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(REVIEW ARTICLE)

Targeting histamine signaling in inflammation and allergy: A mechanistic and therapeutic review

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Abstract

Histamine, which is produced from the amino acid histidine, is involved in allergic reactions because it interacts with various G protein-coupled receptors (H_1, H_2, H_3 and H_4). This study looks into the molecular actions of histamine-mediated signaling in allergy and inflammation, especially how it brings about leukocyte recruitment, regulates the flow of fluid into tissues and activates mast cells and basophils. Today, we can understand more about the origins of disease after advances in how histamine receptors vary their distribution in various cells and the series of reactions they trigger. The research also looks into new drugs designed for specific patients as well as classical therapies targeting the actions of histamine. Research on recent findings is used to highlight both the clinical use of histamine compounds and their potential future roles in allergy disorders, chronic inflammatory diseases and autoimmune diseases. The paper stresses that research into histamine plays a major role in resolving medical issues that patients face and improving their outcomes.

Keywords: Histamin; Allergic reactions; Chronic inflammatory diseases; Autoimmune diseases; Inflammation; Molecular action

1. Introduction

Together with others in 1910, Sir Henry Dale observed that histamine caused the widening of blood vessels and contraction of uterine smooth muscle (Dale and Laidlaw, 1910). Over the past century, it has been realized that histamine plays an important role in various processes, mostly in inflammation and allergic reactions (Panula et al., 2015). Various biological effects of histamine are mediated by four different G protein-coupled receptors (GPCRs) which are identified as H_1, H_2, H_3 and H_4. Every GPCR is found in specific tissues, uses a certain signaling process and leads to different physiological effects (Thurmond et al., 2008).

The breakdown of L-histidine into a different substance by HDC is mainly responsible for forming histamine in mast cells, basophils, histaminergic neurones and ECL cells (Ohtsu, 2010). Simons and Simons state in their work from 2011 that histamine is first stored in secretory granules and it is released if there are signals such as allergen-triggered crosslinking of IgE bound to FcεRI on mast cells and basophils (type I hypersensitivity reactions). Asthma, atopic dermatitis, urticaria, anaphylaxis and allergic rhinitis belong to inflammatory or allergy-related diseases and are

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marked by the release of histamine that causes immediate and delayed reactions leading to inflammation (Church and Maurer, 2018). Besides affecting allergic inflammation, histamine is now linked to neuroinflammation, autoimmune diseases and cancer too, thanks to recent studies (Branco et al., 2018).

Penicillin allergy can be treated with a variety of options such as antihistamines and H_1 receptor antagonists which underlines the importance of histamine in treating allergic conditions. On top of that, there are ongoing scientific trials to create receptor blockers, drugs that influence multiple targets and methods that stop the body from producing or letting out histamine(Fajt and Wenzel, 2017).

The review focuses on the molecular steps related to the formation, storage and release of histamine and looks at how histamine works in allergic and inflammatory events. Besides, we evaluate the available strategies that target histamine pathways and look into new approaches that aim to manage conditions involving inflammation and allergies.

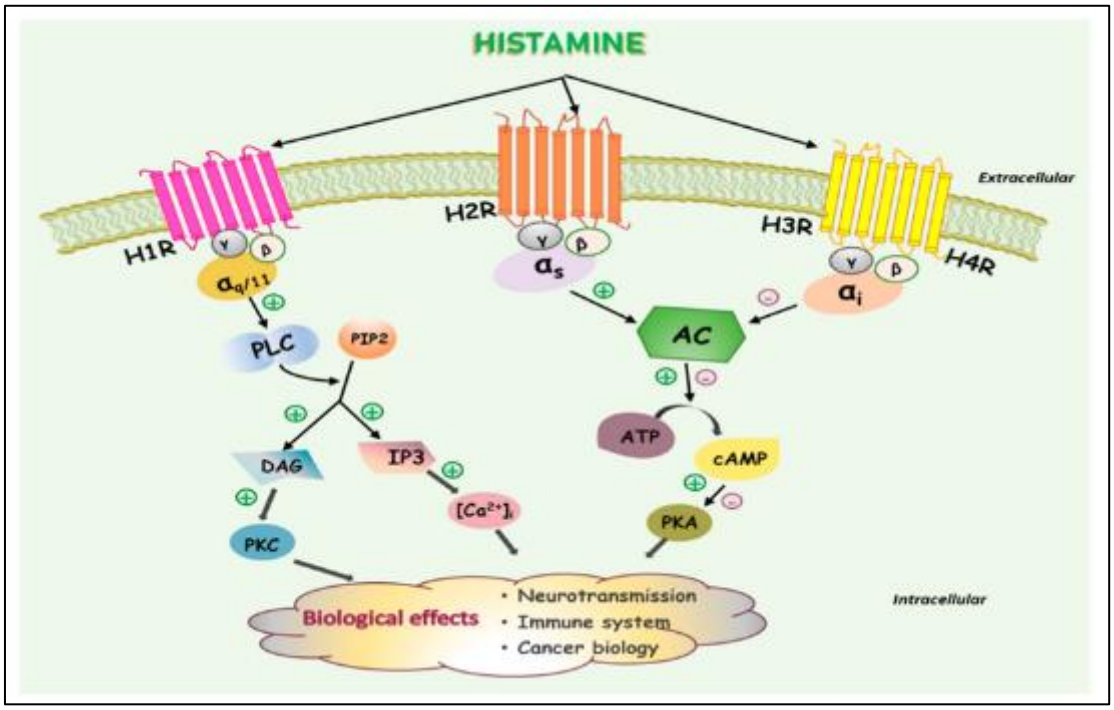

Figure 1 Signaling pathways mediating the biological effects of the histamine receptor subtypes (Nguyen et al,. 2021)

2. Histamine Biochemistry and Metabolism

2.1. Synthesis and Storage

L-histidine decarboxylation which produces histamine, is the only known role of histidine decarboxylase (HDC) and it requires PLP to occur (Ohtsu, 2010). Human chromosome 15q21–23 contains the HDC gene which makes a 74 kDa precursor protein that is changed into the 53 kDa enzyme after translation (Ichikawa et al., 2010).

Mast cells and basophils mainly store histamine in the immune system. Here, the molecules are placed in secretory granules and at this point, around 100 mM of sodium chloride and proteoglycans are just next to each other in storage (Wernersson and Pejler, 2014). As soon as cells become active, this storage helps provide the gas right away and makes sure it doesn't escape. In addition, in the central nervous system, histamine is created by nerve cells called histaminergic neurones, mainly in the posterior hypothalamic tuberomammillary nucleus, where it affects attention, alertness and cognitive activities (Haas et al., 2008).

Moreover, certain bacteria that change histidine into histamine which is an important factor in food poisoning and enterochromaffin-like cells in the stomach, are other significant sources of histamine (Smolinska et al., 2014).

