Histamine Release from Mast Cells and Basophils

Francesco Borriello, Raffaella Iannone, and Gianni Marone

Contents

Abstract

Mast cells and basophils represent the most relevant source of histamine in the immune system. Histamine is stored in cytoplasmic granules along with other

F. Borriello
Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research (CISI), School of Medicine, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy

Division of Infectious Diseases, Department of Medicine, Boston Children's Hospital, Boston, MA 02115, USA

R. Iannone
Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research (CISI), School of Medicine, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy

G. Marone (✉)
Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research (CISI), School of Medicine, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy

Institute of Experimental Endocrinology and Oncology "Gaetano Salvatore" (IEOS), National Research Council (CNR), Naples, Italy
e-mail: marone@unina.it

Handbook of Experimental Pharmacology, DOI 10.1007/164_2017_18

amines (e.g., serotonin), proteases, proteoglycans, cytokines/chemokines, and angiogenic factors and rapidly released upon triggering with a variety of stimuli. Moreover, mast cell and basophil histamine release is regulated by several activating and inhibitory receptors. The engagement of different receptors can trigger different modalities of histamine release and degranulation. Histamine released from mast cells and basophils exerts its biological activities by activating four G protein-coupled receptors, namely H1R, H2R, H3R (expressed mainly in the brain), and the recently identified H4R. While H1R and H2R activation accounts mainly for some mast cell- and basophil-mediated allergic disorders, the selective expression of H4R on immune cells is uncovering new roles for histamine (possibly derived from mast cells and basophils) in allergic, inflammatory, and autoimmune disorders. Thus, the in-depth knowledge of mast cell and basophil histamine release and its biologic effects is poised to uncover new therapeutic avenues for a wide spectrum of disorders.

Keywords
Basophil • Degranulation • Histamine • Histamine receptors • Mast cell

1 Introduction

Mast cells and basophils are the major source of the biogenic amine histamine among immune cells (Graham et al. 1955; Riley and West 1952, 1953). These cells store histamine in cytoplasmic granules along with other amines, proteases, proteoglycans, some cytokines/chemokines, and angiogenic factors that are rapidly released upon triggering with a variety of stimuli (Stone et al. 2010; de Paulis et al. 2006; Marone et al. 2005; Detoraki et al. 2009). Although several differences exist between mast cells and basophils, the stimuli that induce their activation and the mechanisms of degranulation, histamine release from mast cells and basophils is regarded as a central event in the development of rapid anaphylactic reactions and allergic responses due to its activation of histamine receptors expressed on vascular and stromal cells as well as immune cells. In this chapter we will introduce the biology of mast cells, basophils, histamine and histamine receptors to review recent advancements in mast cell and basophil degranulation and histamine release.

2 Biology of Mast Cells and Basophils

Mast cells and basophils are characterized by the expression of the tetrameric ($\alpha\beta\gamma_2$) high affinity receptor for IgE (FcεRI) and the ability to synthesize histamine (Stone et al. 2010; Marone et al. 2005). Nevertheless, they also show crucial differences. Basophils are a rare population of fully mature, short-lived circulating immune cells (they account for approximately 1% of blood leukocytes) that are recruited to tissues upon inflammation (Karasuyama et al. 2011; Borriello et al. 2014a; Marone et al. 2014). On the other hand, mature mast cells are tissue-resident cells distributed throughout mucosal and connective tissues, often in close proximity

to blood and lymphatic vessels, near or within nerves, and beneath epithelial surfaces (Galli and Tsai 2012). In response to IgE crosslinking (e.g., antigens, superantigens, anti-IgE) or IgE-independent stimuli (e.g., cytokines, anaphylatoxins, proteases, Toll-like receptor [TLR] ligands) mast cells and basophils release a partially overlapping set of preformed (e.g., histamine, proteases, some cytokines) and de novo synthesized (e.g., lipids, cytokines/chemokines, angiogenic and lymphangiogenic factors) mediators, albeit differences exist (Stone et al. 2010; de Paulis et al. 2006; Marone et al. 2005; Detoraki et al. 2009; Galli and Tsai 2012; Borriello et al. 2014b; Voehringer 2012; Moon et al. 2014; Patella et al. 2000; Genovese et al. 2003). For example, prostaglandin D_2 (PGD_2) is synthesized only by mast cells, while interleukin (IL)-4 (an important cytokine for the development of type 2 immunity) is produced mainly by basophils.

Mast cells and basophils play a major role in the development of anaphylactic reactions and allergic responses (Stone et al. 2010; Marone et al. 2005). However, their involvement has also been shown in several pathophysiological conditions, such as acute and chronic response to pathogens (including but not limited to ticks and other ectoparasites) (Chan et al. 2012; Eberle and Voehringer 2016), cancer development and progression (Varricchi et al. 2016; Marichal et al. 2013a; Melillo et al. 2010; Visciano et al. 2015), and also resistance to animal venoms (Akahoshi et al. 2011; Metz et al. 2006; Schneider et al. 2007). In this regard, mast cells enhance innate resistance of mice to venoms derived from several species of snakes, the venomous lizard Gila monster, scorpions, and the honeybee at least in part by releasing proteases (i.e., carboxypeptidase A3 and chymase MCP4) that degrades toxins present in some of these venoms. Moreover, mast cell activation by IgE specific for components of honeybee venom or Russell's viper venom protects mice from challenge with lethal doses of these venoms (Marichal et al. 2013b). Interestingly, basophils also exert non-redundant roles in some experimental models (Karasuyama et al. 2011). For example, basophils are required for acquired resistance against *Haemaphysalis longicornis* second infestation (Wada et al. 2010).

In conclusion, the release of mast cell and basophil mediators (including histamine) is involved in several pathophysiological conditions and may result in either beneficial or detrimental effects.

3 Histamine and Histamine Receptors

The first physiological characterization of β-imidazolylethylamine (the chemical formula of histamine) was reported in 1910 by Dale and Laidlaw (Dale and Laidlaw 1910). They demonstrated that this molecule causes vasodilation, the contraction of smooth muscles in the airway, uterus, and the intestine, stimulates heart rate and contractility, and induces a shock-like syndrome when injected into animals. Further investigations showed that histamine also stimulates stomach hydrochloric acid secretion (Popielski 1920). Moreover, in 1924 Lewis and Grant described the classic "Triple Response" elicited by the subcutaneous injection of histamine: a red

spot due to vasodilatation, a wheal due to increased permeability, and flare due to an axon reflex (Lewis and Grant 1924). Nevertheless, the first demonstration of the physiological relevance of histamine came in 1927 when histamine was isolated from liver and lungs (Best et al. 1927). Later, histamine was also recognized as a mediator of experimental anaphylaxis (Feldberg and Kellaway 1937; Feldberg and Keogh 1937; Feldberg and O'Connor 1937). Of note, Riley and West (1952, 1953) demonstrated that mast cells are the predominant cellular source of histamine (Riley and West 1952, 1953). Subsequently, basophils were identified as the main source of histamine among blood cells (Graham et al. 1955).

Histamine binds to four G protein-coupled receptors (GPCRs), namely H1-receptor (H1R), H2-receptor (H2R), H3-receptor (H3R), H4-receptor (H4R) (Panula et al. 2015; Seifert et al. 2013) (Fig. 1). H1R activation mediates many symptoms of type I allergic reactions, including pruritus, erythema and edema. Indeed, H1R

