

# Mast cell function in physiology and pathophysiology

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## Abstract

Mast cells have classically been related to allergic responses. However, recent studies indicate that these cells essentially contribute to other common diseases. Their constitutive residence at the border of the body and environment, their perivascular and perineural locations, combined with their array of diverse mediators suggest that they are strategically situated to initiate immune and inflammatory responses. Understanding the mechanisms by which mast cells modulate and amplify innate and adaptive immunity provides important insights into the pathogenesis of autoimmune disorders, cardiovascular disorders and cancer. The discovery of polymorphisms and mutations in components that regulate mast cell signaling might lead to ways to identify subjects who are most susceptible for such disorders.

## Morphology of mast cells

The mast cell is probably a phylogenetically old cell<sup>1</sup> which apparently occurs in all species with blood circulation. Viewed by light microscopy, human mast cells usually present as round or elongated cells with a diameter ranging between 8 and 20  $\mu\text{m}$  depending on the organ examined. Their non-segmented monolobed nucleus shows a round or oval shape and the cytoplasm contains numerous secretory granules that metachromatically stain with thiazine dyes such as toluidine blue. Besides the metachromatic granules the cytoplasm contains a few mitochondria, short profiles of the rough endoplasmic reticulum and numerous free ribosomes. Mast cells were first described by Paul Ehrlich.<sup>2</sup> He named these cells *Mastzellen* because he speculated that the intracellular granules would contain phagocytosed materials or nutrients. Ehrlich already noted that mast cells lie in close proximity to blood vessels and nerves.

## Development

Mast cells are rather unique among the cells of the immune system in that immature progenitors are released from the bone marrow into the circulating blood and mature within vascularized tissues. Thus, under normal conditions only progenitor cells appear in the blood (about 30000 – 50000 mast cell progenitors per 35 ml whole-blood)<sup>3</sup>. These mast cell progenitors are probably directly derived from multipotential progenitors and not from common myeloid progenitors or granulocyte/macrophage progenitors as previously assumed.<sup>4</sup> Human mast cell progenitors and mature mast cells express a large array of adhesion molecules and

chemokine receptors (Table 1) which are important factors for regulating mast cell distribution within tissues (so-called *homing*). In vitro studies with human mast cells revealed surface expression of at least 61 integrins.<sup>5,6</sup> Also low levels of the „non-integrin intracellular adhesion molecules“ 1 and 3 (ICAM-1, ICAM-3), the leukocyte function-associated antigen-1 and 3 (LFA-1, LFA-3), CD44 and singlec-8 are expressed.<sup>7</sup> Most if not all of the chemokine receptors are involved in mast cell migration. Homing of the mast cell progenitors to the small intestine, at least in mice, is directed by binding of the  $\alpha 4\beta 7$  integrin expressed on mast cell progenitors to the “mucosal addressin cell adhesion molecule-1” (MAdCAM-1) and to “vascular cell adhesion molecule-1” (VCAM-1) as endothelial binding sites for this integrin.<sup>8</sup> The chemokine receptor 2 expressed on mast cell progenitors also influences homing to the intestine. Inflammation-induced recruitment of mast cell progenitors to the lungs was shown to require both  $\alpha 4\beta 7$  and  $\alpha 4\beta 1$  binding to VCAM-1, implicating organ-specific control of mast cell progenitor homing.<sup>9</sup> In addition, there are other factors like the transcription factor T-bet which play an important role in homing of mast cell progenitors.<sup>10</sup>

Local differentiation and maturation of mast cells are regulated by tissue environmental factors. The most important factor for human mast cells is stem cell factor (SCF), the ligand for the receptor tyrosine kinase Kit<sup>11</sup> which is secreted by fibroblasts, stromal cells and endothelial cells. In humans, survival and differentiation of tissue mast cells are also enhanced by other cytokines such as IL(interleukin)-4, IL-6 and IL-10.<sup>12</sup> Although mast cells reside in all vascularized tissues, the highest mast cell numbers can be observed at the interfaces of host and environment, i. e. in skin and mucosal surfaces in lung and gastrointestinal tract. When mast cells are transferred from one anatomical site to a different one, they can interchange their phenotype, underlining the importance of the microenvironment for differentiation.<sup>13</sup> As unique the development of mast cells is, as unique is the fate of the differentiated mast cells. Although mature mast cells are highly differentiated, they retain an extensive proliferation potential.<sup>14,15</sup>

