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Histamine regulation of innate and adaptive immunity

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1. ABSTRACT

Histamine influences many cell types involved in the regulation of innate and adaptive immune responses including antigen-presenting cells (APCs), Natural Killer (NK) cells, epithelial cells, T lymphocytes and B lymphocytes. These cells express histamine receptors (HRs) and also secrete histamine, which can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization and effector functions leading to tolerogenic or pro-inflammatory responses. Histamine and its four receptors represent a complex system of immunoregulation with distinct effects of receptor subtypes and their differential expression, which changes according to the stage of cell differentiation as well as micro-environmental influences. In this review, we discuss histamine receptor expression and differential activation of cells within both the innate and adaptive immune response and the signal transduction mechanisms which influence their activity.

2. INTRODUCTION

The immune response is a tightly regulated process which normally results in protection from infection and tolerance of innocuous environmental antigens. However, in many disease states, the activated immune response results in a chronic pro-inflammatory state characterized by activated innate pathways with aberrant expansion and polarization of T_H1, T_H2, T_H9, T_H17 or T_H22 lymphocyte populations. Thus, the identification of appropriate controlling factors which augment protective immune responses while limiting tissue damaging immune responses is an essential prerequisite to the development of novel therapies. Many cell metabolites influence immune reactivity (e.g. retinoic acid) and one factor that is receiving more attention as an immunomodulator is histamine (1, 2). Histamine, [2-(4-imidazolyl)-ethylamine], is widely distributed through the body. This short-acting endogenous amine is synthesized by a catalytic enzyme called histidine decarboxlase (HDC) which decarboxylates the semi-

essential amino acid L-histidine. Histamine was discovered approximately 100 years ago (3, 4). The first findings described its ability to mimic smooth muscle-stimulating and vasodepressor action during anaphylaxis. Histamine was first isolated from liver and lung tissue in 1927 before isolation from other tissues succeeded and gave histamine its name based on the greek word "histos" which means tissue.

Histamine is produced by a wide variety of different cell types. Mast cells and basophils are the most well-described cellular sources of histamine, but other cell types, e.g. platelets, dendritic cells (DCs) and T-cells can also express HDC upon stimulation. HDC activity is modulated by cytokines, such as IL-1, IL-3, IL-12, IL-18, GM-CSF, macrophage-colony stimulating factor and TNFalpha, *in vitro* (1, 5). Mast cells and basophils store large quantities of histamine, however, other cell types do not store histamine intracellularly, but secrete it immediately following synthesis (6-8). While histamine is well known for its effects in allergic responses (i.e. increased vascular permeability, smooth muscle constriction, activation of nociceptive nerves, wheal and flare reaction and itch response), the clinical relevance of increased histamine levels at diseased sites is less well understood in other diseases such as Inflammatory Bowel Disease and Irritable Bowel Syndrome (9, 10). Histamine is now recognized to influence many functions of the cells involved in the regulation of innate and adaptive immune responses including antigen presenting cells (APCs), Natural Killer (NK) cells, epithelial cells, T lymphocytes and B lymphocytes (11-14). These cells express histamine receptors (HRs) and also secrete histamine, which can selectively recruit the major effector cells into tissue sites and affect their maturation, activation, polarization and effector functions leading to tolerogenic or pro-inflammatory responses. In this review, we discuss histamine receptor expression and differential activation of cells within both the innate and adaptive immune response and the signal transduction mechanisms which influence their activity.

3. HISTAMINE RECEPTORS

The regulatory character of histamine in immunology is attributed to its binding to 4 subtypes of histamine receptors, which are named chronologically H1R-H4R. In 1966 there was first a differentiation between H1R and H2R (15) while in 1999 the third receptor was identified as H3R (16) and in 2000 the fourth receptor was designated H4R (17). All these four receptors belong to the rhodopsin-like family of G-protein-coupled receptors (GPCR), that are differentially expressed in various cell types and contain 7 transmembrane domains (18, 19). Receptor diversity is supported by pharmalogical evidence and by the low protein homology, which is suggestive of their evolution from different ancestral genes (20). For example H1R and H2R show about 35% homology while H3R and H4R are the most closely related histamine receptors and they have a closer phylogenetic relationship with peptide ligand GPCRs, while they are remotely related to other biogenic amine receptors, including H1R and H2R (21).