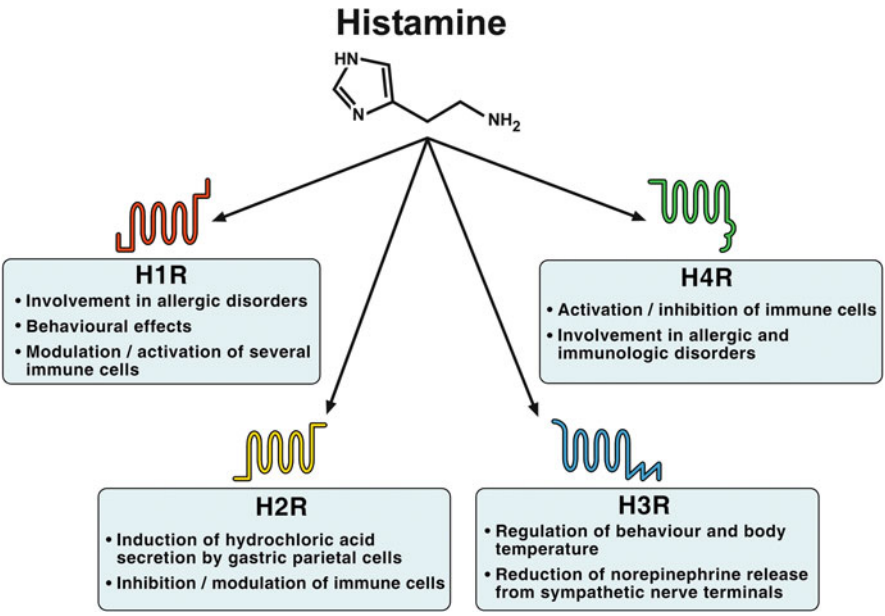

Fig. 1 Biological effects of histamine. Histamine exerts its effects through the engagement of four G-protein coupled receptors (H1R, H2R, H3R, H4R). H1R is expressed on endothelial cells and bronchial smooth muscle cells and plays a major role in allergic disorders. The presence of H1R in the central nervous system mediates several behavioral effects. H1R activation also exerts proinflammatory and immunomodulatory activities due to its expression on several immune cells (e.g., dendritic cells, macrophages, Th1 cells). H2R activation induces the secretion of hydrochloric acid from gastric parietal cells and modulates/inhibits a variety of immune cells (e.g., mast cells, basophils, neutrophils, eosinophils, dendritic cells, γδ cells, Th1 and Th2 cells). H3R regulates various aspects of behavior and body temperature at the level of central nervous system. In addition, H3R inhibits norepinephrine release from sympathetic nerve terminals in the heart. H4R modulates the migration and activation of a wide spectrum of immune cells (e.g., mast cells, basophils, eosinophils, monocytes, dendritic cells, NK, iNK T and γδ cells, $CD8^+$ T cells, Treg and Th2 cells) and is thereby involved in allergic and immune-mediated disorders

antagonists are used for local and systemic treatment of these symptoms (although H2R is also involved in the pathophysiology of IgE-mediated systemic anaphylaxis) (O'Mahony et al. 2011; Wechsler et al. 2013). In addition, H1R knockout mice have impairment in locomotor activity and exploratory behavior (Inoue et al. 1996), a decrease in aggression and anxiety (Yanai et al. 1998), a significant impairment in nociception and an enhancement in the sensitivity to the analgesic effect of morphine (Mobarakeh et al. 2000, 2002). H1R knockout mice also show an impairment of the immune response since several immune cell subsets express H1R. H1R deletion results in lower percentages of IFN-γ-producing T cells and more ovalbumin (OVA)-specific IgG1 and IgE compared with wild-type (Jutel et al. 2001). Interestingly, although allergen-stimulated T cells from H1R knockout mice exhibit an enhanced production of Th2 cytokines, allergen-challenged H1R knockout mice show reduced lung Th2 cytokines associated with lower airway inflammation, goblet cell metaplasia, and airway hyperresponsiveness. These conflicting results can be explained, at least in part, by considering that histamine promotes T cell chemotaxis. Thus, defective T cell trafficking could be responsible for reduced lung inflammation in allergen-challenged H1R knockout mice (Bryce et al. 2006). In addition to T cells, human lung macrophages, monocyte-derived macrophages, and monocyte-derived dendritic cells express higher levels of H1R compared with precursor monocytes. Histamine induces the release of proinflammatory mediators (β-glucuronidase, IL-8 and IL-6) by MDM and HLM through the activation of H1R (Triggiani et al. 2001, 2007; Marone et al. 2001).

H2R is expressed on the parietal cells of the stomach and its activation induces hydrochloric acid secretion. Nevertheless, H2R knockout mice are phenotypically normal and show normal basal gastric pH due to gastric mucosa hypertrophy and increased circulating levels of gastrin (Kobayashi et al. 2000). Interestingly, these mice show a dysregulated T lymphocyte activity, that is upregulation of both Th1 and Th2 cytokines and decreased OVA-specific IgE production compared with wild-type and H1R knockout mice (Jutel et al. 2001). H2R is extensively expressed among immune cells. H2R gene expression increases in human IL-4^+ T cells upon bee venom exposure of non-allergic beekeepers (Meiler et al. 2008) and in basophils during the first hours of ultra-rush venom immunotherapy (Novak et al. 2012). H2R upregulation is responsible for the inhibition of IL-4 and the stimulation of IL-10 secretion by IL-4^+ T cells (Meiler et al. 2008) as well as the inhibition of histamine release and cytokine secretion from basophils (Novak et al. 2012; Lichtenstein and Gillespie 1973). In addition, activation of H2R inhibits histamine release from rodent mast cells (Masini et al. 1982), neutrophil activation (Burde et al. 1989), eosinophil chemotaxis (Clark et al. 1975) and degranulation (Ezeamuzie and Philips 2000), γδ T cell-mediated cytotoxicity (Truta-Feles et al. 2010), and reduces the inflammatory response of dendritic cells to microbial ligands (Frei et al. 2013; Mazzoni et al. 2003). Interestingly, histamine via H2R protects natural killer cells from myeloid cells-dependent inactivation and fosters their killing of human acute myeloid leukemia blasts (Brune et al. 1996).

H3R is expressed mainly in the central nervous system (Sadek et al. 2016). Accordingly, H3R knockout mice exhibit a neurological phenotype: decrease in

locomotor activity, wheel-running behavior, and body temperature (Toyota et al. 2002). In addition, mild obesity (Takahashi et al. 2002) and reduction in anxiety (Rizk et al. 2004) were reported in these mice. Levi and collaborators reported the presence of H3R on sympathetic nerve terminals in the human heart (Imamura et al. 1995). Activation of this receptor leads to the attenuation of norepinephrine release in conditions associated with enhanced adrenergic activity, such as acute myocardial ischemia (Imamura et al. 1994). Moreover, activation of H3R inhibits norepinephrine release during protracted myocardial ischemia (Imamura et al. 1996).

H4R has limited homology with the other histamine receptors and is preferentially expressed on immune cells, namely T cells (Truta-Feles et al. 2010; Gantner et al. 2002; Gutzmer et al. 2009; Leite-de-Moraes et al. 2009; Morgan et al. 2007), NK cells, dendritic cells (Damaj et al. 2007), eosinophils (Buckland et al. 2003; O'Reilly et al. 2002), basophils (Shiraishi et al. 2013), and mast cells (Thurmond et al. 2004; Godot et al. 2007; Hofstra et al. 2003). Interestingly, this receptor modulates immune cell chemotaxis as well as several other functions of these cells. At variance with mast cells from wild type mice, mast cells from H4R knockout mice do not migrate in response to histamine (Hofstra et al. 2003). H4R antagonism prevents histamine-induced $[Ca^{2+}]_i$ increase, mast cell chemotaxis, and submucosal mast cell accumulation in the trachea of mice after histamine inhalation (Thurmond et al. 2004). Histamine acting through H4R enhances C-X-C motif chemokine (CXCL) 12-induced chemotaxis of mast cell precursors, but not mature mast cells (Godot et al. 2007). H4R can impair cardiac mast cell renin release in a model of ischemia/reperfusion (Aldi et al. 2014). A role for H4R was also demonstrated in the modulation of eosinophil and basophil chemotaxis in response to histamine (Buckland et al. 2003; O'Reilly et al. 2002; Shiraishi et al. 2013). In addition, H4R activation reduces basophil expression of CD63 and CD203c and the production of sulfidoleukotrienes following FcεRI cross-linking (Mommert et al. 2016). Interestingly, the involvement of H4R in the development of allergic disorders has also been shown in vivo. For example, in a mouse model of allergic rhinitis histamine released from mast cells recruits H4R-expressing basophils to the nasal cavity, an event that is required for the development of early or late phase nasal responses following allergen challenge (Shiraishi et al. 2013). Combined treatment with H1R and H4R antagonists in the challenge phase prevents the development of diarrhea and intestinal inflammation in an experimental model of peanut sensitization and challenge, probably by affecting dendritic cell chemotaxis and function (Wang et al. 2016). H4R knockout mice develop less skin lesions compared with wild type mice in an experimental model of atopic dermatitis, although pharmacological blockade of H4R is required during both sensitization and challenge to partially mimic the results observed in H4R knockout mice (Rossbach et al. 2016). H4R might also contribute to skin allergic inflammation by activating Th2 cells and inducing pruritus via IL-31 (Gutzmer et al. 2009). Nevertheless, in a murine model of allergic asthma intratracheal administration of the H4R agonist 4-Methylhistamine mitigated airway inflammation, probably by inducing the recruitment of $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory cells (Morgan et al. 2007).

