

Table 1 Selected manifestations of mast cell activation (MCA)

Symptoms	Potential mediators
Dermatologic manifestations	
Urticaria	Histamine
Flush, erythema	Histamine
Angioedema	Histamine, Bradykinin
Hemangiomas, telangiectasias, cherry angiomas, arteriovenous malformations, hemorrhoids, aneurysms, etc.	Probably multiple angiogenic mediators
Wound healing process and keloid formation	Angiopoietin Like 6; Eprexulin
Desquamation in the epidermis	Kallikrein Related Peptidase 5
Respiratory manifestations	
Cough, wheezing	Histamine
Airway inflammation and obstructive dyspnea due to potent smooth muscle contracting activity and proinflammatory activity	Leukotriene C4, D4, E4
Induction of sneezing following exposure to chemical irritants or allergens	Neuromedin B
Anticholinergic symptoms	Acetylcholinesterase
Cardiovascular manifestations	
Hypotension	Adrenomedullin
Hypotension - vasodilator and anti-proliferation agent, counterbalancing the actions of the vasoconstrictor angiotensin II	Angiotensin Converting Enzyme 2
Hypotension - vasodilation and hypotension via bradykinin	Kallikrein 1, Kallikrein Related Peptidase 2, 8, 9, Kininogen 1
Hypotension - plays a key role in mediating cardio-renal homeostasis and vasodilation	Natriuretic Peptide A
Hypotension - vasodilation	Nitric oxide
Hypotension - vasodilation	Platelet activating factor
Hypotension/hypertension - vasodilation at low doses and vasoconstriction at high doses	Prostaglandin D2
Hypertension - a potent vasoconstrictor, affects cardiac contractility and heart rate through its action on the sympathetic nervous system	Angiotensin II, Angiotensinogen
Hypertension - responsible for converting angiotensin I to the vasoactive peptide angiotensin II	chymase 1
Hypertension - potent vasoconstriction	Endothelin 1, 3
Hypertension - vasoconstrictive action	Peptide YY
Hypertension - generation of angiotensin I from angiotensinogen in the plasma, initiating a cascade of reactions which produce hypertension and increased sodium retention by the kidney	Renin
Regulation of heart function	Triiodothyronine, 3-Iodothyroacetic acid; 3-Iodothyroanamine
Atherosclerosis and aortic valve stenosis	Biglycan
Atherosclerosis - disturbed plasma and tissues lipid homeostasis	Apolipoprotein E
Increased erythropoiesis	Erythropoietin, Inhibin subunit α (=activin A)
Gastrointestinal manifestations	
Gastritis – increased gastric acid secretion	Histamine
Anticholinergic symptoms	Acetylcholinesterase
Protective effect - stabilization of the protective mucous gel overlying the gastrointestinal mucosa	Trefoil Factor 1
Enteritis/colitis - important role in the maintenance of intestinal epithelial homeostasis and the promotion of mucosal healing	Milk Fat Globule EGF And Factor V/VIII Domain Containing
Diarrhea – stimulation of colonic smooth muscle contraction	Neuromedin B
Obstipation/dyspepsia - inhibits exocrine pancreatic secretion and inhibits jejunal and colonic mobility	Peptide YY
Obstipation/dyspepsia/gastroparesis– inhibition of gastrointestinal motility and gastric acid secretion	Trefoil Factor 2
Weight gain or loss - regulator of most hormones of the gastrointestinal tract	Somatostatin

Table 1 (continued)