# Mast cell function in physiology and pathophysiology

**Table 1:** Receptors expressed on human mast cells (list not exhaustive).

Receptor	Endogenous ligand	Mast cell response	References
Adenosine receptors A2A, A2B, A3	Adenosine	Degranulation (at low agonist concentration); inhibition of FcεRI-mediated degranulation and chemotaxis (at high agonist concentration); stimulation of inflammatory processes; promotion of angiogenesis by a paracrine mechanism	[36, 37]
β <sub>2</sub> -Adrenoceptor	Adrenaline	Inhibition of FcεRI-mediated degranulation and cytokine production	[38, 39]
C3a receptor	C3a	Degranulation, chemotaxis; chemokine secretion	[40]
C5a receptor	C5a	Degranulation, chemotaxis	[41]
Cannabinoid CB <sub>2</sub> receptor	2-Arachidonoyl-glycerol, anandamide	Suppression of mast cell activity	[42]
CD47 (=integrin-associated protein, IAP)	Integrins	Induction of histamine secretion	[43]
CD200 receptor	CD200 (OX2)	Inhibitory influence on mast cell activity	[44]
CD300a receptor	Eosinophil granule proteins	Inhibition of mast cell activity	[45]
Chemokine receptors CXCR1-4, CX3CR1 CCR1,3-5	Chemokines	Migration of mast cells; degranulation-independent release of cytokines	[46]
Cysteinyl-Leukotriene receptors 1 and 2	Leukotrienes	Induction of cytokine generation and proliferation	[47, 48]
Estrogene receptor	Estrogens	Enhancement of mediator release	[49]
FcαR (CD89)	IgA	Not yet definitely defined.	[50]
FcεRI	IgE	Degranulation	[17]
FcγRI	IgG	Stimulation of mast cell activity	[50]
FcγRIIA	IgG	Stimulation of mast cell activity	[50, 51]
FcγRIIB	IgG	Inhibition of mast cell activity	[52]
FcγRIII		Not yet definitely defined.	[50, 51]
GPR34	Lysophosphatidylserine	Enhancement of mast cell degranulation	[53]
GPR92	Lysophosphatidic acid	Induction of generation and release of cytokines	[54]
Histamine receptors H <sub>1</sub> , H <sub>2</sub> H <sub>4</sub>	Histamine	Mast cell activation Inhibition of mast cell activity	[55]
5-HT <sub>1A</sub>	Serotonin	Mast cell adhesion; chemotaxis	[56]
Kit-receptor tyrosine kinase (CD117)	Stem cell factor	Mast cell activation	[17]
LPA <sub>1</sub> , LPA <sub>3</sub>	Lysophosphatidic acid	Acceleration of development; chemokine secretion	[57]
Leptin receptor	Leptin	Autocrine/paracrine immunomodulatory effects	[58]
MRGX2	Somatostatin, platelet factor-4, Substance P	Degranulation	[59]
Myeloid-associated Ig-like receptor 1	?	Inhibition of mast cell activity and mediator release	[60]
Neurokinin receptors NK1R, NK2R, NK3R VPAC2	Substance P, vasoactive intestinal peptide, nerve growth factor, calcitonin gene-related peptide	Activation of mast cell degranulation and chemokine production	[29]
Nicotinic acetylcholine receptor	Acetylcholine	Potentiating anaphylactic reaction (?)	[61]
OX40	OX40-ligand	Regulatory T-cell-mediated suppression of mast cell activity	[62]
Protease activated receptors PAR1-4	Serine proteases (e.g. trypsin, tryptase)	Activation of mast cells and mediator (histamine) release	[63]
Peripheral benzodiazepine receptor	?	Inhibition of mediator release	[64]
Progesterone receptor	Progesterone	Inhibition of mediator release	[49]
Prostaglandin E receptors EP <sub>2</sub> EP <sub>3</sub> EP <sub>4</sub>	Prostaglandin E	Inhibition of FcεRI-mediated eicosanoid production and mediator release Activation of mast cells	[65]
Purinoceptors P2Y <sub>1</sub> , P2Y <sub>12</sub> , P2Y <sub>13</sub> P2Y <sub>2</sub> P2Y <sub>11</sub>	ADP ATP, UTP ATP	Calcium influx; eicosanoid and cytokine production; exocytosis	[66]
S1P <sub>1</sub> , S1P <sub>2</sub> , S1P <sub>5</sub>	S1P	Degranulation, chemotaxis	[67]
Toll-like receptors TLR1-9	Bacterial products	Induction of cytokine production	[68]
Urokinase receptor	Urokinase	Migration	[69]
Vitamin D receptor	Vitamin D	Mast cell development and function	[70]