These results highlight the complex role of H4R in allergic inflammation. Interestingly, H4R has also been involved in the pathogenesis of non-allergic disorders by affecting multiple cell types. H4R blockade decreases neutrophil accumulation in experimental models of peritonitis (Thurmond et al. 2004) and pleurisy (Takeshita et al. 2003). H4R activation induces chemotaxis of IL-2-activated NK cells, dendritic cells, THP-1 cells (a human acute monocytic leukemia cell line) (Damaj et al. 2007), γδ T cells (Truta-Feles et al. 2010), and enhances cytokine secretion from invariant NK T (iNKT) (Leite-de-Moraes et al. 2009).

4 Mast Cell and Basophil Degranulation and Histamine Release

Mast cell and basophil degranulation and histamine release is a complex process that can be initiated and modulated by IgE-dependent and non-IgE-dependent stimuli activating a wide variety of receptors (Fig. 2), including cytokines like IL-3, IL-33 and SCF and TLR agonists that can also enhance the response to other stimuli (Stone et al. 2010; Marone et al. 2005; Galli and Tsai 2012; Borriello et al. 2014b; Voehringer 2012; Schroeder 2011). Cross-linking of FcεRI-bound IgE induced by antigens, superantigens, and the histamine-releasing factor (which bind a relatively large fraction of IgE and IgG on the Fab portions) (Kawakami et al. 2014) results in the release of histamine as well as other factors, including lipid mediators, cytokines, and chemokines. A key singling protein involved in this process is the cytosolic spleen tyrosine kinase (Syk) that induces the phosphorylation of adaptor and signaling molecules (Borriello et al. 2014b; Havard et al. 2011; Kepley et al. 1999; Lavens-Phillips and MacGlashan 2000; MacGlashan 2007). An important target of Syk is the Tec family Bruton's tyrosine kinase (Btk). Indeed, Btk inhibition blocks mast cell degranulation and IgE-mediated basophil activation (MacGlashan et al. 2011; Hata et al. 1998; Kuehn et al. 2008). Mast cell and basophil activation can also be inhibited by negative regulators of signaling pathways. For example, the lipid phosphatase SHIP-1 dephosphorylates the inositol ring of phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) to yield phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2), thereby reducing calcium influx and cell activation (Huber and Gibbs 2015).

Mast cell and basophil histamine release is also modulated by other factors, like substance P, complement anaphylatoxins C3a and C5a, endothelin 1, formyl-methionyl-leucyl phenylalanine (fMLF), many of them acting through GPCRs (Maurer et al. 2004; Schafer et al. 2013; Yano et al. 1989; Grant et al. 1975; Siraganian and Hook 1977). Interestingly, mast cells express the MAS-related G protein-coupled receptor (MRGPR) B2 (mouse) or X2 (human) that binds to and mediates mast cell activation in response to anti-microbial peptides, basic secretagogues (e.g., substance P, mastoparan, compound 48/80) as well as the peptidergic drug icatibant, neuromuscular blocking drugs, and fluoroquinolones (McNeil et al. 2015; Subramanian et al. 2011, 2013; Kashem et al. 2011). Mast cell degranulation events in response to FcεRI crosslinking and MRGPRB2 or X2 (as well as other

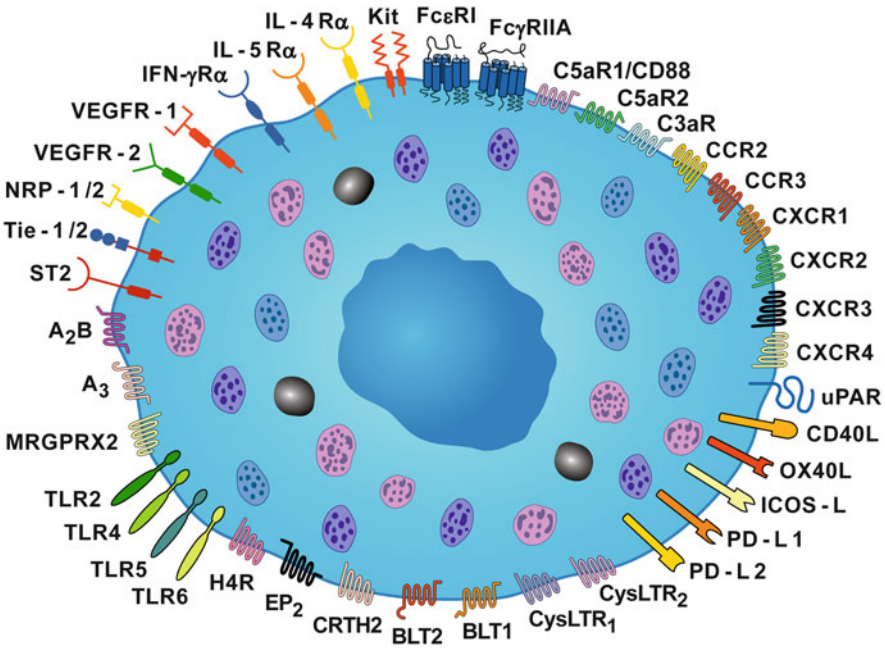

Fig. 2 Surface receptors expressed by human mast cells. Human mast cells express the tetrameric high affinity receptor for IgE (FcεRI) and the FcγRIIA, and their cross-linking induces the release of proinflammatory and immunomodulatory mediators. Mast cells express the KIT receptor (CD117), which is activated by stem cell factor (SCF). These cells express a plethora of receptors such as Toll-like receptor (TLR) 2, TLR4, TLR5, TLR6, receptors for chemokines (CCR2, CCR3, CXCR1, CXCR2, CXCR3, and CXCR4), two receptors for cysteinyl leukotrienes (CysLTR1 and CysLTR2), two leukotriene B_4 receptors (BLT1 and BLT2), the prostaglandin D_2 receptor (CRTH2), the prostaglandin E_2 receptor (EP_2), two adenosine receptors (A_{2B} and A_3), and histamine H4 receptor (H4R). Mast cells express receptor for various cytokines (IL-4Rα, IL-5Rα, IFN-γRα, ST2) and the MAS-related G protein coupled receptor (MRGPRX2). These cells also express receptors for vascular endothelial growth factors (VEGFR1 and VEGFR2), and VEGFR co-receptors, neuropilin-1 and neuropilin-2 (NRP1 and NRP2), for anaphylatoxins (C5aR1/CD88, C5aR2 and C3aR), and the high affinity urokinase plasminogen activator receptor (uPAR). Human mast cells also express co-receptors for T-cell activation [CD40 ligand (CD40L), tumor necrosis factor superfamily member 4 (OX40L), inducible costimulator ligand (ICOS-L), programmed death ligands (PD-L1 and PD-L2)]

GPCRs) activation are qualitatively and quantitatively different. FcεRI crosslinking induces a slower but sustained Ca^{2+} response compared to MRGPRX2 activation and is associated with granule fusion and the release of PGE_2, cytokines, and vascular endothelial growth factors (VEGFs). On the other hand, MRGPRX2-induced activation is rapid and associated with a transient Ca^{2+} response. Inhibition of IκB kinase-β (IKK-β) converted the FcεRI-induced degranulation phenotype to the MRGPRX2-mediated degranulation phenotype. Of note, the different mast cell degranulation profiles were also confirmed in vivo following FcεRI and MRGPRB2

activation (Gaudenzio et al. 2016). Two different modes of degranulation and histamine release that likely require distinct pathways and calcium signaling have also been described for basophils: the anaphylactic degranulation that consists in rapid morphologic changes and exocytosis of intracellular granules and is associated with up-regulation of CD63 (Knol et al. 1991; MacGlashan 2010); the piecemeal degranulation that consists in granule content secretion without exocytosis and may be associated with CD203c up-regulation (MacGlashan 2012; Buhring et al. 2004).