3.1. H1R

The H1R encoding intronless gene is located on chromosome 3p25 and contains 487 amino acids. Expression of this 56kDa H1R is found a broad range of various cell types including neurons in central nervous system (22), smooth muscle cells (airway and vascular), hepatocytes, chondrocytes, neurons of the nervous system, endothelial cells, DCs, monocytes, neutrophils, T- and B-cells (23-25). Histamine activation of H1R causes contraction in airway and vascular smooth muscle cells (25) and various responses in vascular endothelial cells, e.g. changes in vascular permeability, synthesis of prostacyclin and synthesis of platelet-activating factor and release of von Willebrand factor and nitric oxide (26, 27). Typical immediate hypersensitivity responses of allergic reactions type I such as redness, itching and swelling are mainly caused by H1R activation. Rhinorrhea, bronchoconstriction, anaphylaxis, conjunctivitis and urticaria are associated with peripheral H1R mediated effects, while food and water intake, convulsion, attention and sleep regulation are central-mediated H1R effects. H1Rs are also described to mediate bronchoconstriction and enhanced vascular permeability in the lung (23, 27). Furthermore histamine excites neurons in the most brain regions via H1R (28). H1R signaling is known to oppose or amplify H2R mediated responses depending on the time and context of receptor activation (29, 30). A global loss of H1R in mice results in immunological (impairment of T- and B-cell responses), metabolic and behavioral abnormalities (31-33). Both IL-4 and histamine can up-regulate gene expression of the H1R (34).

3.2. H2R

The human H2R is a 40kDa 359 amino acid protein with its intronless gene located on chromosome 5q35.5 and shows a high sequence homology (83-95% identity) to other species (guinea pig, mouse, rat, and dog) (35, 36). Expression of H2R is found in a variety of tissues and cells similar to H1R, including brain, gastric parietal cell, smooth muscle cells, T- and B-cells, DCs, and cardiac tissue. H2R is able to exhibit spontaneous and constitutive activity (37). In contrast to H1R, the absence of histamine can result in a down-regulation of H2R in a tissue specific manner (38). Interestingly, H1R antihistamine treatment (levocetirizine) blocked the expected decrease in H1R:H2R ratio *in vivo* that is usually observed in ultrarush honeybee venom immunotherapy patients(39). As mentioned above, H2R has a number of opposing effects to H1R, for example H2R is responsible for relaxation of smooth muscle cells in the blood vessels, the uterus and in airways. Furthermore H2R is described to inhibit a range of immune system activities such as the negative regulation of mast cell degranulation, inhibition of antibody synthesis, cytokine production and T-cell proliferation (13, 40). Mice deficient in H2R are known to have defects in gastric and immune functions (41) as well as selective cognitive defects with an impairment in hippocampal LTP (42) and abnormalities in nociception (43).

3.3. H3R

The third histamine receptor H3R, a 70kDa 445 amino acid protein located on chromosome 20q13.33 containing 4 exons was discovered by a group in Paris (44). The cloning of this receptor was successful in 1999 (16). Initially this receptor was identified for its ability to control histamine release or release of other neurotransmitters and therefore was classified as a pre-synaptical autoreceptor in the peripheral and central nervous system (45). An unusual feature of the H3R is its high degree of constitutive activity *in vivo* (46-49). A large number of H3R splice variants have been identified (50, 51). The majority of naturally occurring splice variants have been shown to have similar pharmacological properties as the full-length protein, but splice variants with altered or loss of functionality have also been described (47). H3R has been reported to play a role in sleep-wake cycle, cognition, energy, homeostatic regulation and inflammation (45). Studies with H3R-KO mice showed a role of H3R in behavior and locomotion (52). Furthermore these mice display a metabolic syndrome with hyperphagia, late-onset obesity together with increased insulin and leptin levels (53, 54). Other studies associated knockout of H3R with an increased severity of neuro-inflammatory diseases and these mice show enhanced release of MIP-2, IP-10 and CXCR3 from peripheral T-cells (55).

3.4. H4R

A gene containing three exons and two large introns on chromosome 18q11.2 encodes the 390 amino acid human H4R. Cloning of mouse, rat and guinea pig H4R showed a 68, 69 and 65% homology respectively to its human counterpart. Human and guinea pig H4R showed higher affinity for histamine than rat and mouse (56). H4R exhibits molecular and pharmacological similarities to H3R. The overall percentage of homology between H3R and H4R is 37-45% while in transmembrane regions there is 58% homology((57, 58). However, in contrast to H3R, distribution of H4R has been described in bone marrow and leukocytes, neutrophils, eosinophils, mast cells, dendritic cells, T-cells, basophils with a low expression rate in heart, lung, small intestine, spleen, brain and thymus (57, 59). Recent studies suggest that H4R plays a major role in chemoattraction of immunological relevant cells such as eosinophils, mast cells, neutrophils, T-cells and DCs as well as influencing cytokine production by these cells((60-67). Furthermore H4R is important in nociception, autoimmune disorders, colon and breast cancer as well as in allergy (68-70). Animal models of asthma, arthritis, colitis and puritis with H4R antagonists have all suggested a role for this receptor in inflammatory responses (62, 71).