## IgE-dependent and -independent activation

Mast cells act both as effector cells as well as regulatory cells. This versatility is reflected in numerous activation stimuli with intracellular pathways that intersect to modulate the quality and magnitude of the mast cell response. The best characterized mechanism of mast cell activation is cross-linking of IgE bound to FcεRI on mast cells by antigen contact. Apart from IgE, IgG and even IgA might play a role in mast cell activation as suggested by the expression of receptors for IgA and IgG by mast cells (Table 1). In addition, a large number of IgE-independent modes of mast cell activation have been described. Human mast cells express a multiplicity of G-protein-coupled receptors and other recognition sites on their surface (Table 1) which are involved in mast cell activation under physiological and pathophysiological conditions. Stimulation of these receptors can either result in potentiation of FcεRI-mediated mast cell activation or induction of mast cell activation by themselves using different intracellular complementary as well as converging signaling pathways.<sup>16,17</sup>

Human mast cells express the c-kit-encoded receptor for SCF which represents a key feature for distinguishing mast cells from basophils. The expression of this receptor tyrosine kinase Kit on the surface of the mast cells is essential for mast cell functional activity: it does not only determine terminal differentiation of the mast cell but plays also important roles in regulating mast cell activation, degranulation and survival.

## Mast cell mediators

Mast cells produce an impressively broad array of mediators which can be divided into preformed mediators and de-novo synthesized compounds (Table 2). These categories are not absolutely exclusive, since some compounds such as the cytokine TNFα occur both preformed and as a newly synthesized molecule.<sup>18</sup> Interestingly, the profile of mediators and cytokines stored or produced de-novo in mast cells can markedly differ between and within organs/tissues<sup>19</sup> depending upon the micro-environmental factors or the nature of the stimulus.

Preformed mediators are stored in secretory granules. On activation they are released into the extracellular environment within minutes. Main granule components include histamine, serine proteases, carboxypeptidase A and the proteoglycans heparin and chondroitin sulfate E (Table 2). De-novo synthesized lipid mediators comprise the cyclooxygenase product prostaglandin D2 and the lipoxygenase products leukotriene C4, D4 and E4 (Table 2). At present, more than thirty different cytokines have been shown to be produced by human mast cells (Table 2).

Preformed mediators packaged within the secretory granules can be released by two morphologically distinct secretory processes: by exocytosis by mast cell degranulation and by so-called differential mediator release. Exocytosis consists of a rapid and massive secretory process, characteristically occurring during IgE-dependent allergic reactions. In exocytosis, cytoplasmic granule membranes fuse with the plasma membrane, giving rise to open secretory channels which allow the release of granule contents into the local extracellular environment. In contrast, differential mediator release is characterized by a slow discharge of mediators in a selective fashion, without membrane fusion events and granule opening to the extracellular environment.<sup>20</sup>

**Table 2:** Selection of mediators produced by human mast cells and exemplary physiological and/or pathophysiological effects of these mediators.

Mediators	Physiological/pathophysiological effects
<b>Preformed (stored) mediators</b>	
<b>Biogenic amines</b>	
Histamine	Vasodilation, vascular permeability↑, peristalsis↑, angiogenesis, mitogenesis
Serotonin (5-hydroxy-tryptamine)	Vasoconstriction, pain
<b>Enzymes</b>	
Tryptase	Activation of protease activated receptors, bradykinin formation, inflammation, pain, tissue damage, degradation of antigens
Chymase	Tissue damage, pain, angiotensin II synthesis
Carboxypeptidase A	Peptide processing (e.g. angiotensin II synthesis, cleavage of bradykinin and Substance P)
Peroxidase	Free oxygen radical production
β-Hexosaminidase	Carbohydrate processing
Phospholipases	Arachidonic acid generation, inflammation
Matrix metalloproteinases	Tissue damage
<b>Proteoglycans</b>	
Heparin	Angiogenesis, stabilization of tryptase, histamine and nerve growth factor, anticoagulant
Chondroitin sulfate	Connective tissue component, anti-inflammatory
<b>Chemokines</b>	
IL-8 (CXCL8)	Chemoattraction and tissue infiltration of leukocytes
MCP-1 (CCL2)	
MCP-3 (CCL7)	
MCP-4	
RANTES (CCL5)	
Eotaxin (CCL11)	
<b>Polypeptides</b>	
Renin	Angiotensin synthesis
Substance P	Inflammation, pain, mast cell activation
CRH (Corticotropin-releasing hormone)	Inflammation, vasodilation, mast cell vascular endothelial growth factor release
Urocortin	Inflammation, vasodilation, mast cell activation
VIP (Vasoactive intestinal polypeptide)	Vasodilation, mast cell activation
Angiogenin	Angiogenic and ribonucleolytic activity
<b>Mediators produced on activation (de-novo synthesis)</b>	
<b>Phospholipid metabolites</b>	
LTB <sub>4</sub> (Leukotriene B <sub>4</sub> )	Leukocyte chemotaxis
LTC <sub>4</sub> (Leukotriene C <sub>4</sub> )	Vasoconstriction, pain
PGD <sub>2</sub> , PGE <sub>2</sub> (Prostaglandin D <sub>2</sub> , E <sub>4</sub> )	Bronchoconstriction, pain
PAF (Platelet activating factor)	Platelet activation, vasodilation, inflammation
<b>Cytokines</b>	
IL-1,3,4,5,6,8,9,10,12,13,14,16,18,25	Inflammation, leukocyte migration, leukocyte proliferation/activation, pain
MIP-1α and 1β (Macrophage inflammatory protein)	
MCP-1 (Monocyte chemoattractant protein)	
Interferon α, β, γ	
TNFα (Tumor necrosis factor)	
Leptin	
<b>Growth factors</b>	
SCF (Stem cell factor)	Mast cell proliferation, growth of various cell types
GM-CSF (Granulocyte monocyte-colony stimulatory factor)	
VEGF (Vascular endothelial growth factor)	
FGF (Fibroblast growth factor)	
NGF (Nerve growth factor)	
PDGF (Platelet derived growth factor)	
<b>NO (nitric oxide)</b>	Vasodilation, neuromodulation