2.2. Release Mechanisms

These reactions are marked by histamine release from mast cells and basophils, mainly by way of IgE-dependent processes (Gilfillan et al., 2011). Multivalent antigens or allergens connect to IgE molecules on the FcεRI of a cell which then sets in motion a series of intracellular signalling events leading to an immune response. The starting reactions include calcium movement and PKC activation, caused by Lyn, Fyn, Syk kinase, LAT adaptor protein and phospholipase C-γ (Metcalfe et al., 2009).

When calcium rises in the cytoplasm, granules containing histamine fuse with the plasma membrane and release their contents outside through the SNARE complex which is formed at this point (Lorentz et al., 2012). A few minutes after stimulation, the complete histamine content in cells may be released through the process known as degranulation.

Apart from IgE, a variety of things like physical trauma, changes in temperature, medications and products from the complement system (C3a and C5a) plus neuropeptides (substance P, vasoactive intestinal peptide) are capable of stimulating the release of histamine (Lieberman et al., 2015). What we see from these examples is that histamine control is very intricate whether the condition is normal or not.

2.3. Degradation and Elimination

Most histamine gets inactivated by two enzymes that tightly control its effects on the body. Most tissues use histamine N-methyltransferase (HNMT) which desires S-adenosyl-L-methionine to perform the methylation of histamine at the N-tau position, making N-methylhistamine (Maintz and Novak, 2007). This intermediate then passes through further action by MAO-B which produces N-methylimidazole acetic acid. The final step is to get rid of it in urine.

Still, histamine gets deaminated by diamine oxidase (DAO), also known as histaminase or AOC1 which then changes to imidazole acetic acid with the help of aldehyde dehydrogenase (Schwelberger, 2010). Mostly found in the kidneys, placenta and tissues lining the intestines, it plays an important role in protecting from external histamine.

Pathways responsible for removing histamine are used more or less, depending on how much active enzymes there are in each tissue. Most of DAO is found in the intestinal epithelium, placenta and kidneys, while HNMT works in the cytosol and is found in several places such as the liver, kidneys and central nervous system (Maintz and Novak, 2007). Sufficient histamine in the body depends on the controlled way histamine is produced, released and degraded, with disturbances possibly resulting in histamine intolerance and other related problems.

3. Histamine Receptors and Signaling Pathways

3.1. H_1 Receptor

The histamine H 1 receptor (H 1 R) is a 487-amino acid protein that is encoded by the HRH1 gene on human chromosome 3p25 (Bakker et al., 2002). Being a rhodopsin-like G protein-coupled receptor (GPCR), H 1 R mostly interacts with Gq/11 proteins, thus leading to the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP 2) by phospholipase C (PLC) to produce inositol 1,4,5-trisphosphate (IP 3) and diacylglycerol (DAG) (Panula et al., 2015). The IP 3-mediated calcium mobilisation of intracellular stores and the DAG-mediated activation of protein kinase C (PKC) cause different cellular responses.

Among the numerous cell types that express H 1 R are vascular endothelial cells, smooth muscle cells, neurones, hepatocytes and immunological cells including dendritic cells, monocytes, neutrophils, T cells and B cells. Additionally, H 1 R signalling promotes adhesion molecule expression, enhances the chemotaxis of immune cells and increases the production of proinflammatory cytokines and chemokines (Thurmond et al., 2008).

H 1 antihistamines are effective in the treatment of allergic disorders thus showing the clinical significance of H 1 R. These medications do not treat these conditions as neutral antagonists but rather stabilise the inactive receptor conformation and reduce constitutive activity by serving as inverse agonists (Panula et al., 2015). Whereas second-generation agents (e.g., loratadine and cetirizine) have minimal penetration to the central nervous system, thereby minimizing such side effects, the first-generation H 1 antihistamines (e.g., diphenhydramine and chlorpheniramine) readily enter the central nervous system via the blood-brain barrier and induce sedation by centrally blocking H 1R (Church and Maurer, 2018).

3.2. H_2 Receptor

The histamine H 2 receptor (H 2 R) is a 359-amino acid protein encoded by the HRH2 gene on human chromosome 5q35.2 (Parsons and Ganellin, 2006). The activation of protein kinase A (PKA) occurs when H 2 R primarily interacts with Gs proteins, thus stimulating the adenylyl cyclase to increase the intracellular concentration of cyclic adenosine monophosphate (cAMP) (Panula et al., 2015).

H 2 R is expressed throughout the body; nevertheless, it is especially abundant in smooth muscle cells, gastric parietal cells, cardiac tissues, as well as immunological cells like mast cells, basophils, monocytes, dendritic cells, and T cells (Thurmond et al., 2008). The justification of therapeutic application of H 2 receptor antagonist in acid-related diseases is that the parietal cells in the stomach mucosa stimulate acid secretion when H 2R is activated. H 2 R in the cardiovascular system mediates positive chronotropic and inotropic effects on the heart muscle (Parsons and Ganellin, 2006).

Generally, H 2 R signalling exerts immunomodulatory and anti-inflammatory effects with regard to inflammation. These actions are inhibition of mast cell and basophil degranulation, prevention of proinflammatory cytokine production as well as alteration of T cell responses to a Th2 phenotype (Jutel et al., 2009). It is interesting to note that dendritic cells with H 2R activated yield more IL-10 and acquire tolerogenic features, which could be one of the mechanisms of peripheral tolerance (Smolinska et al., 2014).

H 2 receptor antagonists, which include cimetidine, ranitidine, famotidine and nizatidine, have been extensively used to treat peptic ulcer disease, gastro-oesophageal reflux disease and other related disorders. Their use has, however, been diminished by the proton pump inhibitors that provide more effective acid control through a separate mechanism (Schubert and Peura, 2008).

3.3. H_3 Receptor

The histamine H 3 receptor (H 3 R) is a 445-amino acid protein that is encoded by the HRH3 gene located on human chromosome 20q13.33 (Leurs et al., 2005). H 3 R inhibits adenylyl cyclase activity and reduces the level of cAMP; it possesses profound constitutive activity and is mostly coupled via Gi / o proteins. Moreover, H 3 R signalling regulates the phosphatidylinositol 3-kinase (PI3K) signalling, blocks voltage-gated calcium channels, and stimulates the mitogen-activated protein kinase (MAPK) signalling ways (Panula et al., 2015).

H 3 R is mostly expressed in the central and peripheral neurological systems, namely, the cerebral cortex, hippocampus, basal ganglia, and hypothalamus (Haas et al., 2008). Histaminergic neurones have a presynaptic autoreceptor, H 3 R, which utilises negative feedback mechanisms to regulate histamine production and release. Furthermore, H 3 R can serve as a heteroreceptor on non-histaminergic neurones, where its activity concerns the secretion of various neurotransmitters, including serotonin, acetylcholine, dopamine, and norepinephrine (Panula et al., 2015).

The H III R gene generates many isoforms with variant pharmacological properties and tissue expressions, contributing to the complexity of H III R -mediated signalling (Leurs et al., 2005). The diversity of receptors presents opportunities and challenges in the creation of targeted treatment approaches.

Although mainly examined in neurological situations, recent studies show that H 3 R is also expressed on some immune cells, including dendritic cells and eosinophils, and possibly plays a role in allergic inflammation by as yet poorly understood mechanisms (Thurmond et al., 2008).