4. INNATE IMMUNITY

4.1. Antigen-presenting cells

DCs are potent antigen-presenting cells that are present at all mucosal surfaces and are central players in initiating and regulating adaptive immune responses. DC activation, maturation and polarization are largely influenced by local factors within their micro-environment such as microbial components, cytokines and metabolic products. DCs shape the functional differentiation of the dividing T-cells into T_H1, T_H2, T_H9, T_H17 and T_{reg} responses by producing cytokines such as IL-12, IL-18, IL-23, IL-11, IL-10 or TGFbeta. The selection of an appropriate cytokine secretion pattern by DCs is dependent on a number of factors, but is significantly influenced by the binding of microbial ligands, termed pathogen-associated molecular patterns (PAMPs), to pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and C-type lectin receptors (CLRs). DCs are often found in close proximity to degranulated mast cells and can secrete histamine following activation. While DCs have been shown to express H1R, H2R, H3R and H4R, it is not definitively described if the level of HR expression is altered during maturation or if different DC subsets (e.g. myeloid or plasmacytoid DCs) preferentially up-regulate individual HRs under specific micro-environmental influences. DCs exposed to histamine have been shown to up-regulate antigen-presenting capacity and T_H1 polarisation via the H1R and H3R while activation of the H2R on DCs preferentially drives IL-10 secretion and T_H2 polarisation (72-74)(Figure 1). H2R activation on human plasmacytoid DCs leads to a significant down-regulation of IFNalpha and TNFalpha release following CpG stimulation (75). In addition, accumulation of plasmacytoid DCs and $CD11b^+$ DCs, but not $CD8^+$ DCs, in draining lymph nodes is H2R dependent (76). Histamine was found to reduce or inhibit the production of NADPH-oxidase-derived oxygen radicals by several types of myeloid cells, an effect mediated by H2R (77). In contrast to other DC subsets, Langerhans cells found within the epidermis do not express H1R or H2R (78). Stimulated DCs express a functionally active H4R, which can down-regulate secretion of CCL2 and IL-12 (79). In murine studies, inhibition of H4R on DCs lead to decreased cytokine and chemokine production, which limited their ability to induce T_H2 responses (61). Interestingly, certain bacterial strains express the HDC gene and histamine release by these bacteria *in vivo* could impact immunological function and the DC response to the bacterial strain (80).

TLR stimulation of monocytes is altered by histamine co-incubation as secretion of pro-inflammatory cytokines such as TNFα, IL-12 and IL-18 is attenuated, while IL-10 secretion is enhanced. This histamine effect is mediated by the H2R (81, 82). Histamine also down-regulates CD14, ICAM-1 and CD80 expression via H2R on human monocytes. In addition to TLR activation, monocytes stimulated by advanced glycation end products up-regulate adhesion molecule expression and this effect is inhibited by the H2R (83). Macrophages purified from human lung tissue, monocyte-derived macrophages (MDMs) and DCs express higher levels of the H1R compared to precursor monocytes. Monocyte differentiation into macrophages is also associated with down-regulation of the H2R, whereas differentiation into DCs has no significant influence on H2R expression (84).

4.2. Epithelial cells

Human intestinal epithelial cells have been shown to express H1R, H2R and H4R (85). Intestinal epithelial cells exposed to histamine have lower numbers of