## Physiological role of mast cells

Apart from being prominently involved in allergic reactions, mast cells are critical for the maintenance of tissue integrity and function. This correlates with their ubiquitous presence in nearly all tissues. Their central role in immunological as well as non-immunological processes is further reflected by the large number of mediators by which mast cells may influence other cells. These mediators allow mast cells to regulate either local tissue functions or host defense by acting as innate immune cells, by interacting with the specific immune system, or by inducing and regulating inflammation. Since mast cells are located at the border of the body and environment, they are perfectly equipped with their mediators to orchestrate the immune system. They can recruit other immune cells to the site of injury and control the function of various cells such as eosinophilic granulocytes, T and B lymphocytes, thereby being implicated in the protection of the organism against bacterial, parasitic and viral infections. This role can be achieved precisely because mast cells are able to release selective mediators without degranulation (differential release).<sup>20</sup>

Otherwise, activation would always lead to allergic or anaphylactic reactions. In addition, mast cells essentially regulate homeostasis. In this connection, they contribute to wound healing as well as tissue remodeling, e.g. in hair follicles and bones. Mast cells promote homeostasis by degrading certain endogenous toxins such as endothelin-1 or neurotensin released in response to bacterial infection by means of their potent proteases. Similarly, mast cells are involved in the control of exogenous toxins such as venoms and bacterial toxins.

## Involvement of mast cells in the pathogenesis of diseases

The very same features that enable mast cells to protect the organism can wreak havoc to the organism when running out of control. Mast cells are known to be the primary responders in allergic reactions, orchestrating strong responses to minute amounts of allergens. Because of the high affinity of the FcεRI for IgE, mast cells are constantly coated with antigen-specific IgE.<sup>21</sup> Exposure to specific antigens induces bridging of surface-bound IgE molecules resulting in a rapid discharge of preformed mediators from secretory granules, as well as the release of de-novo synthesized mediators, which all act on distinct effector cells to produce the symptoms of allergy and anaphylaxis.

The broad spectrum of functions of mast cells might explain why mast cells can be involved in so many different pathologies beyond allergy (Table 3). An increase in the number of mast cells within tissues is observed in many pathophysiological conditions. Current data indicate that migration of mature mast cells might be one of the key mechanisms responsible for rapid local accumulation of these cells.

**Table 3:** Non-allergic diseases for which an involvement of mast cells in their pathogenesis has been demonstrated.

<b>Asthma/COPD</b> <sup>71,72</sup>	<b>Multiple sclerosis</b> <sup>89</sup>
<b>Atherosclerosis</b> <sup>73,74</sup>	<b>Neurofibromatosis</b> <sup>90,91</sup>
<b>Autoimmune diseases</b> <sup>75-77</sup>	<b>Non-cardiac chest pain</b> <sup>92</sup>
<b>Atopic dermatitis</b> <sup>78</sup>	<b>Osteoporosis</b> <sup>93</sup>
<b>Cardiac arrhythmias</b> <sup>79,80</sup>	<b>Peritoneal adhesions</b> <sup>94</sup>
<b>Fibromyalgia</b> <sup>81</sup>	<b>Psoriasis</b> <sup>78</sup>
<b>Heart failure</b> <sup>80,82-84</sup>	<b>Rheumatoid arthritis</b> <sup>95,96</sup>
<b>Inflammatory bowel disease</b> <sup>85</sup>	<b>Rosacea</b> <sup>97</sup>
<b>Interstitial cystitis</b> <sup>86</sup>	<b>Sarcoidosis</b> <sup>98-100</sup>
<b>Systemic mastocytosis</b> <sup>3,23,87</sup>	<b>Tumor growth</b> <sup>22,101</sup>
<b>Migraines</b> <sup>88</sup>	