Despite the promise of H III R antagonists shown in preclinical models of narcolepsy, obesity, and cognitive disorders, receptor heterogeneity, species differences, and potential off-target effects have proven to be challenges to clinical development (Panula et al., 2015). Pitolisant, a selective H 3 R inverse agonist, is the first licensed H 3 R -targeted medicine to be used in the treatment of narcolepsy, showing the possible clinical usefulness of this receptor (Kollb-Sielecka et al., 2017).

3.4. H_4 Receptor

The histamine H 4 receptor (H 4 R) is a 390-amino acid protein encoded by HRH4 on human chromosome 18q11.2 that shares approximately 37 percent of its sequence with H 3 R (Thurmond et al., 2008). Like H 3 R, H 4 R also inhibits adenylyl cyclase and decreases the levels of cAMP through the coupling with Gi/o proteins. In addition, the activation of H 4 R modifies the signalling pathway of MAPK and JAK-STAT and induces the calcium mobilisation through the activation of phospholipase C (PLC) (Leurs et al., 2009).

The primary cells that express H 4 R include haematopoietic and immunological cells including mast cells, basophils, eosinophils, dendritic cells, monocytes, and T cells; this is in contrast to the widespread expression pattern of the other histamine receptors (Thurmond et al., 2008). This pattern of distribution highlights its degree of importance in the management of inflammation and immunity.

Activation of H4R enhance the release of cytokines and chemokines, induce the expression of cell adhesion molecules and promote the chemotaxis of mast cells, eosinophils and T lymphocytes to histamine gradients in allergic and inflammatory environments (Thurmond et al., 2008). More so, H IVR signalling has been found to regulate the polarisation of T cells, the migration of dendritic cells as well as their maturation, which can all contribute to adaptive responses in immunology (Jutel et al., 2009).

The HRH4 gene has a notable polymorphic variation with a number of single nucleotide polymorphisms (SNPs) associated with the altered receptor activity and disease susceptibility, particularly in atopic dermatitis, asthma, and autoimmune diseases (Gutzmer et al., 2011). Such genetic variations could cause heterogeneity of illness and influence the individual response to H Hawkins IV -related therapeutics.

Selective H 4 R antagonists have been promising in preclinical models of pruritus, atopic dermatitis, asthma, and allergic rhinitis (Thurmond et al., 2014). The potential and challenges of targeting H 4 R in inflammatory diseases can be discussed based on the varying success of various drugs that have already reached clinical trials, including ZPL-3893787, toreforant, and JNJ-39758979 (Kollmeier et al., 2018). To enhance therapeutic usefulness of H Fourth R antagonists, present efforts are focused on enhancement of safety profile, pharmacokinetics and selectivity.

4. Histamine in Allergic Responses

4.1. Role in Immediate Hypersensitivity Reactions

Histamine has been shown to play a major role in type I acute hypersensitivity responses which are the immunological basis of allergic diseases including anaphylaxis, urticaria, and allergic rhinitis (Galli et al., 2008). These events are initiated by allergen-specific IgE bound to FcεRI receptors on mast cells and basophils crosslinking, leading to the prompt release of prepared mediators, most notably histamine, by cytoplasmic granules (Gilfillan et al., 2011).

The effects of the released histamine on various target tissues result in some unique symptoms. In the vasculature, histamine induces contraction of endothelial cells, largely via H 1 R activation. The result is vascular permeability and plasma extravasation leading to urticaria and oedema (Church and Maurer, 2018). At the same time, histamine makes endothelial cells release nitric oxide (NO), leading to vasodilation and resulting in hypotension observed during severe anaphylactic reactions (Brown et al., 2013).

Histamine induces bronchoconstriction of the respiratory system, both directly by action on smooth muscle H 1 receptors and indirectly via vagal reflexes, and this action is one part of the bronchospasm that is the key feature of allergic asthma (Holgate, 2012). Moreover, histamine worsens airway obstruction through its effect of causing the secretion of mucus by mucosal glands and goblet cells.

The itch that is usually associated with allergic skin diseases is caused by the effect of histamine on the sensory nerve terminals in the skin through H 1 and H 4 receptors (Thurmond et al., 2014). Moreover, having noted that histamine enhances the excitability of sensory neurones, it could play a role in neurogenic inflammation through the release of neuropeptides.
Of note are the kinetics of the action of histamine in allergic reactions. Histamine may play a role in the late-phase response, which occurs hours later and is characterized by infiltration of the tissues with eosinophils, T cells, and other inflammatory cells, despite being overshadowed by the early phase reaction that occurs minutes after exposure to an allergen (Galli et al., 2008).

4.2. Interaction with Other Inflammatory Mediators

Theoharides et al. (2012) observe that histamine, like all other inflammatory mediators produced during allergic episodes, acts in collaboration to facilitate the development of complex interactions whereby the inflammatory cascade becomes aggravated and modified. As well as the several prepared mediators released with histamine in the degranulation of mast cells and basophils, including tryptase, chymase, carboxypeptidase A3 and proteoglycans. These mediators also collaborate to enhance vascular permeability, tissue remodelling and cell recruitment (Wernersson and Pejler, 2014).

Histamine influences the synthesis and release of newly synthesised lipid mediators i.e., platelet-activating factor, leukotrienes, and prostaglandins. Interestingly, histamine is able to stimulate mast cell H 4 R-dependent signalling of cytosolic phospholipase A 2 (cPLA 2) as well as enhancing secretion of arachidonic acid and the production of eicosanoids (Thurmond et al., 2008). Conversely, a numbers of prostaglandins (particularly, PGE 2) themselves are a part of negative feedback loop, and are able to block the histamine production in mast cells (Metcalfe et al., 2009).

Also, histamine interacts with cytokine and chemokine production of various immunological and structural cells. Histamine promotes IL-6 and the IL-8 generation in mast cells via H 1 R and H 4 R signalling, and IL-10 secreted in dendritic cells using H 2 R (Jutel et al., 2009). Histamine in T cells varies the production of cytokines, depending on the subtype of receptor utilized: H 1R signalling and stimulation promotes Th1 responses, yet H 2R activation predisposes Th2 polarisation (Jutel et al., 2001).

One more important interaction is the bond between histamine and the complement system. As histamine causes greater complement activation through the up-regulation of vascular permeability and facilitating the deposition of complement components, anaphylatoxins C3a and C5a might achieve its effect on the production of histamine by mast cells and basophils directly (Kolev et al., 2014).

IL-33, thymic stromal lymphopoietin (TSLP) and IL-25 are the examples of alarmins that have been found to communicate with histamine in both directions. Although presence of histamine controls production of alarmin by epithelial cells, cytokines produced by epithelial cells enhance sensitivity of mast cell and secretion of histamine which could lead to positive feedback loop in chronic allergic inflammation (Saluja et al., 2015).