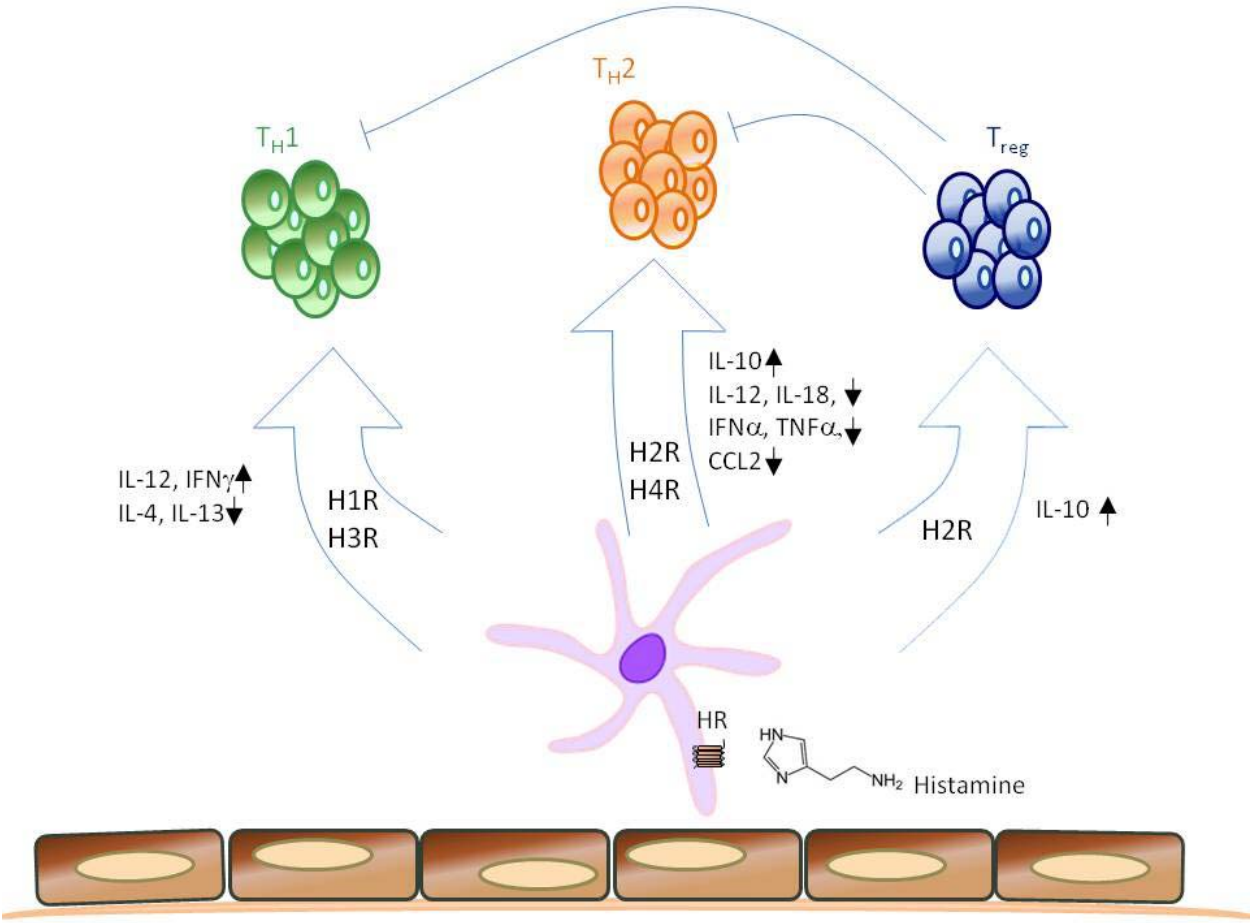

Figure 1. Antigen-presenting cell modulation of T cell polarisation is Influenced by Histamine Receptor Activation. Differential triggering of histamine receptors leads to altered T_H1, T_H2 or T_{reg} polarization due, in part, to altered cytokine secretion.

invasive intracellular pathogens *in vitro*, which was mediated in part by the H1R (86). In contrast, co-culture experiments with gastrointestinal epithelial cells and mast cells suggested that TLR2/NOD2 activated mast cells secrete histamine which reduces epithelial barrier function (87, 88). Modulation of conjunctival and nasal epithelial cell adhesion molecule expression (e.g. ICAM1) by H1R antagonists suggests that the H1R is directly or indirectly involved in epithelial up-regulation of adhesion molecules expression following allergen exposure (89). In addition to their essential role in maintaining barrier function, epithelial cells respond to the presence of various microbes due to the expression of PRRs. H1R activation on pulmonary epithelial cells enhanced expression of TLR3 and stimulation of these cells with the TLR3 ligand poly (I:C) in the presence of histamine resulted in enhanced IL-8 secretion and NF-kappaB phosphorylation (90). However, it is unknown if HRs activation alters the epithelial cell cytokine response to other PRR ligands or adherent microbes.

4.3. Natural killer cells

NK cells are large granular lymphocytes that use a battery of activating and inhibitory receptors to distinguish normal cells that are to be spared from aberrant cells that are to be eradicated. Thus, activating receptors on NK cells, such as the family of natural cytotoxicity receptors (NCRs) and NKG2D bind their corresponding ligands on target cells to activate NK cells, while inhibitory receptors, such as killer cell immunoglobulin-like receptors KIR interact with specific MHC class I molecules on target cells, with subsequent NK cell inactivation (91). NK cells express the H4R, which mediates chemotaxis of NK cells to histamine (92). Interestingly, histamine in combination with IL-2 is being assessed as a possible immunotherapy for maintaining remission in patients with cancer. It is thought that histamine inactivation of the NADPH-oxidase system (via H2R) protects NK cells from inactivation and thereby allows effector lymphocytes to respond to IL-2 stimulation. In the presence of radical-producing myeloid cells, the combination of histamine and IL-2 was shown to trigger efficient NK cell-mediated killing of several types of leukemic cells, including freshly recovered human AML blasts, whereas IL-2 alone was ineffective (93). In addition, post-consolidation immunotherapy with histamine and IL-2 is superior to IL-2 alone in the prevention of relapse in AML patients (94).