The presence of mast cells in human cancer has been established for many years (for review, see [22]). Mast cells are typically found to accumulate at the periphery of tumors. Their involvement in tumor biology seems to be complex. A large body of evidence supports a negative role for mast cells in tumorigenesis, whereas there are also studies demonstrating a protective role for mast cells in cancer suggested by an association of an increased mast cell number in certain human tumors with good prognosis.

Besides the involvement of an accumulation of probably normal mast cells in the diseases discussed so far (Table 3), there is the potential for disturbances due to an increase of pathological mast cells within tissues, with attendant consequences both locally and systemically from the excess mast cell burden and from an increased releasability of mast cell mediators. Such disorders are generally termed *mastocytosis*. The clinical manifestation is produced by episodic release of mast cell mediators either in response to trigger stimuli or spontaneously. Patients present a variable and often changing pattern of symptoms related to the tissue responses to released mediators from mast cells and to the local tissue mast cell burden. Such patients often have a history of chronic and acute mediator-related symptoms such as pruritus, flushing, tachycardia, palpitations, light-headedness, dizziness, shortness of breath, nausea, diarrhoea and headache that form the *mast cell mediator release syndrome*. Linking symptoms to mast cell-derived mediators depends on the known actions of mediators (Table 2) and the efficacy of target-based interventions that suppress or control those symptoms (e.g. antihistamines, 5-HT<sub>3</sub> receptors antagonists, leukotriene receptor antagonists; Table 5). The diagnosis of the *monoclonal mast cell activation syndrome*, a subvariant form of systemic mastocytosis, that seems to be relatively common in everyday practice, relies primarily on the recognition of this complex clinical picture of mast cell mediator-induced symptoms because specific reliable laboratory biomarkers are still lacking. In this context it is important to note that the consensus criteria to define systemic mastocytosis, also known as WHO-criteria<sup>23</sup>, should not be mixed up with diagnostic criteria. These WHO-criteria represent the inclusion criteria for a provisional state-of-the-art consensus on systemic mastocytosis that addresses predominantly one certain variant form of systemic mastocytosis (namely that which is associated with the mutation of the tyrosine kinase Kit at codon 816).<sup>3,24</sup>

### Methods in mast cell research

To date, mast cell lines and mast cell-deficient mice have been used in this research field. Readers are referred to Krishnaswamy and Chi<sup>25</sup> for detailed discussion of research protocols.

### Human mast cell lines

It has become evident that human and rodent mast cells show different responses to cytokines and to anti-allergic drugs. For example, interleukin 3, which is a key growth factor for rodent mast cells, does not support the proliferation of human mast cells.<sup>26</sup> Therefore, most in vitro mast-cell experiments have been carried out with human transformed cell lines (Table 4). Some cell lines (e.g., HMC1) have proved of limited functional significance as model for normal mast cells because of their phenotype characterized by the independence of SCF. The stem cell factor-dependent LAD2 cell line derived from a patient with mast cell sarcoma/leukemia has many of the characteristics of mature tissue mast cells and can offer a more useful model for studies with mast cells.

To avoid such limitations, primary cultures of human mast cells are desirable. Human mast cells can be isolated from solid tissues (Table 4) and purified by complicated selection means and long-term cultures (for review, see [25]). As an alternative approach protocols for in vitro differentiation and culture of human mast cells from different progenitors (Table 3) have been established (for review, see [25]) that could provide mature, functional mast cells in high numbers.<sup>27</sup>