Mast cell and basophil degranulation and histamine release may also be hindered by the concurrent activation of inhibitory receptors (Fig. 3). Inhibitory receptors can be divided into the Ig receptor and the C-type (calcium dependent) lectin superfamilies and are characterized by immunoreceptor tyrosine-based inhibition motifs (ITIMs) that downregulate the activation signals transmitted through immunoreceptor tyrosine-based activation motifs (ITAMs). Upon activation of ITIM-containing receptors, tyrosine residues within the motifs become phosphorylated. This leads to the recruitment of phosphatases, namely tyrosine phosphatases SHP-1 and SHP-2 and lipid phosphatase SHIP-1. SHP-1/2 inhibits the action of tyrosine kinase, while SHIP-1 terminates the phosphoinositide 3-kinase (PI3K)-mediated

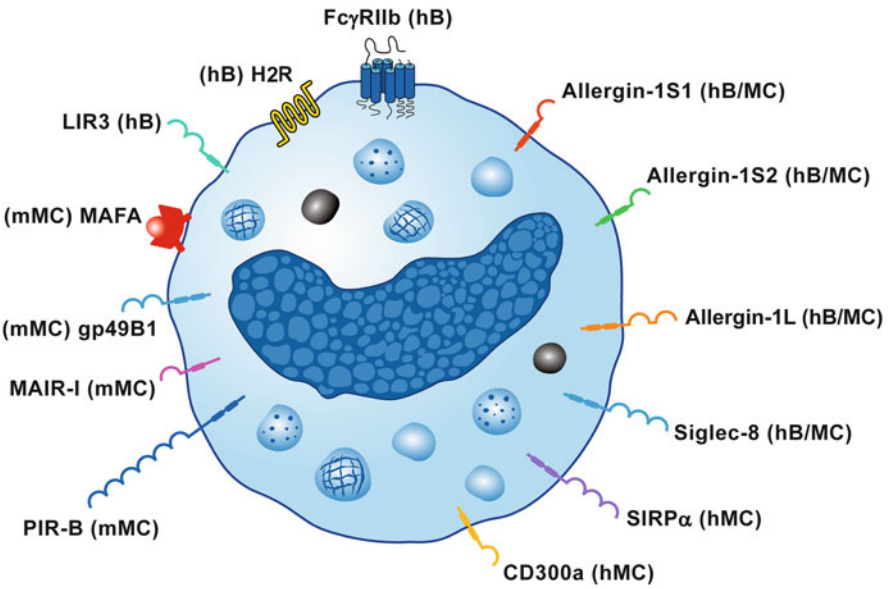

Fig. 3 Inhibitory receptors expressed by human mast cells (hMC) and basophils (hB) and murine mast cells (mMC). Human basophils and mast cells share the expression of three inhibitory allergin receptors (Allergin-1S1, Allergin-1S2, and Allergin-1L) and sialic acid immunoglobulin (Ig)-like lectins (Siglec)-8. Human mast cells express signal-regulatory protein-α [SIRPα] and CD300a, whereas human basophils express FcγRIIb, histamine H2 receptor (H2R), and leukocyte Ig-like receptor (LIR3). Mouse mast cells express paired Ig-like receptor B (PIR-B), myeloid-associated Ig-like receptor (MAIR)-I, the mast cell function associated antigen (MAFA) and gp49B1

pathway (Daeron et al. 2008; Karra and Levi-Schaffer 2011). Several inhibitory receptors on mast cells and basophils have been characterized, including FcγRIIB, CD300, and sialic acid binding Ig-like lectin (Siglec)-8.

FcγRIIB is a low affinity IgG receptor that can inhibit IgE-mediated responses of both mast cells and basophils (Macglashan et al. 2014; Zhu et al. 2002). Co-aggregation of FcγRIIB and FcεRI suppresses FcεRI-mediated activation. Interestingly, a chimeric protein composed of key portions of the human γ1 and the human ε immunoglobulin heavy chains can inhibit FcεRI-mediated activation of human basophils in vitro and FcεRI-mediated degranulation of murine mast cell expressing the human FcεRI in an in vivo model of passive cutaneous anaphylaxis.

The CD300 molecules are a family of immunoglobulin receptors that includes activating (CD300b, CD300e) and inhibitory (CD300a, CD300f) members (Clark et al. 2009). Mast cells express CD300a and CD300f and their respective murine orthologs LMIR1 and LMIR3 (Kumagai et al. 2003). LMIR1/CD300a cross-linking inhibits both FcεRI-dependent and SCF-dependent signaling (Bachelet et al. 2005). Interestingly, bispecific antibodies that co-aggregate LMIR1/CD300a with either FcεRI or KIT (CD117) inhibit allergic responses in vivo (Bachelet et al. 2006, 2008). LMIR3/CD300f binding to its ligands ceramide and sphingomyelin inhibits FcεRI-mediated activation of mast cells in vitro and in vivo (Izawa et al. 2012, 2014). Basophils also express CD300a in the peripheral blood of both healthy and allergic subjects, and its activation inhibits IgE-mediated anaphylactic degranulation (Sabato et al. 2012, 2014; Gibbs et al. 2012).

Siglecs are a group of sialic acid-binding cell surface proteins predominantly expressed by immune cells. In particular, Siglec-8 is expressed on human eosinophils, mast cells, and to a lesser extent on basophils (Kiwamoto et al. 2012). Siglec-8 cross-linking inhibits FcεRI-dependent histamine and PGD_2 release from human mast cells (Yokoi et al. 2008). However, mouse mast cells do not express Siglec-F, which makes it difficult to understand its function on these cells in vivo.

5 Biological Effects of Mast Cell and Basophil Histamine Release

Mast cells and basophils have been involved in several pathophysiological conditions. Since these cells release a variety of preformed and de novo synthesized mediators, a specific role for mast cell- or basophil-derived histamine has not always been identified. Mast cell-derived histamine plays an important role in conditions associated with vascular leakage like urticaria and anaphylaxis (Meyer et al. 2013; Cohen and Rosenstreich 1986; Lieberman and Garvey 2016). Its involvement in other disorders like atopic dermatitis, asthma, and rheumatoid arthritis might be supported by the pre-clinical results showing that genetic or pharmacological blockade of H4R ameliorates these conditions (Liu 2014). Whether H4R activation in these models relies on mast cell- or basophil-derived histamine has still to be demonstrated. Indeed, in a model Th2-dependent skin

inflammation H4R blockade was effective in reducing itch and edema even in mast cell-deficient mice (Cowden et al. 2010).

Mast cell- and basophil-derived histamine may mediate the communication with other cell types. For example, in a mouse model of allergic rhinitis histamine released following IgE-mediated activation of mast cells recruits H4R-expressing basophils to the nasal cavity, an event that was required for the development of early or late phase nasal responses following allergen challenge (Shiraishi et al. 2013). Mast cell-derived histamine enhances the proliferation and activation of cholangiocytes and hepatic stellate cells, an event that might be relevant for the development of sclerosing cholangitis (Jones et al. 2016). Moreover, human dermal mast cell-derived tumor necrosis factor (TNF)-α and histamine increase CXCL8/IL-8 expression in human melanoma cell lines (Artuc et al. 2011). Mast cells activated by IL-33 and immune complexes release IL-10 and histamine that in turn inhibit LPS-mediated monocyte activation (Rivellese et al. 2015). Similarly, monocyte activation can also be restrained by basophil-derived histamine released upon IL-33 stimulation and FcεRI-crosslinking (Rivellese et al. 2014), while monocyte alternative activation relies on basophil-derived IL-4 and IL-13 following IL-3 stimulation and FcεRI-crosslinking (Borriello et al. 2015). Basophil-derived histamine also enhances IL-17 production by memory CD4 T cells at least in part by activating H2R and H4R on T cells (Wakahara et al. 2012). Interestingly, basophil histamine release is altered in some clinical conditions. For example, basophils isolated from patients with food allergy or severe asthma show spontaneous histamine release in vitro (May 1976; Sampson et al. 1989; Schroeder et al. 2013; Findlay and Lichtenstein 1980). IgE-mediated basophil histamine release is reduced in chronic idiopathic urticaria (CIU) patients (Kern and Lichtenstein 1976). In particular, CIU patients can be classified as responders (CIU-R) or non-responders (CIU-NR) on the basis of basophil histamine release in response to anti-IgE ($>10\%$ or $<10\%$ of cellular histamine content, respectively). There is evidence that the pattern of basophil IgE-mediated histamine release observed in these patients results from altered FcεRI-mediated signaling (Saini 2009; Vonakis and Saini 2008; Vonakis et al. 2007).