4.3. Histamine in Chronic Allergic Inflammation

The role of histamine in chronic allergic inflammation remains the subject of ongoing research with major therapeutic importance even though it is known to play a pivotal role in acute allergic conditions (Branco et al., 2018). New studies indicate that the immunomodulatory properties of histamine on T cells, dendritic cells and structural cells influence tissue remodelling and chronic inflammation besides induced response (Smolinska et al., 2014).

Histamine mediates maturation of dendritic cells, their mobility and antigen presentation through variable receptor engagement. Whereas H 2R signalling can produce tolerogenic phenotypes characterised by high rates of IL-10 production and generation of regulatory T cell, the activation of H 1R and H 4R triggers maturation, motility and the th2 polarizing capacity of dendritic cell (Jutel et al., 2005). Whether this receptor distinct regulation contributes to the resolution or perpetuation of allergic inflammation may depend on the current signalling route.

Histamine possesses receptor mediated effects which can shape the allergic inflammatory environment and has a direct effect on T cell differentiation and functioning. Although Th2 polarisation is enhanced by activation of H 2 R, which mediates decreasing IL-12 and increasing IL-4 signalling, Th1 responses are enhanced on H 1 R to increase production of IFN-y (Jutel et al., 2001). Moreover, a recent study has identified H IV R expression on T cells and this has been shown to play role in Th17 responses and IL-17 production. This could possibly be correlated to the histamine and neutrophilic inflammation as exhibited in severe asthma (Gutzmer et al., 2011).

With regards to the allergic airways inflammation, histamine exerts direct effects to the location of structural cells, e.g. fibroblasts, epithelial cells and smooth muscle cells at the airways, which results into tissue remodelling. Histamine enhances the mural thickening and fibrosis that is typical of chronic asthma by fostering the migration of smooth muscle cells, proliferation, facilitating the synthesis of collagen by fibroblasts and creating an epithelial-mesenchymal recombination using H1 R signals (Holgate, 2012).

The other component of the role of histamine in chronic inflammation is uncovered with the emergence of recent research findings on histamines epigenetic outcomes. Caron et al. (2015) reported that histamine has shown to remodel the DNA methylation levels and histone acetylation in different cell types that might lead to lasting changes in gene expression beyond the transient signal transmission. Such epigenetic modifications could be prospective targets of novel treatment approaches and could contribute to chronicity of allergic inflammation. The role of histamine in the chronic inflammatory consequence can now be comprehended better due to the discovery of a particular receptor antagonist, and particularly on the usage of H 4 R. Preclinical studies involving the use of H 4 R antagonists demonstrate potential as therapies in models of atopic dermatitis, allergic rhinitis, and chronic asthma that can supplement the well-known application of H 1 antihistamines (Kollmeier et al., 2018).

5. Histamine in Inflammatory Responses

5.1. Regulation of Vascular Permeability

The influence of histamine on vascular permeability is one of the most established functions of this peptide in the process of inflammation (Ashina et al., 2015). Upon release, histamine moves at fast pace to the endothelium and its source of release is the mast cells, which are strategically located near arteries into the blood. There it majorly acts on the H1 receptors to enhance permeability in a wide range of compliant means.

At the cellular level, histamine induces the cytoskeletal rearrangement via myosin light chain (MLC) phosphorylation characterized by the endothelial cell contraction, and development of the intercellular gap (Mikelis et al., 2015). Such a mechanism involves the phosphorylation of vascular endothelial cadherin (VE-cadherin) and other proteins in adherens junctions and the activation of the RhoA/ROCK signalling pathway and phosphorylation of MLC via H1R (Ashina et al., 2015).

On forming vesiculo-vacuolar organelles (VVOs), histamine also facilitates transendothelial vesicular transport (transcytosis) which presents plasma proteins with alternative means of diffusion across the endothelial barrier (Nagy et al., 2008). This two mechanisms of paracellular and transcellular permeability increase play their role in enhancing fast plasma extravasation in acute inflammation.

Histamine is also highly specific and its kinetics of vascular leakage is quite rapid and short-lived as breakdown caused by histamine and negative feedback processes puts histamine-induced changes in permeability out of sight in a few seconds and making it disappear within 15 to 30 minutes (Ashina et al., 2015). The temporal profile of histamine distinguishes it among other permeability factors, which include bradykinin and leukotrienes, that produce prolonged responses.

Recent investigations show that allergy symptoms distribution is correlated, tissue-specific difference in endothelial response to histamine exists: post-capillary venules of human skin, respiratory tract, and gastrointestinal mucosa are highly sensitive to histamine (Nagy et al., 2008). Anatomical regional specialisation could be due to differences in receptor expression, coupling of signalling pathways, or organisation of endothelial junctions between vascular beds. Also besides the direct action on endothelial cells that are exhibited by histamine there is the indirect effect of histamine which is on the vascular permeability. The reason is that it enhances activation of the sensory nerves and consequent liberation neuropeptides, in particular substance P and calcitonin gene-related peptide (CGRP), which in turn aggravate the extravasation of the plasma (Rosa and Fantozzi 2012). What is more, histamine furthers the permeability-increasing properties of bradykinin, thrombin, and other mediators of inflammation through synergistic signalling interactions (Ashina et al., 2015).

The vascular leakage caused by histamine is clinically relevant in various inflammatory diseases, e.g., in urticaria, angioedema and anaphylaxis, where the H 1 antihistamines are effective in blockade of the oedema formation. However, they are not very effective in chronic inflammatory conditions indicating the emergence of tachyphylaxis due to repetitive histamine administration or involvement of histamine independent permeability path in it (Church and Maurer, 2018).

5.2. Leukocyte Recruitment and Activation

By means of both direct chemotactic actions and regulating egression of adhesion molecules, histamine comes into intricate role in directing leukocyte transport through inflammatory responses (Thurmond et al., 2008). The comprehension of histamine immunomodulatory functions outside of its vascular effects has become infinitely more relatively, with the determination and description of the expression of the H 4 R by the various leukocytes.

Histamine has a direct stimulatory effect on mast cell, eosinophil, dendritic cell and T cell chemotaxis via histamine receptor 4 (H 4/R) signalling, by forming concentration gradients guiding cellular recruitment to regions of inflammation (B 27992008). This chemotactic effect is of particular relevance to the accumulation of eosinophils in allergic inflammation because H 4 R antagonists have already proven their efficacy in the reduction of tissue eosinophilia in animal models of both asthma and atopic dermatitis (Thurmond et al., 2014).

Histamine besides acting as a direct chemotactic agent, it facilitates the interaction between leukocytes and their vessels easily by altering the expression of adhesion molecules on the cells. Histamine effectively increases leukocyte rolling, adhesion and transmigration by up regulating endothelium production of ICAM-1, P-selectin, VCAM-1, and E-selectin

via H1R signalling (Moy et al., 2016). In addition, histamine enhances the adhesive capacity of the neutrophils and eosinophils by augmenting manufacture and preparation of 2-integrin (Baumer et al., 2008).