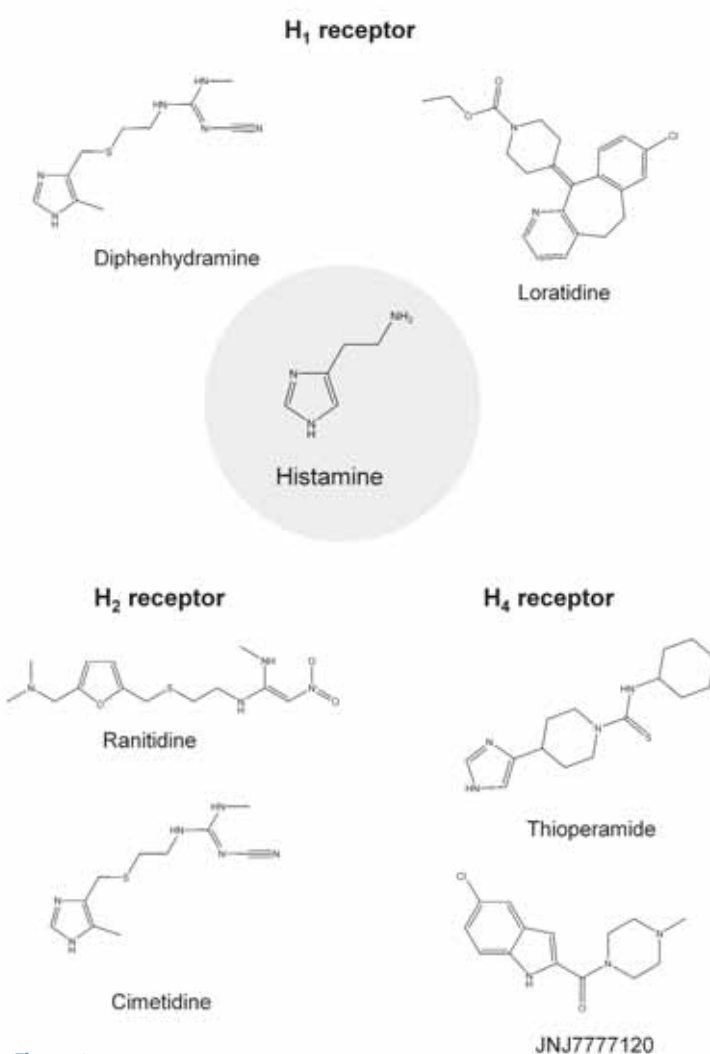
**Table 4:** Laboratory tools to study human mast cells.

<b>Human mast cell lines</b>	HMC1 ( <i>human mast cell</i> ) LAD2 ( <i>leukocyte-adhesion-deficiency</i> ) USF-MC1 Immortalized human mast cell line	[102] [103] [104] [105]
<b>Primary cultures of mast cells from progenitor cells</b>	Cord-blood-derived mast cells Peripheral-blood-derived mast cells	for review, see [25]
<b>Primary cultures of tissue mast cells</b>	Human skin mast cells Human mucosal (lung/intestine) mast cells Human mast cells of other origin (heart, spleen, kidney, liver, uterus)	

### In-vitro stimulation of mast cells

The activation of mast cells by allergen binding to specific IgE on high-affinity receptors (FcεRI) can be mimicked experimentally using antiserum specific for IgE which can crosslink membrane-bound IgE. The calcium ionophore ionomycin (Table 5) is also useful as experimental stimulus, and like anti-IgE, can induce the activation of all populations of mast cells. Another non-immunological stimulus for mast cell activation is histamine. Mast cells are not only the major source of histamine but can themselves be modulated by histamine as they express histamine H<sub>1</sub>, H<sub>2</sub> and H<sub>4</sub> receptors (Table 1; [28]). Selective ligands have been identified for all four histamine receptor subtypes (Table 5; Figure 1) and are useful tools for dissecting the physiological function of the individual receptors. Dimaprit and 4-methylhistamine which have been

used for many years as histamine H<sub>2</sub> receptor agonists, have been shown to be also histamine H<sub>4</sub> receptor agonists. In addition, many histamine H<sub>3</sub> receptor ligands, such as R-α-methylhistamine and thioperamide (Figure 1), are also histamine H<sub>4</sub> receptor ligands. Other non-immunological stimuli for mast cell activation include substance P, vasoactive intestinal peptide<sup>29</sup>, C5a and C3a, compound 48/80, morphine, adenosine, eosinophil major basic protein, platelet activating factor, and very low density lipoproteins (for review, see [25]). These stimuli have differential effects on mast cells from different sources of tissue.



**Figure 1.** Representative histamine receptor ligands.

## Animal models for mast cell research

Genetically mast cell-deficient c-kit mutant mice are important tools for identifying and quantifying the contributions of mast cells in many biological responses in vivo. Mice carrying certain mutations in the white spotting (W) locus (i.e. the c-kit gene) exhibit reduced Kit tyrosine kinase-dependent signaling.<sup>30</sup> The most commonly used c-kit-mutant mouse for studies of mast cell function is the WBB6F<sub>1</sub>-Kit<sup>W<sup>v</sup>/W<sup>v</sup></sup> mouse. The W mutation is a loss of function mutation, resulting from a 234 basepair in frame deletion in the c-kit coding sequence resulting in the loss of the transmembrane domain and amino acids of the kinase domain (position 513-590). The W<sup>v</sup> mutation leads to a loss-of-function phenotype as the result of a single missense mutation within the canonical kinase sequence (nt c2007t) leading to the change T660M. The c-kit mutations in Kit<sup>W<sup>v</sup>/W<sup>v</sup></sup> mice impair melanogenesis and result in anemia, sterility, markedly reduced levels of tissue mast cells, lack of interstitial cells of Cajal and other phenotypic abnormalities.