6 Conclusions

Several stimuli can induce or modulate mast cell and basophil histamine release. Although the pathophysiological relevance of this phenomenon has been demonstrated in some pre-clinical or clinical disorders, the discovery of H4R expressed mainly on immune cells has uncovered new roles for histamine (possibly derived from mast cells and basophils) in a wider range of inflammatory and autoimmune disorders. Moreover, the identification and characterization of inhibitory receptors expressed by mast cells and basophils as well as distinct modalities of mediator release upon triggering of different classes of receptors may uncover new therapeutic approaches for modulating mast cell and basophil degranulation and histamine release.

Acknowledgments This work was supported in part by grants from Regione Campania CISI-Lab Project, CRèME Project, and TIMING Project (G.M.). G.M. is the recipient of the Ferdinando Palasciano Award 2016.

References

Akahoshi M, Song CH, Piliponsky AM, Metz M, Guzzetta A, Abrink M, Schlenner SM, Feyerabend TB, Rodewald HR, Pejler G, Tsai M, Galli SJ (2011) Mast cell chymase reduces the toxicity of Gila monster venom, scorpion venom, and vasoactive intestinal polypeptide in mice. J Clin Invest 121:4180–4191

Aldi S, Takano K, Tomita K, Koda K, Chan NY, Marino A, Salazar-Rodriguez M, Thurmond RL, Levi R (2014) Histamine H4-receptors inhibit mast cell renin release in ischemia/reperfusion via protein kinase C epsilon-dependent aldehyde dehydrogenase type-2 activation. J Pharmacol Exp Ther 349:508–517

Artuc M, Guhl S, Babina M, Unger T, Steckelings UM, Zuberbier T (2011) Mast cell-derived TNF-alpha and histamine modify IL-6 and IL-8 expression and release from cutaneous tumor cells. Exp Dermatol 20:1020–1022

Bachelet I, Munitz A, Moretta A, Moretta L, Levi-Schaffer F (2005) The inhibitory receptor IRp60 (CD300a) is expressed and functional on human mast cells. J Immunol 175:7989–7995

Bachelet I, Munitz A, Levi-Schaffer F (2006) Abrogation of allergic reactions by a bispecific antibody fragment linking IgE to CD300a. J Allergy Clin Immunol 117:1314–1320

Bachelet I, Munitz A, Berent-Maoz B, Mankuta D, Levi-Schaffer F (2008) Suppression of normal and malignant kit signaling by a bispecific antibody linking kit with CD300a. J Immunol 180:6064–6069

Best CH, Dale HH, Dudley HW, Thorpe WV (1927) The nature of the vaso-dilator constituents of certain tissue extracts. J Physiol 62:397–417

Borriello F, Granata F, Marone G (2014a) Basophils and skin disorders. J Invest Dermatol 134:1202–1210

Borriello F, Granata F, Varricchi G, Genovese A, Triggiani M, Marone G (2014b) Immunopharmacological modulation of mast cells. Curr Opin Pharmacol 17:45–57

Borriello F, Longo M, Spinelli R, Pecoraro A, Granata F, Staiano RI, Loffredo S, Spadaro G, Beguinot F, Schroeder J, Marone G (2015) IL-3 synergises with basophil-derived IL-4 and IL-13 to promote the alternative activation of human monocytes. Eur J Immunol 45:2042–2051

Brune M, Hansson M, Mellqvist UH, Hermodsson S, Hellstrand K (1996) NK cell-mediated killing of AML blasts: role of histamine, monocytes and reactive oxygen metabolites. Eur J Haematol 57:312–319

Bryce PJ, Mathias CB, Harrison KL, Watanabe T, Geha RS, Oettgen HC (2006) The H1 histamine receptor regulates allergic lung responses. J Clin Invest 116:1624–1632

Buckland KF, Williams TJ, Conroy DM (2003) Histamine induces cytoskeletal changes in human eosinophils via the H(4) receptor. Br J Pharmacol 140:1117–1127

Buhring HJ, Streble A, Valent P (2004) The basophil-specific ectoenzyme E-NPP3 (CD203c) as a marker for cell activation and allergy diagnosis. Int Arch Allergy Immunol 133:317–329

Burde R, Seifert R, Buschauer A, Schultz G (1989) Histamine inhibits activation of human neutrophils and HL-60 leukemic cells via H2-receptors. Naunyn Schmiedeberg's Arch Pharmacol 340:671–678

Chan CY, John ALS, Abraham SN (2012) Plasticity in mast cell responses during bacterial infections. Curr Opin Microbiol 15:78–84

Clark RA, Gallin JI, Kaplan AP (1975) The selective eosinophil chemotactic activity of histamine. J Exp Med 142:1462–1476

Clark GJ, Ju X, Tate C, Hart DN (2009) The CD300 family of molecules are evolutionarily significant regulators of leukocyte functions. Trends Immunol 30:209–217

Cohen RW, Rosenstreich DL (1986) Discrimination between urticaria-prone and other allergic patients by intradermal skin testing with codeine. J Allergy Clin Immunol 77:802–807

Cowden JM, Zhang M, Dunford PJ, Thurmond RL (2010) The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. J Invest Dermatol 130:1023–1033

Daeron M, Jaeger S, Pasquier LD, Vivier E (2008) Immunoreceptor tyrosine-based inhibition motifs: a quest in the past and future. Immunol Rev 224:11–43

Dale HH, Laidlaw PP (1910) The physiological action of beta-iminazolylethylamine. J Physiol 41:318–344

Damaj BB, Becerra CB, Esber HJ, Wen Y, Maghazachi AA (2007) Functional expression of H4 histamine receptor in human natural killer cells, monocytes, and dendritic cells. J Immunol 179:7907–7915

de Paulis A, Prevete N, Fiorentino I, Rossi FW, Staibano S, Montuori N, Ragno P, Longobardi A, Liccardo B, Genovese A, Ribatti D, Walls AF, Marone G (2006) Expression and functions of the vascular endothelial growth factors and their receptors in human basophils. J Immunol 177:7322–7331

Detoraki A, Staiano RI, Granata F, Giannattasio G, Prevete N, de Paulis A, Ribatti D, Genovese A, Triggiani M, Marone G (2009) Vascular endothelial growth factors synthesized by human lung mast cells exert angiogenic effects. J Allergy Clin Immunol 123:1142–1149, 1149.e1–5

Eberle JU, Voehringer D (2016) Role of basophils in protective immunity to parasitic infections. Semin Immunopathol 38:605–613

Ezeamuzie CI, Philips E (2000) Histamine H(2) receptors mediate the inhibitory effect of histamine on human eosinophil degranulation. Br J Pharmacol 131:482–488

Feldberg W, Kellaway CH (1937) Liberation of histamine from the perfused lung by snake venoms. J Physiol 90:257–279

Feldberg W, Keogh EV (1937) Liberation of histamine from the perfused lung by staphylococcal toxin. J Physiol 90:280–287

Feldberg W, O'Connor WJ (1937) The liberation of histamine from the perfused lung by peptone. J Physiol 90:288–295

Findlay SR, Lichtenstein LM (1980) Basophil "releasability" in patients with asthma. Am Rev Respir Dis 122:53–59

Frei R, Ferstl R, Konieczna P, Ziegler M, Simon T, Rugeles TM, Mailand S, Watanabe T, Lauener R, Akdis CA, O'Mahony L (2013) Histamine receptor 2 modifies dendritic cell responses to microbial ligands. J Allergy Clin Immunol 132:194–204

Galli SJ, Tsai M (2012) IgE and mast cells in allergic disease. Nat Med 18:693–704

Gantner F, Sakai K, Tusche MW, Cruikshank WW, Center DM, Bacon KB (2002) Histamine h(4) and h(2) receptors control histamine-induced interleukin-16 release from human CD8(+) T cells. J Pharmacol Exp Ther 303:300–307

Gaudenzio N, Sibilano R, Marichal T, Starkl P, Reber LL, Cenac N, McNeil BD, Dong X, Hernandez JD, Sagi-Eisenberg R, Hammel I, Roers A, Valitutti S, Tsai M, Espinosa E, Galli SJ (2016) Different activation signals induce distinct mast cell degranulation strategies. J Clin Invest 126:3981–3998

Genovese A, Borgia G, Bjorck L, Petraroli A, de Paulis A, Piazza M, Marone G (2003) Immunoglobulin superantigen protein L induces IL-4 and IL-13 secretion from human Fc epsilon RI+ cells through interaction with the kappa light chains of IgE. J Immunol 170:1854–1861