Histamine also influences neutrophil activities in a diverse way depending on the receptor subtype involved. H 1R signalling prevents neutrophil oxidative burst, the release of neutrophil extracellular traps and the production of proinflammatory cytokines whilst H 1R stimulation enhances chemotaxis and degranulation in neutrophils. This could be a self regulatory process to check neutrophil-mediated tissue damage (Smuda et al., 2011).

Histamine stimulates phagocytosis cell processes through a receptor-mediation manner which has an effect on the monocyte and the macrophages. Although H 2 R and H 4 R stimulation are considered to favour alternative (M 2) activation, which can be described as increased production of IL-10 and low-level production of IL-12, H 1 R stimulation promotes the production of proinflammatory cytokines (TNF-a, IL-1b, and IL-6) and initiates classical (M 1) activation (Mazzoni et al., 2001).

Remarkable are time dynamics effects of the impact of histamine on the recruitment of leukocytes. Sustained production of histamine could play a role in recruiting eosinophils, monocytes, and lymphocytes that typify late-phase allergic reactions and chronic inflammation despite the early stage of histamine release by mast cells favoring initial recruitment of neutrophils (Moy et al., 2016).

New mechanisms by which histamine influences the leukocyte functions, including the modulation of autophagy, (inflammasome-mediated) inflammation and metabolism, have been discovered in recent studies. These results expand on the previously accepted paradigm of the immunomodulatory properties of histamine to include not only chemotaxis and adhesion (Branco et al., 2018).

5.3. Histamine and Neurogenic Inflammation

The intricate relationship between histamine and neurogenic inflammation constitutes a new discipline that proves relevant in the understanding of the pathophysiology of allergic diseases, particularly those that are characterized by itch (pruritus) and over-responsiveness in the nerves (Rosa and Fantozzi, 2013). Neurogenic inflammation refers to the process where sensory nerves synthesize neuropeptides, which can attract inflammatory responses establishing an inflammatory loop that can not only exacerbate but also sustain tissue inflammation. Histamine also stimulates sensory neurones, primarily C-fibers, by direct binding to H 1 and H 4 receptors in nerve terminals. The effect is the generation of action potentials and neuropeptide release including those of substance P, calcitonin gene-related peptide (CGRP), and neurokinin A (Shim and Oh, 2008). These neuropeptides add to the first histamine mediated response and in addition further elevate vascular permeability, promote vasodilation, mucus secretions, and recruitment of more inflammatory cells.

Histamine, as recent data indicate, sensitises the sensory neurones, causing the levels of activation to lower under the influence of the processes that occur through the TRP (transient receptor potential) channels such as TRPV1 and TRPA1 (Shim et al., 2007). Bautista et al. (2014) suggested that histamine leads to phosphorylation of these channels using PKC and PLA2 pathways, which makes them hypersensitive to mechanical, chemical and thermal sensations, which further links to the chronic pruritus and sensory hypersensitivity widened during atopic dermatitis and other allergic skin diseases.

Reciprocal interaction between mast cells and sensory neurones allows positive feedback loop to develop, a possible mechanism leading up to continuous inflammation. In a positive feedback loop, activated sensory neurone creates a response in the release of neuropeptides, which induces mast cell degranulation and the release of histamine, exciting the neighboring neurones (Luo et al., 2018). This neuro-immune interaction may contribute to the chronicy of some diseases caused by allergy even when the cause of the disease, the allergen, seems to be eradicated.

By the means of a central and local reflex, the stimulation of sensory nerve terminals of the respiratory system by histamine leads to the development of reflex bronchospasm, coughing, and hypersecretion of mucus (Mazzone and Undem, 2016). Histamine could contribute to hyperresponsiveness of airways that characterises asthma by sensitising vagal afferent neurones to various stimulation. Neurogenic inflammation could also be boosted by chronic exposure to histamine, which stimulates structural and functional neuroplastic changes, including increased production of neuropeptides and their receptors (Myers et al., 2019).

Histamine has an impact on the functioning of the autonomic nervous systems both in the central and peripheral mechanisms as well as on the sensory neurones. Histamine alters the release of neurotransmitters released by the

autonomic nerve ends and shifts which are sympathetic and parasympathetic by acting on H 1 and H 3 receptors (Rosa and Fantozzi, 2013). These consequences may compound the gastrointestinal, respiratory and cardiovascular symptoms that are associated with acute allergic responses.

The role of histamine in neurogenic inflammation implicates its therapeutic implications besides the known conventional antihistamine use. Among the strategies that would require further exploration as the definite ways of treating the neurogenic side to allergic inflammation, there is a variety of new molecules aimed at interfering with the neuro-immune interactions, including TRP channel antagonists, neuropeptide receptor antagonists, or dual-targeted molecules with both antihistaminic and TRP channel blocking activities (Bautista et al., 2014).

6. Therapeutic Approaches Targeting Histamine Pathways

6.1. Classical Antihistamines

The principalstay of histamine-based therapy, and notably of allergic disorders, are H 1 receptor antagonists, which are also termed antihistamines. Instead of being neutral antagonists, these substances stabilise the inactive receptor conformation and reduce the constitutive activity by being inverse agonists (Simons and Simons, 2011). The clinical application of H 1 antihistamines has given a wide range to the use of this drug in mild-to-severe allergies such as allergic rhinitis, urticaria, and adjuvant therapy in anaphylaxis since H 1 antihistamines are able to overcome the effects of histamine on vascular permeability, smooth muscle spasm, and sensory nerve stimulation (Church and Maurer, 2018).

H the antihistamines are traditionally grouped into the first- and the second-generation ones based upon the pharmacokinetic properties, spectra of adverse effects, and chemical design. Being lipophilic, the first-generation agents (ex: diphenhydramine, chlorpheniramine, and hydroxyzine) cross the blood-brain barrier with ease. Sedation, thought impairment, and anticholinergic effects are because of central H 1 receptor blockade and unintended activity at muscarinic, serotonergic, and alpha adrenergic receptors (Simons and Simons, 2011).

In order to counteract these drawbacks, the second-generation H 1 antihistamines (e.g., cetirizine, loratadine, fexofenadine, desloratadine, levocetirizine, and bilastine) were developed, which have a lower central nervous system penetration, increased selectivity at H 1 receptors, and more friendly pharmacokinetics which enables once daily dosing (Church and Maurer, 2018). Current global recommendations are against regular use of first-generation antihistamines not only because they have had an unfavourable risk-benefit ratio but also because second-generation antihistamines have become used as first-line treatment of a number of allergic diseases (Simons and Simons, 2011).

The most popular antihistamines are H 1 which does not show optimum performance across different types of allergy. Their effect is particularly compromised in scenarios involving the scenario whereby histamine is among several mediators as well as cases where histamine actions are mediated by non-H 1 R receptors. Such examples include H 1 antihistamines, which are effective against the symptoms of allergic rhinitis but not asthma, where other inflammatory mechanisms are more dominant (Casale et al., 2019).

One of the more recent advances in our knowledge of the pharmacology of the antihistamines has been the discovery of their anti-inflammatory properties beyond the direct antagonism at their receptor sites. Second-generation antihistamines at clinically relevant concentrations have exhibited inhibitory results on the presence of adhesion molecules, cytokine synthesis, and recruitment of inflammatory cells that are possibly significant in featuring their clinical effectiveness on long-lasting allergy disorders (Church and Maurer, 2018).