Another mutation, W-sash (W<sup>sh</sup>), also results in a mast cell-deficient phenotype. W<sup>sh</sup> is an inversion mutation in the transcriptional regulatory elements upstream of the c-kit transcription start site. W<sup>sh</sup>/W<sup>sh</sup> mice are viable, fertile, and do not have the anemia that occurs in Kit<sup>W<sup>v</sup>/W<sup>v</sup></sup> mice but also lack melanocytes and interstitial cells of Cajal.<sup>31</sup> An advantage of both strains is that normal mast cell populations can be restored to many tissues by the transfer of a population of bone marrow-derived mast cells.<sup>32</sup> By comparing mast-cell-deficient mice with these so-called *mast cell knock-in mice* it is possible to characterize the role of mast cells in various pathological and physiological processes.<sup>31,33</sup>

Recently, the generation of a novel transgenic mouse expressing Cre recombinase under the control of the mast cell protease 5 promoter has been reported.<sup>34</sup> Crossing of these mice with the recently generated iDTR mice<sup>35</sup> results in a mouse in which mast cells exclusively express a high affinity diphtheria toxin receptor. The subsequent application of diphtheria toxin then leads to the depletion of these cells. This conditional mast-cell-ablated mouse may allow analysis of the role of mast cells in disease models without affecting other immune cell subsets.

**Table 5:** Compounds used in mast cell research (available from BIOTREND with catalogue numbers in brackets)

### Histamine H<sub>1</sub> receptor antagonists

Compound	Comments
Cetirizine (BG0436)	Histamine H <sub>1</sub> R antagonist, anti-allergic agent
Doxepin (BG0175)	Histamine H <sub>1</sub> R antagonist, also binds to histamine H <sub>4</sub> R
Fexofenadine (BG0191)	Histamine H <sub>1</sub> R antagonist, anti-allergic agent
Ketotifen (BG0229)	Histamine H <sub>1</sub> R antagonist, anti-allergic agent, mast cell stabilizer
Mirtazepine (BN0638)	Histamine H <sub>1</sub> R antagonist, 5-HT <sub>2,3</sub> and α <sub>2</sub> -adrenoceptor antagonist
Terfenadine (BG0333)	Histamine H <sub>1</sub> R antagonist, anti-allergic agent

### Histamine H<sub>2</sub> receptor selective drugs

Compound	Comments
Dimaprit (BN0189)	Histamine H <sub>2</sub> R agonist, moderately potent histamine H <sub>3</sub> /H <sub>4</sub> R antagonist
Ranitidine (BG0304)	Selective, potent histamine H <sub>2</sub> R antagonist

### Histamine H<sub>3</sub> and H<sub>4</sub> receptor selective drugs

Compound	Comments
N <sup>α</sup> -Methylhistamine (BN0366)	Non-selective histamine H <sub>3</sub> R agonist
4-Methylhistamine (BN0030)	Potent, selective histamine H <sub>4</sub> R agonist
Thioperamide maleate (BN0519)	Potent histamine H <sub>3</sub> /H <sub>4</sub> R antagonist

### 5-HT<sub>3</sub> receptor antagonists

Compound	Comments
Tropisetron (BG0349)	Selective, potent 5-HT <sub>3</sub> receptor antagonist
Ondansetron (BG0279)	Selective, potent 5-HT <sub>3</sub> receptor antagonist