Gibbs BF, Sabato V, Bridts CH, Ebo DG, Ben-Zimra M, Levi-Schaffer F (2012) Expressions and inhibitory functions of CD300a receptors on purified human basophils. Exp Dermatol 21:884–886

Godot V, Arock M, Garcia G, Capel F, Flys C, Dy M, Emilie D, Humbert M (2007) H4 histamine receptor mediates optimal migration of mast cell precursors to CXCL12. J Allergy Clin Immunol 120:827–834

Graham HT, Lowry OH, Wheelwright F, Lenz MA, Parish HH Jr (1955) Distribution of histamine among leukocytes and platelets. Blood 10:467–481

Grant JA, Dupree E, Goldman AS, Schultz DR, Jackson AL (1975) Complement-mediated release of histamine from human leukocytes. J Immunol 114:1101–1106

Gutzmer R, Mommert S, Gschwandtner M, Zwingmann K, Stark H, Werfel T (2009) The histamine H4 receptor is functionally expressed on T(H)2 cells. J Allergy Clin Immunol 123:619–625

Hata D, Kawakami Y, Inagaki N, Lantz CS, Kitamura T, Khan WN, Maeda-Yamamoto M, Miura T, Han W, Hartman SE, Yao L, Nagai H, Goldfeld AE, Alt FW, Galli SJ, Witte ON, Kawakami T (1998) Involvement of Bruton's tyrosine kinase in FcepsilonRI-dependent mast cell degranulation and cytokine production. J Exp Med 187:1235–1247

Havard S, Scola AM, Kay LJ, Ishmael SS, MacGlashan DW Jr, Peachell PT (2011) Characterization of syk expression in human lung mast cells: relationship with function. Clin Exp Allergy 41:378–388

Hofstra CL, Desai PJ, Thurmond RL, Fung-Leung WP (2003) Histamine H4 receptor mediates chemotaxis and calcium mobilization of mast cells. J Pharmacol Exp Ther 305:1212–1221

Huber M, Gibbs BF (2015) SHIP1 and the negative control of mast cell/basophil activation by supra-optimal antigen concentrations. Mol Immunol 63:32–37

Imamura M, Poli E, Omoniyi AT, Levi R (1994) Unmasking of activated histamine H3-receptors in myocardial ischemia: their role as regulators of exocytotic norepinephrine release. J Pharmacol Exp Ther 271:1259–1266

Imamura M, Seyedi N, Lander HM, Levi R (1995) Functional identification of histamine H3-receptors in the human heart. Circ Res 77:206–210

Imamura M, Lander HM, Levi R (1996) Activation of histamine H3-receptors inhibits carrier-mediated norepinephrine release during protracted myocardial ischemia. Comparison with adenosine A1-receptors and alpha2-adrenoceptors. Circ Res 78:475–481

Inoue I, Taniuchi I, Kitamura D, Jenkins NA, Gilbert DJ, Copeland NG, Watanabe T (1996) Characteristics of the mouse genomic histamine H1 receptor gene. Genomics 36:178–181

Izawa K, Yamanishi Y, Maehara A, Takahashi M, Isobe M, Ito S, Kaitani A, Matsukawa T, Matsuoka T, Nakahara F, Oki T, Kiyonari H, Abe T, Okumura K, Kitamura T, Kitaura J (2012) The receptor LMIR3 negatively regulates mast cell activation and allergic responses by binding to extracellular ceramide. Immunity 37:827–839

Izawa K, Isobe M, Matsukawa T, Ito S, Maehara A, Takahashi M, Yamanishi Y, Kaitani A, Oki T, Okumura K, Kitamura T, Kitaura J (2014) Sphingomyelin and ceramide are physiological ligands for human LMIR3/CD300f, inhibiting FcepsilonRI-mediated mast cell activation. J Allergy Clin Immunol 133:270–273.e1–7

Jones H, Hargrove L, Kennedy L, Meng F, Graf-Eaton A, Owens J, Alpini G, Johnson C, Bernuzzi F, Demieville J, DeMorrow S, Invernizzi P, Francis H (2016) Inhibition of mast cell-secreted histamine decreases biliary proliferation and fibrosis in primary sclerosing cholangitis Mdr2(−/−) mice. Hepatology 64:1202–1216

Jutel M, Watanabe T, Klunker S, Akdis M, Thomet OA, Malolepszy J, Zak-Nejmark T, Koga R, Kobayashi T, Blaser K, Akdis CA (2001) Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. Nature 413:420–425

Karasuyama H, Mukai K, Obata K, Tsujimura Y, Wada T (2011) Nonredundant roles of basophils in immunity. Annu Rev Immunol 29:45–69

Karra L, Levi-Schaffer F (2011) Down-regulation of mast cell responses through ITIM containing inhibitory receptors. Adv Exp Med Biol 716:143–159

Kashem SW, Subramanian H, Collington SJ, Magotti P, Lambris JD, Ali H (2011) G protein coupled receptor specificity for C3a and compound 48/80-induced degranulation in human mast cells: roles of Mas-related genes MrgX1 and MrgX2. Eur J Pharmacol 668:299–304

Kawakami T, Kashiwakura J, Kawakami Y (2014) Histamine-releasing factor and immunoglobulins in asthma and allergy. Allergy Asthma Immunol Res 6:6–12

Kepley CL, Youssef L, Andrews RP, Wilson BS, Oliver JM (1999) Syk deficiency in nonreleaser basophils. J Allergy Clin Immunol 104:279–284

Kern F, Lichtenstein LM (1976) Defective histamine release in chronic urticaria. J Clin Invest 57:1369–1377

Kiwamoto T, Kawasaki N, Paulson JC, Bochner BS (2012) Siglec-8 as a drugable target to treat eosinophil and mast cell-associated conditions. Pharmacol Ther 135:327–336

Knol EF, Mul FP, Jansen H, Calafat J, Roos D (1991) Monitoring human basophil activation via CD63 monoclonal antibody 435. J Allergy Clin Immunol 88:328–338

Kobayashi T, Tonai S, Ishihara Y, Koga R, Okabe S, Watanabe T (2000) Abnormal functional and morphological regulation of the gastric mucosa in histamine H2 receptor-deficient mice. J Clin Invest 105:1741–1749

Kuehn HS, Swindle EJ, Kim MS, Beaven MA, Metcalfe DD, Gilfillan AM (2008) The phosphoinositide 3-kinase-dependent activation of Btk is required for optimal eicosanoid production and generation of reactive oxygen species in antigen-stimulated mast cells. J Immunol 181:7706–7712

Kumagai H, Oki T, Tamitsu K, Feng SZ, Ono M, Nakajima H, Bao YC, Kawakami Y, Nagayoshi K, Copeland NG, Gilbert DJ, Jenkins NA, Kawakami T, Kitamura T (2003) Identification and characterization of a new pair of immunoglobulin-like receptors LMIR1 and 2 derived from murine bone marrow-derived mast cells. Biochem Biophys Res Commun 307:719–729

Lavens-Phillips SE, MacGlashan DW Jr (2000) The tyrosine kinases p53/56lyn and p72syk are differentially expressed at the protein level but not at the messenger RNA level in nonreleasing human basophils. Am J Respir Cell Mol Biol 23:566–571

Leite-de-Moraes MC, Diem S, Michel ML, Ohtsu H, Thurmond RL, Schneider E, Dy M (2009) Cutting edge: histamine receptor H4 activation positively regulates in vivo IL-4 and IFN-gamma production by invariant NKT cells. J Immunol 182:1233–1236

Lewis T, Grant RT (1924) Vascular reactions of the skin to injury. Part 11. The liberation of histamine-like substance in the injured skin, the underlying cause of factitious urticaria and of wheals produced by burning: and observations upon the nervous control of certain skin reactions. Heart 11:209–265

Lichtenstein LM, Gillespie E (1973) Inhibition of histamine release by histamine controlled by H2 receptor. Nature 244:287–288

Lieberman P, Garvey LH (2016) Mast cells and anaphylaxis. Curr Allergy Asthma Rep 16:20

Liu WL (2014) Histamine H4 receptor antagonists for the treatment of inflammatory disorders. Drug Discov Today 19:1222–1225