The most common H 2 receptor blockers included cimetidine, ranitidine, famotidine and nizatidine used primarily in case of GI tract infections and not in case of allergic diseases. Multiple histamine receptor blocking could also be advantageous, as was seen in the superior combined blocking H 1/H 2 receptor in certain contexts, particularly the urticaria which is refractory to H 1 antihistamine block (Fedorowicz et al., 2012).

6.2. Novel Receptor-Targeted Approaches

The area of histamine-directed medications has expanded with the discovery of H 3 and H 4 receptors, providing the way to a greater control of some histamine-mediated processes (Panula et al., 2015). Having been largely found to be presented at immune cells and its role in leukocyte chemotaxis, cytokine production, as well as pruritus, particular H 4R has become a target of interest in allergy disorders, as well as inflammatory ones (Thurmond et al., 2008).

Several selective H 4 R antagonists have demonstrated possibilities of working in preclinical models of asthma, atopic dermatitis, allergic rhinitis, and pruritus (Thurmond et al., 2014). The results in the literature are interesting in that these drugs in experimental conditions show stronger antipruritic properties than conventional H 1 receptor antihistamines, which leads to a conclusion about the importance of H 4R in the histamineopathy of itching (Kollmeier et al., 2018). It is also possible that H 4R antagonists will be helpful in the treatment of allergy diseases due to their anti-inflammatory effects which are reduced eosinophil recruitment, reduced secretion of Th2 cytokines and suppressed activation of dendritic cells (Thurmond et al., 2014).

The clinical development of the H 4 R antagonists has not been effective. In the case of atopic dermatitis, asthma, and rheumatoid arthritis, compounds like ZPL-3893787, toreforant (JNJ-38518168), and JNJ-39758979 have reached clinical trials; many of them were stopped due to safety or efficacy concerns; however, one of such substances has shown some promise (Kollmeier et al., 2018). These challenges lead to the attention to the challenge of translating preclinical findings into a clinical setting and the potential differentiation in H H R involvement in different types of inflammation and allergy.

Having in mind that the receptor is highly examined in the central nervous system, the H 3 R antagonists have been predominantly observed against neurological disorders. Increased histaminergic neurotransmission caused by it makes pitolisant, a selective H 3 R inverse agonist, an approved regulator in narcolepsy treatment (Kollb-Sielecka et al., 2017). In the diagnosis of allergy, particularly allergic rhinitis, a little information shows that H 3 R antagonist could be applied to the condition, possibly by regulating the activities of sensory nerves that often induce neurogenic inflammation (Rosa and Fantozzi, 2013). Further research is required to demonstrate their clinical utility in conditions such as allergic illnesses.

Dual-targeting is another groundbreaking strategy towards histamine receptor antagonistic treatment. Mixed H 1/H 4 -antagonist compounds have also demonstrated greater efficacy, relative to selective H 1 antagonists, in in vivo preclinical models of allergic conjunctivitis and pruritus including alcaftadine, JNJ-39758979, and others (Thurmond et al., 2014). When many mediators play a role in pathophysiology, drugs aimed at both histamine receptors and complementary pathways can also be found to be more effective, e.g., combination H 1 antihistamine/ leukotriene receptor antagonists (Church and Maurer, 2018).

A new avenue that has the potentially to enhance specificity in therapy is the production of biassed ligands that strongly modulate specific signalling pathways downstream of the histamine receptors (Violin et al., 2014). Although the study on histamine receptors is in its initiation phase, these drugs can be used to exploit a full potential in effect and reduce the deleterious effects by activation/inhibition of positive vs negative signalling cascades.

6.3. Targeting Histamine Synthesis and Release

Other means of controlling histamine-dependent reactions include methods aimed at the release or production of histamine, which can be seen as the advantage of avoiding the problems that receptor antagonism presents, particularly in a scenario where multiple subtypes of receptors contribute to the pathophysiology (Babe et al., 2015).

A reasonable way of reducing the concentration of histamine would be by inhibiting the enzyme it is made in histidine decarboxylase (HDC). The efficacy of various HDC inhibitors that includes catechin derivatives and a-fluoromethylhistidine was revealed in experimental models of allergic inflammation (Ohtsu, 2010). Nevertheless, the barriers to clinical development have been based on pharmacokinetic issues, specificity issues, and potentially compensating processes that could impair long-term efficacies (Babe et al., 2015). As well, global reduction in the manufacture of histamine can disrupt immunological regulation, neurotransmission and the secretion of stomach acid.

The other way to minimise the influence of histamine is through the use of mast cell stabilisers, which in the current situation are cromolyn sodium and nedocromil sodium, which inhibit the degranulation of mast cells and consequential firing of histamine (Theoharides et al., 2012). The mechanisms of action of these substances involve inhibition of calcium dependent exocytosis of secretory granules by bloc between calcium entry following Fc e R I crosslinking. Their use in certain diseases, primarily rhinitis and allergic conjunctivitis, on the one hand, is advantageous, but there are limitations to their clinical usefulness due to slow onset, ineffective mast cell deactivation, and depending on orally consumed high doses, the need to use them topically or via the respiratory tract (Babe et al., 2015).

Perhaps a more specific approach to histamine release prevention is to block a few signalling molecules that have been found to play a role in mast cell activation. Immunomodulatory effects of syk kinase inhibitors, e.g. fostamatinib and entospletinib, are successful in terms of preventing mast cell degranulation blocking a pivot of key signalling events

down-stream of FcεRI (Gilfillan et al., 2011). Equally, a synthetically produced molecule known as bruton tyrosine kinase (BTK) inhibitor (example, ibrutinib and acalabrutinib), has proven useful in preclinical models to blunt mast cell activation and release of histamine, thus potentially useful in allergic diseases in its use alongside well-established use against B cell malignancies (Gilfillan et al., 2019).

Omalizumab, a humanised monoclonal antibody against IgE, blunts the mast cell triggering by blocking IgE to attach FcεRI and in turn block the release of histamine indirectly (Casale et al., 2019). Such a strategy against upstream processes of histamine in conditions related to it may be advantageous, which is implied by its efficacy in treating chronic spontaneous urticaria, a histamine-mediated disease condition that is often refractory to conventional antihistamines (Tharp et al., 2019).

Recent identification of other mechanisms regulating mast cell degranulation includes autophagy-related proteins, microRNAs and inhibitory receptors (e.g. FcγRIIB, CD300a), potentially providing new histamine release modification targets (Gilfillan et al., 2019). In addition, a better understanding of the individuality of the mast cells activation pathways in different illnesses might enable the possibility to design more specific ways of histamine prevention in some cases of allergies and inflammatory conditions.