Invariant NK T (iNKT) cells constitute a distinctive population of mature T lymphocytes positively selected by the nonpolymorphic MHC class-I-like molecule CD1d. These cells are both numerically and functionally impaired in histamine-deficient mice with diminished secretion of IL-4 and IFNgamma following stimulation with alpha-galactosylceramide (95). These authors further demonstrated that histamine activation via the H4R is critical for iNKT cytokine secretion.

4.4. Granulocytes

There are three types of granulocytes, namely neutrophils, eosinophils and basophils. Histamine regulates granulocyte accumulation to tissues in a number of ways. Allergen-induced accumulation of eosinophils in the skin, nose and airways is potently inhibited by H1R antagonists (96). The effect of histamine on eosinophil migration is different depending on the dose. High histamine levels inhibit eosinophil chemotaxis via H2R, while low doses enhance eosinophil chemotaxis via H1R (97). In addition, eosinophil recruitment is also mediated by H4R (66). Relative to other chemoattractive substances such as the CCR3-binding chemokines, the chemoattractive effect of histamine is weaker (60, 64, 66, 97). However, histamine, upon activation of the H4R induces enhanced migration of eosinophils towards eotaxin and eotaxin 2 (60, 64). In addition, the potential for histamine to act as an eosinophil chemoattractant *in vivo* might be augmented by other factors, such as growth factors or cytokines like IL-5, which is the specific cytokine for the differentiation, activation and survival of eosinophils (66). Triggering of H4R also induces chemotaxis of mast cells (65). Experiments in mice showed that mast cells from wild-type and H3R-deleted mice migrated in response to histamine, while mast cells from the H4R-deleted mice did not. Thus, chemotaxis of eosinophils and mast cells via histamine is triggered mainly through the H4R. Combination therapies with H4R and H1R antagonists may provide additional efficacy in dampening the pro-inflammatory effects of histamine. Histamine inhibits neutrophil chemotaxis due to H2R triggering, while neutrophil activation, superoxide formation and degranulation is also suppressed via histamine binding to H2R (84).

5. ADAPTIVE IMMUNITY

5.1. T cells

In addition to the effects of histamine on cytokine secretion by APCs, which would result in altered T-cell polarization, T-cells themselves express histamine receptors and respond differently to histamine stimulation depending on the receptors that they express. T_H1 cells express high levels of H1R while T_H2 cells show increased expression of H2R. IL-3 stimulation significantly increases H1R expression on T_H1, but not on T_H2 cells (12). Histamine enhances T_H1-type responses by triggering the H1R, whereas both T_H1- and T_H2-type responses are negatively regulated by HR2, due to activation of different biochemical intracellular signals (12). Histamine dose-dependently enhanced TGF-beta-mediated suppression of CD4+ T cells which was mediated by H2R and was cAMP/PKA dependent (98). This pathway is activated by the H2R, which is preferentially expressed on Th2 cells.It has also been shown that histamine stimulation induced IL-10 secretion from T-cells through HR2 (99). Increased IL-10 production by T-cells may account for an important regulatory mechanism in the control of inflammatory responses through histamine. On the other hand, inhibition of H2R in vaccination models resulted in a more robust $CD4^+$ T-cell antigen-specific secretion IL-4 and IFNgamma while $CD8^+$ T-cells secreted significantly more IFNgamma suggested that vaccination against certain infectious organisms may be improved by H2R inhibition (100). In mice, deletion of HR1 specifically results in the suppression of IFNgamma and dominant secretion of T_H2 cytokines (IL-4 and IL-13). HR2-deleted mice show up-regulation of both T_H1 and T_H2 cytokines. HR1-deleted mice showed delayed disease onset and decreased disease severity when immunized to develop experimental allergic encephalomyelitis (101). In addition, H1R signaling at the time of TCR ligation was required for activation of p38 MAPK, a known regulator of IFNgamma expression. Importantly, selective re-expression of H1R in $CD4^+$ T-cells fully complemented both the IFNgamma production and the EAE susceptibility of H1R-deficient mice. These data suggest that the presence of H1R in $CD4^+$ T-cells and its interaction with histamine regulates early TCR signals that lead to T_H1 differentiation and autoimmune disease (102). In addition, histamine functions as a T-cell chemotactic factor which is a H1R mediated effect (103). T-cells isolated from the peripheral blood of allergic asthma patients had increased expression of both H1R and H2R on CD4 and CD8 positive T-cells. Incubation of these cells with histamine decreased the percentage of T-cells staining positive for IL-4, IL-13 and IFNgamma, an effect that was not blocked by an H1R antagonist suggesting that the H2R may play a role in this inhibitory effect (104). However, histamine stimulation of peripheral blood cells from allergic rhinitis patients did not result in suppression of IL-4 and IL-13 production. T regulatory cells express H1R and activation of the H1R by histamine decreases T regulatory cell suppressive function which was associated with decreased expression of CD25 and the transcription factor Foxp3 (105). H4R is expressed by CD4 T-cells but it is unknown if there is differential expression between polarized T-cell subsets. H4R or H2R stimulation of CD8 T-cells induced production of the T-cell chemoattractant IL-16 and selective activation of the H4R in murine models induced the migration of $CD25^+Foxp3^+$ T regulatory cells (106, 107). *In vivo*, the rapid promotion of antigen-specific T regulatory cells is thought to be a key feature protecting the host from allergic disease. This was clearly shown in beekeepers who during the bee season (associated with multiple bee stings) had increased numbers of allergen-specific $IL\text{-}10^+$ T-cells with reduced numbers of allergen-specific $IL\text{-}4^+$ or $IFNgamma^+$ T-cells. This situation was reversed out of season (i.e. no bee stings) with higher levels of $IL\text{-}4^+$ and $IFNgamma^+$ T-cells and reduced $IL\text{-}10^+$ T-cells (108). H2R gene expression increased in allergen-specific T-cells during the bee season while H1R and H4R expression did not change. This increase in H2R was localized to $IL\text{-}4^+$ T-cells and stimulation of these cells with histamine resulted in decreased secretion of IL-4 and