MacGlashan DW Jr (2007) Relationship between spleen tyrosine kinase and phosphatidylinositol 5′ phosphatase expression and secretion from human basophils in the general population. J Allergy Clin Immunol 119:626–633

MacGlashan D Jr (2010) Expression of CD203c and CD63 in human basophils: relationship to differential regulation of piecemeal and anaphylactic degranulation processes. Clin Exp Allergy 40:1365–1377

MacGlashan D Jr (2012) Marked differences in the signaling requirements for expression of CD203c and CD11b versus CD63 expression and histamine release in human basophils. Int Arch Allergy Immunol 159:243–252

MacGlashan D Jr, Honigberg LA, Smith A, Buggy J, Schroeder JT (2011) Inhibition of IgE-mediated secretion from human basophils with a highly selective Bruton's tyrosine kinase, Btk, inhibitor. Int Immunopharmacol 11:475–479

Macglashan D Jr, Moore G, Muchhal U (2014) Regulation of IgE-mediated signalling in human basophils by CD32b and its role in syk down-regulation: basic mechanisms in allergic disease. Clin Exp Allergy 44:713–723

Marichal T, Tsai M, Galli SJ (2013a) Mast cells: potential positive and negative roles in tumor biology. Cancer Immunol Res 1:269–279

Marichal T, Starkl P, Reber LL, Kalesnikoff J, Oettgen HC, Tsai M, Metz M, Galli SJ (2013b) A beneficial role for immunoglobulin E in host defense against honeybee venom. Immunity 39:963–975

Marone G, Florio G, Petraroli A, de Paulis A (2001) Dysregulation of the IgE/Fc epsilon RI network in HIV-1 infection. J Allergy Clin Immunol 107:22–30

Marone G, Triggiani M, Genovese A, De Paulis A (2005) Role of human mast cells and basophils in bronchial asthma. Adv Immunol 88:97–160

Marone G, Borriello F, Varricchi G, Genovese A, Granata F (2014) Basophils: historical reflections and perspectives. Chem Immunol Allergy 100:172–192

Masini E, Blandina P, Brunelleschi S, Mannaioni PF (1982) Evidence for H2-receptor-mediated inhibition of histamine release from isolated rat mast cells. Agents Actions 12:85–88

Maurer M, Wedemeyer J, Metz M, Piliponsky AM, Weller K, Chatterjea D, Clouthier DE, Yanagisawa MM, Tsai M, Galli SJ (2004) Mast cells promote homeostasis by limiting endothelin-1-induced toxicity. Nature 432:512–516

May CD (1976) High spontaneous release of histamine in vitro from leukocytes of persons hypersensitive to food. J Allergy Clin Immunol 58:432–437

Mazzoni A, Leifer CA, Mullen GE, Kennedy MN, Klinman DM, Segal DM (2003) Cutting edge: histamine inhibits IFN-alpha release from plasmacytoid dendritic cells. J Immunol 170:2269–2273

McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, Dong X (2015) Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. Nature 519:237–241

Meiler F, Zumkehr J, Klunker S, Ruckert B, Akdis CA, Akdis M (2008) In vivo switch to IL-10-secreting T regulatory cells in high dose allergen exposure. J Exp Med 205:2887–2898

Melillo RM, Guarino V, Avilla E, Galdiero MR, Liotti F, Prevete N, Rossi FW, Basolo F, Ugolini C, de Paulis A, Santoro M, Marone G (2010) Mast cells have a protumorigenic role in human thyroid cancer. Oncogene 29:6203–6215

Metz M, Piliponsky AM, Chen CC, Lammel V, Abrink M, Pejler G, Tsai M, Galli SJ (2006) Mast cells can enhance resistance to snake and honeybee venoms. Science 313:526–530

Meyer J, Gorbach AM, Liu WM, Medic N, Young M, Nelson C, Arceo S, Desai A, Metcalfe DD, Komarow HD (2013) Mast cell dependent vascular changes associated with an acute response to cold immersion in primary contact urticaria. PLoS One 8:e56773

Mobarakeh JI, Sakurada S, Katsuyama S, Kutsuwa M, Kuramasu A, Lin ZY, Watanabe T, Hashimoto Y, Watanabe T, Yanai K (2000) Role of histamine H(1) receptor in pain perception: a study of the receptor gene knockout mice. Eur J Pharmacol 391:81–89

Mobarakeh JI, Sakurada S, Hayashi T, Orito T, Okuyama K, Sakurada T, Kuramasu A, Watanabe T, Watanabe T, Yanai K (2002) Enhanced antinociception by intrathecally-administered morphine in histamine H1 receptor gene knockout mice. Neuropharmacology 42:1079–1088

Mommert S, Kleiner S, Gehring M, Eiz-Vesper B, Stark H, Gutzmer R, Werfel T, Raap U (2016) Human basophil chemotaxis and activation are regulated via the histamine H4 receptor. Allergy 71:1264–1273

Moon TC, Befus AD, Kulka M (2014) Mast cell mediators: their differential release and the secretory pathways involved. Front Immunol 5:569

Morgan RK, McAllister B, Cross L, Green DS, Kornfeld H, Center DM, Cruikshank WW (2007) Histamine 4 receptor activation induces recruitment of FoxP3+ T cells and inhibits allergic asthma in a murine model. J Immunol 178:8081–8089

Novak N, Mete N, Bussmann C, Maintz L, Bieber T, Akdis M, Zumkehr J, Jutel M, Akdis C (2012) Early suppression of basophil activation during allergen-specific immunotherapy by histamine receptor 2. J Allergy Clin Immunol 130:1153–1158.e2

O'Mahony L, Akdis M, Akdis CA (2011) Regulation of the immune response and inflammation by histamine and histamine receptors. J Allergy Clin Immunol 128:1153–1162

O'Reilly M, Alpert R, Jenkinson S, Gladue RP, Foo S, Trim S, Peter B, Trevethick M, Fidock M (2002) Identification of a histamine H4 receptor on human eosinophils – role in eosinophil chemotaxis. J Recept Signal Transduct Res 22:431–448

Panula P, Chazot PL, Cowart M, Gutzmer R, Leurs R, Liu WL, Stark H, Thurmond RL, Haas HL (2015) International Union of Basic and Clinical Pharmacology. XCVIII. Histamine receptors. Pharmacol Rev 67:601–655

Patella V, Florio G, Petraroli A, Marone G (2000) HIV-1 gp120 induces IL-4 and IL-13 release from human Fc epsilon RI+ cells through interaction with the VH3 region of IgE. J Immunol 164:589–595

Popielski L (1920) β-Imidazolylathylamin und die Organextrakte Erster Teil: b-Imidazolylathylamin als mechtiger Errezer der Magendrucken. Pfluegers Arch 178:214–236

Riley JF, West GB (1952) Histamine in tissue mast cells. J Physiol 117:72P–73P

Riley JF, West GB (1953) The presence of histamine in tissue mast cells. J Physiol 120:528–537

Rivellese F, Suurmond J, de Paulis A, Marone G, Huizinga TW, Toes RE (2014) IgE and IL-33-mediated triggering of human basophils inhibits TLR4-induced monocyte activation. Eur J Immunol 44:3045–3055

Rivellese F, Suurmond J, Habets K, Dorjee AL, Ramamoorthi N, Townsend MJ, de Paulis A, Marone G, Huizinga TW, Pitzalis C, Toes RE (2015) Ability of interleukin-33- and immune complex-triggered activation of human mast cells to down-regulate monocyte-mediated immune responses. Arthritis Rheumatol 67:2343–2353

Rizk A, Curley J, Robertson J, Raber J (2004) Anxiety and cognition in histamine H3 receptor−/− mice. Eur J Neurosci 19:1992–1996

Rossbach K, Schaper K, Kloth C, Gutzmer R, Werfel T, Kietzmann M, Baumer W (2016) Histamine H4 receptor knockout mice display reduced inflammation in a chronic model of atopic dermatitis. Allergy 71:189–197

Sabato V, Verweij MM, Bridts CH, Levi-Schaffer F, Gibbs BF, De Clerck LS, Schiavino D, Ebo DG (2012) CD300a is expressed on human basophils and seems to inhibit IgE/FcepsilonRI-dependent anaphylactic degranulation. Cytometry B Clin Cytom 82:132–138