### Calcium ionophore

Ionomycin (BN0275)
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<i>Histamine H<sub>1</sub> selective</i>		
<i>Cat. No.</i>	<i>Product</i>	<i>Category</i>
BG0041	Antazoline hydrochloride	Histamine H <sub>1</sub> antagonist, I ligand, neuroprotective agent
BG0092	Astemizole	Histamine H <sub>1</sub> antagonist, anti-allergic agent, P450 substrate
BG0098	Azelastine hydrochloride	Histamine H <sub>1</sub> antagonist, anti-allergic agent
BG0436	Cetirizine dihydrochloride	Histamine H <sub>1</sub> antagonist, anti-allergic agent
BG0140	Cinnarizine	Histamine H <sub>1</sub> antagonist
BG0169	Diphenhydramine hydrochloride	Histamine H <sub>1</sub> antagonist, anti-allergic agent
BG0175	Doxepin hydrochloride	Potent histamine H <sub>1</sub> antagonist, also binds to H <sub>4</sub>
BG0191	Fexofenadine hydrochloride	Histamine H <sub>1</sub> antagonist, anti-allergic agent
BG0229	Ketotifen fumarate	Potent histamine H <sub>1</sub> antagonist, anti-allergic agent
BG0136	Levocetirizine dihydrochloride	Histamine H <sub>1</sub> antagonist, anti-allergic agent, active enantiomer
BG0241	Loratadine	Peripheral histamine H <sub>1</sub> antagonist, anti-allergic agent
BG0398	Mepyramine maleate	Potent, selective histamine H <sub>1</sub> antagonist
BN0638	Mirtazepine	Potent histamine H <sub>1</sub> antagonist, 5-HT <sub>2,3</sub> and $\alpha_1$ antagonist
BG0299	Promethazine hydrochloride	Histamine H <sub>1</sub> antagonist
BG0333	Terfenadine	Histamine H <sub>1</sub> antagonist, anti-allergic agent

<i>Histamine H<sub>2</sub> selective</i>		
<i>Cat. No.</i>	<i>Product</i>	<i>Category</i>
BN0189	Dimaprit dihydrochloride	Histamine H <sub>2</sub> agonist, moderately potent H <sub>3</sub> /H <sub>4</sub> antagonist
BG0139	Cimetidine	Histamine H <sub>2</sub> antagonist, I <sub>1</sub> ligand
BG0187	Famotidine	Selective, potent histamine H <sub>2</sub> antagonist
BN0604	ICI 162,846	Potent histamine H <sub>2</sub> antagonist
BG0304	Ranitidine dihydrochloride	Selective, potent histamine H <sub>2</sub> antagonist
BN0521	Tiotidine	Selective, potent histamine H <sub>2</sub> antagonist
BG0391	Zolantidine dimaleate	Selective, potent histamine H <sub>2</sub> antagonist

**Histamine H<sub>3</sub> and H<sub>4</sub> selective**

<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
BN0270	Imetit dihydrobromide	Histamine H <sub>3</sub> /H <sub>4</sub> agonist (H <sub>3</sub> > H <sub>4</sub> )
BN0271	Immepip dihydrobromide	Histamine H <sub>3</sub> /H <sub>4</sub> agonist
BN0272	Immethridine dihydrobromide	Potent histamine H <sub>3</sub> agonist, highly selective over H <sub>4</sub>
BN0332	(R)-(-)- $\alpha$ -Methylhistamine dihydrobromide	Potent histamine H <sub>3</sub> agonist
BN0333	(S)-(+)- $\alpha$ -Methylhistamine dihydrobromide	Histamine H <sub>3</sub> agonist, less active enantiomer
BN0030	4-Methylhistamine dihydrochloride	Potent, selective histamine H <sub>4</sub> agonist
BN0366	N <sup>α</sup> -Methylhistamine dihydrochloride	Non-selective histamine H <sub>3</sub> agonist
BN0152	Clobenpropit dihydrobromide	Potent histamine H <sub>3</sub> antagonist, partial H <sub>4</sub> agonist
BN0605	Iodophenpropit dihydrobromide	Potent, selective histamine H <sub>3</sub> antagonist
BN0556	JNJ 10191584 maleate	Potent, selective histamine H <sub>4</sub> antagonist
BN0519	Thioperamide maleate	Potent histamine H <sub>3</sub> /H <sub>4</sub> antagonist

**5-HT<sub>3</sub> receptor antagonists**

<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
BG0428	Tropisetron hydrochloride	Selective, potent 5-HT <sub>3</sub> receptor antagonist
BG0279	Ondansetron hydrochloride	Selective, potent 5-HT <sub>3</sub> receptor antagonist
BG0450	Granisetron hydrochloride	Selective 5-HT <sub>3</sub> receptor antagonist
BN0006	2-[1-(4-Piperonyl)piperazinyl]benzothiazole	Moderate 5-HT <sub>3</sub> receptor antagonist, also 5-HT <sub>4</sub> receptor agonist
BN0326	MDL 72222	Selective 5-HT <sub>3</sub> receptor antagonist
BN0548	Y-25130 hydrochloride	Selective, potent 5-HT <sub>3</sub> receptor antagonist
BN0554	Zacopride hydrochloride	Potent 5-HT <sub>3</sub> receptor antagonist, also 5-HT <sub>4</sub> receptor agonist

**Other**

<b>Cat. No.</b>	<b>Product</b>	<b>Category</b>
BN0275	Ionomycin calcium salt	Calcium ionophore

**Mast cell function in physiology and pathophysiology**  
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