increased secretion of IL-10 which was H2R dependant (108). This study strongly supports a growing body of evidence that the H2R represents an essential receptor that participates in peripheral tolerance to allergens by the induction of IL-10 and direct suppression of the proliferation of allergen-specific T-cells *in vivo*. The histamine receptor profile of recently described T-cell lineages such as T_H9, T_H17 and T_H22 cells is currently unknown.

5.2. B cells

The impact of histamine on B-cell immunoglobulin secretion depends on the requirement for T-cell help. For T-cell-independent antigens (e.g. TNP-Ficoll), antibody levels are decreased in H1R KO mice (109). In addition, histamine enhanced anti-IgM-induced proliferation of B-cells, which was abolished in H1R-deleted mice suggesting an important role of H1R signaling in responses triggered from B-cell receptors. In contrast, antibody responses to T-cell-dependent antigens (e.g. Ovalbumin) show a different pattern(109). H1R KO mice produced higher levels of OVA-specific IgG1 and IgE in comparison with wild-type mice while H2R KO mice showed decreased serum levels of OVA-specific IgE in comparison with wild-type mice and H1R KO mice. In addition, mice lacking H1R displayed increased specific antibody response with increased IgE, IgG1, IgG2b and IgG3 compared with mice lacking H2R (21). Thus, differential activation of H1R or H2R on T-cells plays a dominant role in the suppression or activation of the humoral immune response.

6. HISTAMINE RECEPTOR SIGNALLING

The key to developing more effective immunotherapeutic strategies for the manipulation of HRs is to elucidate the signaling pathways which are triggered and their molecular interactions with other cellular targets. H1R – H4R are G protein-coupled receptors (GPCRs) which are also know as seven-transmembrane domain receptors (7TM receptors), heptahelical receptors, serpentine receptors, and G protein-linked receptors (GPLR) of which over 800 different receptors have been described (110, 111). These receptors are characterized by an extracellular N-terminal domain followed, as the name suggests, by 7 transmembrane domains (alpha-helices) connected by three intracellular and three extracellular domains. These receptors are expressed in eukaryotes, including yeast, choanoflagellates and animals. G protein means a protein able to bind guanyl nucleosides and act as an exchanging factor by catalyzing replacement of the bound guanosine diphosphate (GDP) by guanosine triphosphate (GTP). The ligands, varying in size from small molecules to even large proteins, for these GPCRs include a broad range of different types of substances, e.g. light-sensitive compounds, pheromones, hormones and neurotransmitters. GPCRs are the target of nearly 30% of modern medical drugs because these receptors are involved in so many different disease processes (112).

