according to mounting data. In vivo investigations have shown that eosinophils are readily identifiable in the nasal secretions of allergic rhinitis patients following exposure to the allergen and that the number of eosinophils correlate with the severity of rhinitis symptoms during the pollen season. New antihistamines have been shown in studies to reduce the recruitment of eosinophils to the sites of allergic inflammation by inhibiting ICAM-1 expression or, for example, by inhibiting the release of histamine, entering the skin of platelet-activating-factor (PAF). Antihistamines, such as cetirizine, have been demonstrated to inhibit PAF-induced eosinophil chemotaxis at therapeutic doses. Eosinophil chemotaxis has also been studied with other antihistamines. Ketotifen, in the example, has been shown to inhibit PAF-induced eosinophil chemotaxis in vitro at concentrations lower than those required to suppress LTC4 synthesis. Both loratadine and terfenadine were found to prevent chemotaxis of human eosinophils caused by PAF at concentrations comparable to or marginally above those expected in the blood following a single oral dose in research by Eda et al. Desloratadine

has been shown to reduce platelet-aggregation factor-induced chemotaxis by up to 36% in vitro tests involving eosinophils.[2] These eosinophils in vitro effects have now been extended to human research. During allergy season, circulating eosinophil progenitors often decrease, as trafficking from the circulation to the nasal mucosa is thought to occur preferentially under the impact of local and systemic allergic inflammatory mediators. A double-blind, randomized placebo Desloratadine's influence on eosinophil progenitors in the peripheral blood was studied in a controlled study. During a four-week treatment with desloratadine or placebo, progenitor cells from 45 patients with symptomatic SAR were investigated. After 14 days, the number of peripheral blood eosinophil progenitors decreased more with placebo than with desloratadine. Although the underlying mechanism is unknown, these findings show that desloratadine can impact the systemic trafficking of eosinophil precursors during the allergic response in individuals with SAR. Antihistamines have an extra anti-inflammatory effect on neutrophil activities. Superoxide anions, which induce tissue damage, are produced by neutrophils. Studies have demonstrated that new antihistamines inhibit superoxide generation. An early investigation of human neutrophils found that ketotifen decreased superoxide radical production driven by calcium ionophore A23187, concavalin A, and fMLP and that this effect required lower drug doses than chemotaxis inhibition. Cetirizine, on the other hand, has been shown to reduce neutrophil superoxide radical generation only at doses greater than 35 mg/mL, which are higher than those required to suppress chemotaxis. Antihistamines' suppressive effects on neutrophils have been proven in numerous studies since then. Cetirizine can block the release of neutrophil lysosomal enzymes, according to Van Epps et al & Werner et al. discovered that azelastine and arteriole suppress MLP-induced neutrophil elastase release. Desloratadine inhibits superoxide formation in neutrophil and monocyte preparations, according to Paubert-Braquet albeit these effects may be more significant in lung/bronchial inflammation than allergic inflammation of the nasal mucosa. Finally, we discovered that the quantity and function of -adrenoceptors were increased. This action increases the effectiveness of -adrenergic bronchodilators, which are used to treat bronchial asthma. Long-term therapy of bronchial asthmatics with basophils may result in 2- adrenoceptor desensitization. Agonists, and may reduce the effectiveness of -adrenergic agonists.[7] The density of -adrenoceptors on circulating lymphocytes has been utilized to explore the function of 2-adrenoceptors in humans. On lymphocytes from bronchial asthmatics who have been treated with -adrenergic bronchodilators, ketotifen enhances 2-adrenoceptor density. In reaction to inhaled salbutamol, there was a substantial rise in the peak expiratory flow rate. In addition, the number of β2-adrenoceptors was higher in azelastine and terbutaline-treated guinea pig lungs than in lungs treated with terbutaline alone, showing that azelastine may prevent β-adrenergic agonist-induced downregulation of the number of β2-adrenoceptors. T lymphocytes play a critical role in the modulation of the immune response in allergic reactions. Th2 cells secrete various cytokines including IL4, IL5, IL 6, IL 9, IL 10 and IL 13. The release of IL 4 and IL 5 is of particular significance because these cytokines have been shown to contribute to the activation of basophils and eosinophils IL 4 and IL13 also play an important role in the inflammatory response through their involvement in the proliferation and differentiation of B cells into plasma cells that secrete IgE. As the secretion of cytokines from lymphocytes, particularly the Th2 subset of lymphocytes, appears to be central to the establishment and maintenance of allergic inflame Antihistamines including azelastine, terfenadine, and ketotifen stop mitogen-stimulated peripheral blood lymphocytes from producing IL 2, IL 3, IL 4, and IL 5. Nori et al. have investigated the effect of ebastine on Th2-type cytokine production. They found that ebastine decreased the secretion of IL 4, and IL 5, but not IL2 or INF in T cells taken from healthy non-atopic subjects in vitro. With ketotifen, this effect was not found. Antihistamines, on the other hand, may interfere with cytokine-basophil and epithelial cells. Desloratadine was reported to be an inhibitor of Ige-mediated IL 4 and IL 13 secretion from human basophils by Schroeder et ablation, it seemed pertinent to examine the effects of antihistamines on these cytokines production by T cells.[14] Antihistamines such as azelastine, terfenadine, and ketotifen inhibit IL 2, IL 3, IL 4, and IL 5 production by mitogen-stimulated peripheral blood lymphocytes Nori et al. have recently evaluated the effect of ebastine on the production of Th2-type cytokines. Using T cells derived from healthy non-atopic volunteers, they showed that ebastine inhibited the secretion in vitro of IL 4, and IL-5 but not IL2 and INF-γ. This effect was not observed with ketotifen. However, antihistamines could interfere with cytokine-basophil and epithelial cells too. In particular, Schroeder et al. found that desloratadine was an inhibitor of Ige-mediated IL 4 and IL 13 secretion from human basophils. As is well known, such regulation is important because IL 4 and IL13 control Ige production, mast cell growth and development, and expression of adhesion molecules such as ICAM-1, VLA-4, and B-cell growth and development. The effect of antihistamines on cytokine production by epithelial cells was investigated by Arnold et al. They demonstrated that cetirizine reduced the release of IL 8 from A549 cells stimulated with PMA and TNFα. IL 8 is a chemokine that possesses chemotactic activity for neutrophils, and, as a consequence, plays a causative role in the pathogenesis of many acute inflammatory reactions [14].

XX. CONCLUSION

During inflammation, an acute phase response is produced. Histamine is a vasoactive amine that is involved in the early stages of the acute inflammatory response. Mast cells, basophils, and platelets all store histamine in their granules. Stimuli that cause acute inflammation, anaphylatoxins, and histamine-releasing factors all release histamine from these cells. In the immediate transitory phase of an acute inflammatory reaction, histamine causes vasodilation and increases vascular permeability. In acute inflammation, histamine also works as a chemical mediator. Histamine receptors are also involved in the acute inflammatory response. The importance of histamine in acute inflammation is highlighted in this review. It also has other activities, such as stomach secretion, smooth muscle effects, cardiovascular effects, itching, and effects on the nasal mucosa, in addition to its inflammatory response. The events that occur in acute inflammation, the etiology of acute inflammation, the action of histamine in acute inflammation, and the involvement of their

receptors in the process of acute inflammation are all covered in depth in this review article.

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