6.4. Emerging Therapeutic Strategies

Advancements in the understanding of histamine biology and allergic inflammation are creating many new approaches, which extend beyond classical strategies, which aim at histamine production, liberation, or receptor antagonism (Thurmond et al., 2014). Epigenetic regulation could be one of the possible mechanisms that solve the chronic changes of gene expression causing chronic allergic inflammation (Caron et al., 2015). Histamine has been shown to modulate epigenetic events of DNA methylation and histone acetylation which can lead to the establishment of what is referred to as an inflammatory memory causing the continued existence of allergic reactions. Conversely, there are epigenetic modifiers that can repress genes and histamine-related signalling pathways. As an example, histone deacetylase (HDAC) inhibitors have been found to be of anti-inflammatory utility in preclinical models of allergic inflammation mediated in part through alterations of mast cell activity and histamine receptor expression (Grausenburger et al., 2010).

The other novel approach would be to focus on microRNAs (miRNAs) that regulate the expression of the genes related to histamine. Several miRNAs are associated with mast cell building, survival, and activation, which include miR-142-3p, miR-155, and miR-221 (Jimenez-Andrade et al., 2017). In addition to conventional pharmaceutical interventions, histamine production and release could be affected by modifying these miRNAs using mimics or inhibitors, imposing an additional level of control.

Mast cell-defined interventions are a recent notion that could indirectly change the actions of histamine by relating to unique manipulation of mast cells, which turn out to be the primary biological supplier of histamine in allergic reactions (Theoharides et al., 2012). Possible ways involve small molecule inhibitors of mast cell survival factors (e.g. SCF/CD117 pathway inhibitors), monoclonal antibodies to specific mast cell surface receptors (e.g. Siglec-8, CD117), and targeted Nano-particle delivery systems that deliver therapeutic agents to mast cells with the specificity of drug-receptor (e.g. Siglec-8, CD117) binding only (Gilfillan et al., 2019).

The alternative approach is to suppress the activity of histamine by inhibiting diamine oxidase (DAO) or histamine N-methyltransferase (HNMT). This is of particular relevance to histamine intolerance that is defined as poor breakdown of histamine (Maintz and Novak, 2007). Though to a lesser degree, few studies have been conducted clinically in the field, possible interventions can be the use of recombinant DAO to treat the liver and use drug or genetic alterations to boost natural enzyme activity.

Histamine-based therapies can be enhanced with barrier-strengthening drugs, especially when treating a disease in which the permeability of the vascular system or the failure of the epithelial barrier contributes to the pathophysiology (Ashina et al., 2015). Then, again, without targeting histamine pathways, agents which enhance tight junction properties or stabilise adherens junctions in the airway or intestine might potentially down-regulate the effect of histamine release.

The new sector of microbiome-based medicines can be of benefit to histamine-related diseases (Barcik et al., 2016). The gut microbiota influences histamine levels systemically, in a number of ways including direct production of histamine by some bacterial species, alteration of host synthesis and degradation of histamine, and regulation of mast cell formation and activity. Among probiotics is the potential of benefiting allergic inflammation in preclinical models- in which strains capable of degrading histamine or reducing proinflammatory stimums that lead to mast cell activation have shown some promise which suggested the potential translational applications (Oksaharju et al., 2011).

7. Clinical Applications and Future Perspectives

7.1. Current Clinical Applications

Treatment with histamine, i.e., H 1 antihistamines is required to address several allergic conditions, although they vary in usage and efficiency, based on the condition (Church and Maurer, 2018). The 2nd generation of H 1 antihistamines effectively relieve nasal itching, runny nose, and the sneezing that is caused by the allergic rhinitis, but they work inferiorly on congestion (Casale et al., 2019). Under the existing protocol, it is recommended that second-generation antihistamines against H l should be prescribed as the first-line medication of mild-to-moderate allergic rhinitis. Antihistamines that are applied intranasally like azelastine are worth considering due to their faster onset of effect and greater antinociceptive efficacy against nasal congestion (Dykewicz et al., 2017).

The primary treatment plan in the case of urticaria is Helta antihistamines, and second-generation ones are more preferable due to their favourable safety profile (Zuberbier et al., 2018). Since histamine is a key component of chronic spontaneous urticaria, in case of non-responsiveness with normal dosage, it is recommended that patients can use up to fourfold higher doses of H 1 antihistamines (Zuberbier et al., 2018). Omalizumab is an otherwise practicable intervention against an antihistamine-resistant disease, but combination therapy based on H 2 Hand mu antihistamines or leukotriene receptor antagonists could be an additional advantage in refractory patients (Tharp et al., 2019).

Antihistamines also play only a small role in the management of asthma since histamine is just one of the many inflammatory substances in the complex pathophysiology of asthma (Global Initiative for Asthma, 2021). Even though H 1 antihistamines can be considered an option in patients with comorbid allergic rhinitis and, potentially, reduce asthma attacks by diminishing inflammation of the upper airways, H 1 antihistamines are not recommended as controller medications by current asthma guidelines (Dykewicz et al., 2017).

The H 1 and H 2 antihistamines are only medicines to complement the treatment of anaphylaxis as opposed to primary treatment; they are able to tackle gastrointestinal and dermatological symptoms, but cannot address the symptoms of the cardiovascular and respiratory systems requiring epinephrine to be administered as the first measure (Lieberman et al., 2015). The inability of antihistamines to deal with anaphylaxis demonstrates the importance that severe systemic allergic reactions are associated with more than histamine.

Topical antihistamines are applied in the treatment of allergic conjunctivitis (e.g. olopatadine, emedastine) and in selected dermatological disorders (e.g. diphenhydramine, doxepin) which is due to the benefits of a rapid onset of action and high levels at the site of action combined with little systemic exposure (Church and Maurer, 2018). Recent developments are the use of dual-action medications which are a combination of the antihistamine and mast cell-stabilizing properties, resulting in a better effect due to the synergetic actions of both (Bielory et al., 2010). H 2 receptor antagonists have since been replaced by proton pump inhibitors but are still predominantly used to treat acid conditions and related diseasesered pointer ulcer disease and gastro-oesophageal reflux disease (Schubert and Peura, 2008). Their mechanistically justified off-label use as adjuvants of allergic diseases, such as urticaria and anaphylaxis lacks supporting data (Lieberman et al., 2015).

7.2. Challenges and Limitations

Histamine-directed therapies find extensive usage yet the therapeutic utility of such treatments on wide range of various inflammatory and allergic disorders has several questions and constraints (Simons and Simons, 2011). Various histamine receptor expression and activity in tissues and diseases complicate targeting this therapeutically. The effectiveness of conventional antihistamines H 1 is different based on the implication of the receptors varying (Thurmond et al., 2008).

Examples of patient-specific factors which determine the efficacy of antihistamines and other forms of histamine-related interventions are receptor polymorphisms, differences in metabolism and comorbidities. Although polymorphisms of enzymes that process drugs such as CYP2D6 and CYP3A4 have certain effect on pharmacokinetics, as well as potential drug interactions, genetic variations of the HRH1 gene have been implicated in variable responses to H1 antihistamines (Church and Maurer, 2018).