Both receptors and G proteins, are generally inactive if no ligand is available. Following activation, an association of GPCRs with the heterotrimeric G proteins, consisting of alpha-beta-gamma subunits, takes place and this leads to activation of classical and non-classical signaling pathways. The classical pathway involves the association of specific Galpha subunits ($Galpha_q$, $Galpha_s$ and $Galpha_{i/o}$) to activate distinct molecular signaling cascades (Figure 2). For the HRs it is known that H1R stimulation leads to activation of $Galpha_q$, H2R is coupled to $Galpha_s$, while H3R and H4R are both activators of $Galpha_{i/0}$ (113). Although all receptors have highly conserved aspartate residue in the third transmembrane helix, they strongly differ in receptor distribution, ligand binding, signaling pathways and functions. Receptors coupled to $Galpha_s$ activate adenylate cyclase which promotes cAMP formation and activation of protein kinase A (PKA). PKA leads to CREB activation resulting in altered gene expression while PKA can also phosphorylate other protein targets with diverse effects on the cell. In addition, $Galpha_s$ is also able to open ion channels, e.g. Na^+, Ca^{2+} and Cl^- channels. In contrast to the activation of $Galpha_s$, initiation of $Galpha_{i/o}$ blocks adenylate cylcase activity and reduces cAMP levels. $Galpha_q$ interacting receptors activate phospholipase C (PLC) which cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into diacyl glycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 diffuses through the cytosol to bind to IP3 receptors including calcium channels in the endoplasmic reticulum. This increases cytosolic calcium levels, resulting in a cascade of intracellular changes and activity. In addition, calcium and DAG activate protein kinase C, which goes on to phosphorylate other molecules (114). The non-classical pathways are induced by betagamma subunits of G proteins and are described to activate mitogen-associated protein kinase (MAPK), extracellular signal-related kinase (Erk) and Jun (111). In addition, betagamma-subunits of histamine-stimulated GPCRs have been shown to activate phosphoinositide 3-kinase (PI3K) leading to the phosphorylation of protein kinase B (also known as Akt) and the subsequent activation of phosphodiesterase (PDE), resulting in a decreased intracellular cAMP levels (115). Furthermore, Akt1 has been shown to be critical in mediating the histamine-induced junctional permeability changes in endothelial cells via interaction with the epithelial NO-synthase and vascular endothelial (VE)-cadherin (116).

In addition to the pathways that are directly activated by histamine receptors, the resultant signaling cascades can interact with many other intracellular targets resulting in altered activation, phosphorylation and gene expression thus further influencing cellular maturation and polarisation. As described above, dendritic cells exposed to microbial ligands secrete IL-12p70 and IL-10 and the level of cytokine produced is significantly influenced by H1R or H2R activation by histamine (117). Activation of cAMP by H2R could potentially be important for histamine modulation of DC function but the classical downstream signaling pathway from cAMP may not be involved. To date there are many reports describing cAMP-responsive genes with a broad range of functions that have been shown to be regulated in a PKA-independent manner. These include thyroglobulin (118), glial fibrillary acidic protein