Sabato V, Boita M, Shubber S, Bridts CH, Shibuya A, De Clerck LS, Falcone FH, Ebo DG (2014) Mechanism of phosphatidylserine inhibition of IgE/FcepsilonRI-dependent anaphylactic human basophil degranulation via CD300a. J Allergy Clin Immunol 134:734–737.e3

Sadek B, Saad A, Sadeq A, Jalal F, Stark H (2016) Histamine H3 receptor as a potential target for cognitive symptoms in neuropsychiatric diseases. Behav Brain Res 312:415–430

Saini SS (2009) Basophil responsiveness in chronic urticaria. Curr Allergy Asthma Rep 9:286–290

Sampson HA, Broadbent KR, Bernhisel-Broadbent J (1989) Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. N Engl J Med 321:228–232

Schafer B, Piliponsky AM, Oka T, Song CH, Gerard NP, Gerard C, Tsai M, Kalesnikoff J, Galli SJ (2013) Mast cell anaphylatoxin receptor expression can enhance IgE-dependent skin inflammation in mice. J Allergy Clin Immunol 131:541–548.e1–9

Schneider LA, Schlenner SM, Feyerabend TB, Wunderlin M, Rodewald HR (2007) Molecular mechanism of mast cell mediated innate defense against endothelin and snake venom sarafotoxin. J Exp Med 204:2629–2639

Schroeder JT (2011) Basophils: emerging roles in the pathogenesis of allergic disease. Immunol Rev 242:144–160

Schroeder JT, Bieneman AP, Chichester KL, Keet CA, Hamilton RG, MacGlashan DW Jr, Wood R, Frischmeyer-Guerrerio PA (2013) Spontaneous basophil responses in food-allergic children are transferable by plasma and are IgE-dependent. J Allergy Clin Immunol 132:1428–1431

Seifert R, Strasser A, Schneider EH, Neumann D, Dove S, Buschauer A (2013) Molecular and cellular analysis of human histamine receptor subtypes. Trends Pharmacol Sci 34:33–58

Shiraishi Y, Jia Y, Domenico J, Joetham A, Karasuyama H, Takeda K, Gelfand EW (2013) Sequential engagement of FcepsilonRI on mast cells and basophil histamine H(4) receptor and FcepsilonRI in allergic rhinitis. J Immunol 190:539–548

Siraganian RP, Hook WA (1977) Mechanism of histamine release by formyl methionine-containing peptides. J Immunol 119:2078–2083

Stone KD, Prussin C, Metcalfe DD (2010) IgE, mast cells, basophils, and eosinophils. J Allergy Clin Immunol 125:S73–S80

Subramanian H, Gupta K, Guo Q, Price R, Ali H (2011) Mas-related gene X2 (MrgX2) is a novel G protein-coupled receptor for the antimicrobial peptide LL-37 in human mast cells: resistance to receptor phosphorylation, desensitization, and internalization. J Biol Chem 286:44739–44749

Subramanian H, Gupta K, Lee D, Bayir AK, Ahn H, Ali H (2013) Beta-defensins activate human mast cells via Mas-related gene X2. J Immunol 191:345–352

Takahashi K, Suwa H, Ishikawa T, Kotani H (2002) Targeted disruption of H3 receptors results in changes in brain histamine tone leading to an obese phenotype. J Clin Invest 110:1791–1799

Takeshita K, Sakai K, Bacon KB, Gantner F (2003) Critical role of histamine H4 receptor in leukotriene B4 production and mast cell-dependent neutrophil recruitment induced by zymosan in vivo. J Pharmacol Exp Ther 307:1072–1078

Thurmond RL, Desai PJ, Dunford PJ, Fung-Leung WP, Hofstra CL, Jiang W, Nguyen S, Riley JP, Sun S, Williams KN, Edwards JP, Karlsson L (2004) A potent and selective histamine H4 receptor antagonist with anti-inflammatory properties. J Pharmacol Exp Ther 309:404–413

Toyota H, Dugovic C, Koehl M, Laposky AD, Weber C, Ngo K, Wu Y, Lee DH, Yanai K, Sakurai E, Watanabe T, Liu C, Chen J, Barbier AJ, Turek FW, Fung-Leung WP, Lovenberg TW (2002) Behavioral characterization of mice lacking histamine H(3) receptors. Mol Pharmacol 62:389–397

Triggiani M, Gentile M, Secondo A, Granata F, Oriente A, Taglialatela M, Annunziato L, Marone G (2001) Histamine induces exocytosis and IL-6 production from human lung macrophages through interaction with H1 receptors. J Immunol 166:4083–4091

Triggiani M, Petraroli A, Loffredo S, Frattini A, Granata F, Morabito P, Staiano RI, Secondo A, Annunziato L, Marone G (2007) Differentiation of monocytes into macrophages induces the upregulation of histamine H1 receptor. J Allergy Clin Immunol 119:472–481

Truta-Feles K, Lagadari M, Lehmann K, Berod L, Cubillos S, Piehler S, Herouy Y, Barz D, Kamradt T, Maghazachi A, Norgauer J (2010) Histamine modulates gammadelta-T lymphocyte migration and cytotoxicity, via Gi and Gs protein-coupled signalling pathways. Br J Pharmacol 161:1291–1300

Varricchi G, Galdiero MR, Marone G, Granata F, Borriello F, Marone G (2016) Controversial role of mast cells in skin cancers. Exp Dermatol 26:11–17

Visciano C, Liotti F, Prevete N, Cali G, Franco R, Collina F, de Paulis A, Marone G, Santoro M, Melillo RM (2015) Mast cells induce epithelial-to-mesenchymal transition and stem cell features in human thyroid cancer cells through an IL-8-Akt-Slug pathway. Oncogene 34:5175–5186

Voehringer D (2012) Basophil modulation by cytokine instruction. Eur J Immunol 42:2544–2550

Vonakis BM, Saini SS (2008) Syk-deficient basophils from donors with chronic idiopathic urticaria exhibit a spectrum of releasability. J Allergy Clin Immunol 121:262–264

Vonakis BM, Vasagar K, Gibbons SP Jr, Gober L, Sterba PM, Chang H, Saini SS (2007) Basophil FcepsilonRI histamine release parallels expression of Src-homology 2-containing inositol phosphatases in chronic idiopathic urticaria. J Allergy Clin Immunol 119:441–448

Wada T, Ishiwata K, Koseki H, Ishikura T, Ugajin T, Ohnuma N, Obata K, Ishikawa R, Yoshikawa S, Mukai K, Kawano Y, Minegishi Y, Yokozeki H, Watanabe N, Karasuyama H (2010) Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks. J Clin Invest 120:2867–2875

Wakahara K, Baba N, Van VQ, Begin P, Rubio M, Ferraro P, Panzini B, Wassef R, Lahaie R, Caussignac Y, Tamaz R, Richard C, Soucy G, Delespesse G, Sarfati M (2012) Human basophils interact with memory T cells to augment Th17 responses. Blood 120:4761–4771

Wang M, Han J, Domenico J, Shin YS, Jia Y, Gelfand EW (2016) Combined blockade of the histamine H1 and H4 receptor suppresses peanut-induced intestinal anaphylaxis by regulating dendritic cell function. Allergy 71:1561–1574

Wechsler JB, Schroeder HA, Byrne AJ, Chien KB, Bryce PJ (2013) Anaphylactic responses to histamine in mice utilize both histamine receptors 1 and 2. Allergy 68:1338–1340

Yanai K, Son LZ, Endou M, Sakurai E, Nakagawasai O, Tadano T, Kisara K, Inoue I, Watanabe T, Watanabe T (1998) Behavioural characterization and amounts of brain monoamines and their metabolites in mice lacking histamine H1 receptors. Neuroscience 87:479–487

Yano H, Wershil BK, Arizono N, Galli SJ (1989) Substance P-induced augmentation of cutaneous vascular permeability and granulocyte infiltration in mice is mast cell dependent. J Clin Invest 84:1276–1286

Yokoi H, Choi OH, Hubbard W, Lee HS, Canning BJ, Lee HH, Ryu SD, von Gunten S, Bickel CA, Hudson SA, Macglashan DW Jr, Bochner BS (2008) Inhibition of FcepsilonRI-dependent mediator release and calcium flux from human mast cells by sialic acid-binding immunoglobulin-like lectin 8 engagement. J Allergy Clin Immunol 121:499–505.e1

Zhu D, Kepley CL, Zhang M, Zhang K, Saxon A (2002) A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation. Nat Med 8:518–521