The second drawback of some of the antihistamines is tachyphylaxis, i.e. reduced responsiveness on long-term use, although that appears to be drug- and condition-specific (Simons and Simons, 2011). The processes which lead to tachyphylaxis are not exactly known but may involve compensatory up-regulation of other inflammatory cascades, down-regulation or desensitisation of receptors.

Histamine-centered therapies are limited in their efficacy limited as a matter of course to the presence of histamine-devoid pathways in many forms of allergy and inflammatory-based diseases. Some of the mediators that are identified to be a part of the pathophysiology of the chronic allergic inflammation include leukotrienes, prostaglandins, cytokines, and chemokines, which require a combination or an alternative approach in the case of therapy (Casale et al., 2019).

New histamine receptors antagonists, particularly those directed to the H 4 R have proved hard to translate promising preclinical data into clinical success (Kollmeier et al., 2018). That may be because of the differences in receptor expression and functions across species, the failure of animal models to fully recapitulate the complex human disease and differences in the implication of receptor across people (Thurmond et al., 2014).

Another aspect that restrictions the development and use of histamine-targeting therapeutics is due to safety considerations. Although second-generation H 1 antihistamines might be hazardous in some clinical categories, e.g., pregnant, elderly, and impaired hepatic or renal patients, first-generation drugs have clearly identified side effects on the central nervous system and anticholinergic axes (Simons and Simons, 2011). Lessening of physiological histamine activities including neurotransmission, gastric acid secretion, and immunoregulation is a concern in histamine production or histamine release-based novel technologies (Ohtsu, 2010).

Financial consequences of treatment based on histamine are some of the other things to consider. More recent agents, including third-generation antihistamines and new receptor antagonists, tend to have high prices that can restrict their availability and heath system integration, despite most of the second-generation H 1 antihistamines being accessible in low-cost generic forms (Church and Maurer, 2018).

7.3. Future Directions and Unmet Needs

However, the limitations of the current histamine-based strategies require innovative innovative strategies justified by their increased understanding of histamine biology and allergic inflammation (Thurmond et al., 2014). One of the promising ways to enhance treatment outcomes is the precision medicine approach, the application of biomarkers in defining the patients that respond better to specific histamine-based pharmaceuticals (Casale et al., 2019).

Some of the possible sampling items are genetic differences in receptors of histamine or enzymes metabolizing it, their basal or turnover histamine levels, receptor expression patterns, and patterns of inflammatory mediators (Rosa and Fantozzi, 2013). Clinical decision making which takes into consideration these factors can perhaps permit the use of more personalised selection of therapy, dose and combination approaches that are specific to the characteristics of each patient.

One more method to promote efficacy is combination medicines to hit on different aspects of histamine biology or other complementary inflammation routes (Church and Maurer, 2018). Reasonable combinations are receptor antagonists coupled with mast cell stabilisers, or histamine-directed therapy coupled with antagonists targeted on other inflammatory mediators (e.g. cytokine inhibitors or leukotriene modifiers), or dual receptor antagonists (e.g. H 1/H 4). An important area of research is systematic evaluation of different combinations, considering potential synergistic effects and issues with safety.

New modes of drug delivery may also offer opportunities to enhance the safety, efficacy and selectivity of histamine-based therapies (Bielory et al., 2010). Local delivery routes, formulations with controlled release, or tailored delivery to specific tissues of cell types are some therapies, which help to optimise therapeutic exposure at target sites and minimise exposure to other portions of the body. As an example, inhalable H R antagonists can enhance the effectiveness of asthma treatment and reduce the systemic side effects (Kollmeier et al., 2018).

The additional one is the treatment of the role of histamine in less- known therapeutic conditions. Recent studies suggest that histamine is involved in gastric problems and neuroinflammatory diseases, and certain autoimmune disorders, and this enlarges the case of potential applications of histamine-based therapies historically focused on classical allergy diseases (Branco et al., 2018). Similarly, the immunoregulatory and inflammatory effects reported in evidenced by histamine due to cancer may be of interest to oncological application, which requires additional research (Yang et al., 2011).

Therapeutically, on the research level, it is also important to continue enhancing receptor-specific molecules with desirable pharmacokinetic and safety profiles (Thurmond et al., 2014). Other developments in structural biology, such as the recent crystallisation of histamine receptors, also offer a hope of structure-based drug design to increase potency and selectivity (Shimamura et al., 2011). Also, therapeutic specificity could be enhanced through development of

biassed ligands which have the potential to specifically modify favorable vs unfavorable signalling cascades upon histamine receptors downstream (Violin et al., 2014). New options in the form of emerging gene-based and cell-based therapeutics are potential ways to manipulate histamine biology beyond pharmaceutical tool sets (Barcik et al., 2016).

lthough cell therapies can provide cells that are modified to preferentially degrade histamine or change receptor count in selected organs, CRISPR/Cas9 gene editing can potentially treat genetic variations that cause histamine, increase or other defects. In histamine-related diseases, they remain largely hypothetical, though with improvement in technology, they give new exciting prospects of pursuing research.

The next area of concern is the lack of clinical trial design regarding the kinds of treatment that act on histamine (Casale et al., 2019). It involves development of more specific and sensitive end points to measure the multifaceted effects of histamine modulation, determination of which subgroups of patients are most likely to respond to a given treatment and development of optimal dosage schedules taking receptor pharmacology and chronobiology of the disease into account.

8. Conclusion

The observations of histamine over a century ago have helped us understand a lot about the nature of allergy and inflammatory responses because it has been classified as a biogenic amine with numerous biological functions assisted by four types of subtypes of receptors. Since the initial characterization of the involvement of histamine in acute hypersensitivity reactions through recent findings on its immunomodulatory properties, its role in neurogenic inflammation and its epigenetic potential, the role of histamine is becoming clear, and this leads to the possibility of creating new forms of treatment.

The most current history being dictated by the H 1 receptor antagonists which have been promising in the treatment of various allergic ailments including urticaria and allergic rhinitis. Nevertheless, their use is in therapeutically limited circumstances by disadvantages like heterogeneous strength, non-histaminergic inflammatory actions, and potentially harmful effects. These problems can be addressed by new approaches that aim at other histamine receptors, histamine synthesis, histamine release or downstream signalling and the path to translation of preclinical effectiveness to clinical efficacy remains unfinished.

The future approach to research and treatment of histamine will most probably be targeted to precision medicine, combination treatment regimen which affects more processes of histamine biology or other parallel pathway of inflammation and new drug delivery systems which improves their effectiveness and safety. Also, the study of the role of histamine in less-discussed clinical scenarios and the utilization of new technology, such as state-of-the-art drug design approaches and gene- or cell-based treatments, can be a source of discovering novel solutions to unmet medical requirements.

Because we are learning more and more about how histamine works in the body, both in basic, translational, and clinical studies, we are also building up the knowledge that can be turned into more effective, targeted, and personalized methods of controlling allergic and inflammatory conditions. The fact that the histamine research conducted more than a century ago is still relevant today may be considered a testament to the central role that this mediator plays in human physiology and pathophysiology the proof that it will retain its place in biomedical research and treatment development in the future.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to disclose.

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