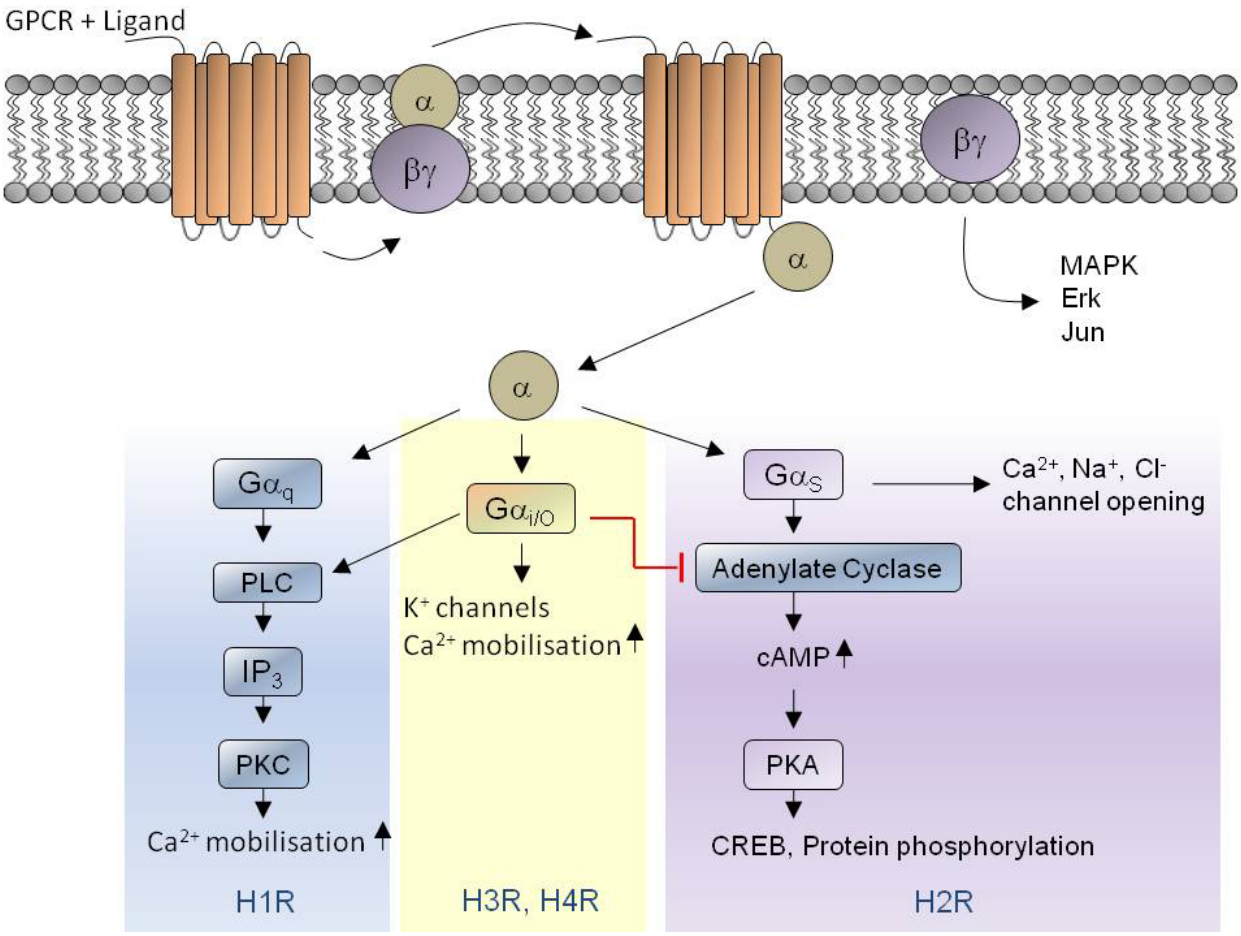

Figure 2. Histamine receptor signal transduction. HRs are GPCRs which bind to heterotrimeric G proteins, consisting of alpha-beta-gamma subunits, following ligand binding. The classical pathway involves the association of specific Galpha subunits ($Galpha_q$, $Galpha_s$ and $Galpha_{i/o}$) to activate distinct molecular signaling cascades.

(119), vasoactive intestinal peptide (120), neuronal nitric oxide synthase (121), prostaglandin G/H synthase (122), cyclin D1 (123), prolactin (124), proglucagon (125) and its transactivator Cdx-2 (126), aquaporin (127), IL-1beta, IL-6 (128) and supressor of cytokine signaling 3 (SOCS3) (129). Alternative cAMP sensors, such as Epac-1 (Exchange protein directly activated by cAMP-1), mediate the PKA-independent cAMP effects. For example, activation of adenylate cyclase promotes induction of a gene encoding SOCS3 in epithelial cells, resulting in a reduced ability of leptin and soluble IL-6 receptor a/IL-6 trans-signaling complex to activate the Jak/Stat pathway and this effect is PKA-independent. These authors demonstrated that EPAC1, not PKA, appeared to be necessary for promotion of cAMP-mediated activation of SOCS3 following the activation of CCAAT/enhancer binding protein family transcription factors (129, 130). In addition, Woolson *et al.* proposed that other PKA- and EPAC1-independent cAMP sensors are responsible for transient activation of ERK which is required for subsequent inhibition of cytokine receptor activation of both Jak/Stat and Erk signaling pathways (131). EPAC1 has also been shown to be involved in H3R functional effects in type I carotid cells. These authors reported that activation via H3R leads to activation of $Galpha_{i/o}$ and thereby blocks adenylate cyclase activity resulting in reduced cAMP levels. The reduced level of cAMP negatively regulates EPAC with an associated reduced level of IP3 activation finally resulting in inhibition of Ca^{2+} release which was induced by activation of muscarinic receptors (132). Activation of the H1R leads to transcription of IL-8 via NFAT (133)and stimulation with TNFalpha, IL-1alpha or LPS enhances IL-8 levels if combined with histamine. This effect was blocked by inhibitors of MAPK, NF-kappaB and PLC, indicating involvement of H1R in these pathways (134). A recent study showed that H1R-mediated histamine blockade of cell proliferation involves PLC, RAC and JNK-dependent pathways (135). While T cells express different HRs, it has not been conclusively shown which molecular mechanism(s) are responsible for the preferential induction by histamine of T-bet$^+$ T_H1 cells, GATA-3$^+$ T_H2 cells or Foxp3$^+$ T regulatory cells. It is likely that both direct and indirect mechanisms are involved, for example, modulation of cytokine secretion by the naïve T cell could be partly responsible for the histamine polarization effect via H1R or H2R.

7. CONCLUSIONS

The recent developments in histamine research have prompted the re-evaluation of histamine in influencing both the innate and adaptive immune responses. Histamine and its four receptors represent a complex system of immunoregulation with distinct effects of receptor subtypes and their differential expression, which changes according to the stage of cell differentiation as well as micro-environmental influences. The role for differential activation of histamine receptors on immune competent cells in chronic inflammatory diseases is surprisingly poorly described to date and further examination of this potent immunoregulatory network will likely lead to new advances in our understanding of these disorders. In particular, determination of the molecular mechanisms underpinning histamine receptor cross-talk with immune-relevant pathways will identify novel therapeutic targets.

8. ACKNOWLEDGEMENTS

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