Symptoms	Potential mediators
Weight gain or loss - key regulator of energy balance and body weight control	Leptin
Weight gain or loss - disturbed plasma and tissues lipid homeostasis	Apolipoprotein E
Neurologic manifestations	
Increased amyloid precursor protein	A Disintegrin And a Metalloprotease (=ADAM) Domain 9
Increased neuroendocrine stress responses	Adenylate Cyclase Activating Polypeptide 1
Influences on cortical excitability, stress response, food intake, circadian rhythms, and cardiovascular function	Neuropeptide Y
Neurotransmitter and neuromodulator	Neurotensin
Influence on neurogenesis and neuroplasticity associated with learning, memory, depression and chronic pain	VGF Nerve Growth Factor Inducible
Coagulopathic manifestations	
Increased bleeding	
Cleavage of the von Willebrand Factor	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 13
Inhibiting prothrombin activation	Alpha-1-Microglobulin/Bikunin Precursor
May prevent activation of the intrinsic blood coagulation cascade by binding to phospholipids on the surface of damaged cells	Apolipoprotein H
Anticoagulant	Heparin
Inhibition of collagen-induced platelet aggregation	Leukocyte Associated Immunoglobulin Like Receptor 2
Conversion of plasminogen to the fibrinolytic enzyme plasmin	Plasminogen Activator, Tissue Type; Plasminogen Activator, Urokinase
Decreased bleeding/thrombophilia	
Activation of factor XIII	Cathepsin C
Polymerization to form an insoluble fibrin matrix as one of the primary components of blood clots	Fibrinogen α , β , γ -chains
High-molecular-weight kininogen essential for blood coagulation and assembly of the kallikrein-kinin system	Kininogen 1
Platelet action	Platelet activating factor
Neutralization of heparin on the endothelial surface of blood vessels, thereby inhibiting local antithrombin activity and promoting coagulation	Platelet Factor 4
As well as	
Bind coagulation factor XII leading to its autoactivation	Complement C1q Binding Protein
Inhibition of thrombin, trypsin, plasminogen activator and urokinase	Serpin family A, B, E members
Skeletal manifestations	
Osteolysis	
Increased osteoclast formation	ADAM Metallopeptidase Domain 12
Stimulation of osteoclasts and inhibition of osteoblasts	Activin-A
Autocrine factor which heightens osteoclast formation and bone resorption	Annexin A2
Thiol protease involved in osteoclastic bone resorption	Cathepsin K
Antagonistic effect on osteogenesis due to its direct binding to BMP proteins	DAN (=differential screening-selected gene in neuroblastoma) Domain BMP (=bone morphogenic protein) Antagonist Family Member 5
Negative regulator of bone mineralization	Extracellular Matrix Protein 1
Osteogenesis	
Increased bone growth	Biglycan
Increased osteogenesis	Bone Morphogenetic Protein 2
Ectopic bone formation and promotion of fracture healing	Bone Morphogenetic Protein 7
Regulation of calcium and bone homeostasis	Bone Morphogenetic Protein 8b
Promotes osteogenesis by stimulating the differentiation of mesenchymal progenitors into mature osteoblasts	C-Type Lectin Domain Containing 11A
Stimulates the growth of chondrocytes and osteoblasts	Leukocyte Cell Derived Chemotaxin 2

Table 1 (continued)

Symptoms	Potential mediators
Pain manifestation	
Inducing pain	
Nociception	Galanin And GMAP Prepropeptide
Headache	Histamine
Direct activation of pain nerve fibers; in the posterior horn of the spinal cord amplification or weakening of pain impulses	Serotonin (5-hydroxytryptamine)
Preprotein of the pain-inducing tachykinin peptide hormone family: substance P, neurokinin A, neuropeptide K, neuropeptide gamma	Tachykinin Precursor 1
Chronic pain	VGF Nerve Growth Factor Inducible
Induction of acute itch	Neuromedin B
Neuromodulation	Nitric oxide
Inhibition of pain	
Preproprotein for the formation of the secreted endogenous opioid peptides beta-neoendorphin, dynorphin, leu-enkephalin, rimorphin, and leumorphin	Prodynorphin
Precursor of β -Endorphin	Proopiomelanocortin
Neurologic manifestations	
Myasthenia	Acetylcholinesterase
Neuroendocrine modulator of pituitary corticotroph function	Cardiotrophin Like Cytokine Factor 1
Mediating the autonomic, behavioral and neuroendocrine responses to stress	Corticotropin Releasing Hormone
Depression of neuronal activity	Cortistatin
Elevated expression of alpha-B crystallin occurs in many neurological diseases	Crystallin Alpha B
Acts as neurotransmitter	Histamine
Modulatory effects on the immune system	
Reduced T-cell activation and proliferation; numbers of hematopoietic stem cells in bone marrow	Activated Leukocyte Cell Adhesion Molecule
Control of the immune response	ADAM Like Decysin 1; Macrophage Migration Inhibitory Factor
Upregulated in multiple inflammatory diseases	Angiopoietin-2
B-cell stimulatory agent	Cardiotrophin Like Cytokine Factor 1
Important role in innate immunity defense against bacteria and viruses	Cathelicidin Antimicrobial Peptide
Activates serine proteases such as elastase, cathepsin G and granzymes A and B	Cathepsin C
Probably involved in the processing of antigenic peptides during MHC class II-mediated antigen presentation; may play a role in activation-induced lymphocyte depletion in the thymus	Cathepsin D
Participates in the killing and digestion of engulfed pathogens; it has bacteriocidal activity	Cathepsin G
Chemotaxis	
	C-C Motif Chemokine Ligand 1, 2, 3, 4, 4L1, 5, 7, 8, 11, 13, 15, 17, 18, 19, 20, 22-25, 28; C17orf99; Ninjurin 1; X-C Motif Chemokine Ligand 1 and 2
Controlling the production, differentiation, and function of white cell populations of the blood, the granulocytes and mononuclear phagocytes; promotes the release of pro-inflammatory chemokines	Colony Stimulating Factor 1, 2, 3
Triggering of the complement cascade	Complement C1q A Chain, Complement C1q Binding Protein, Complement C3, C5 Complement Factor D, Complement Factor Properdin
Chemoattractants for various immune cells	
	C-X3-C Motif Chemokine Ligand 1; C-X-C Motif Chemokine Ligand 1, 2, 3, 5, 8, 9, 10, 11, 12, 14, 16, 17, ISG15 Ubiquitin Like Modifier, Leukocyte Cell Derived Chemotaxin 2, Leukotrien B4
Antibacterial, fungicide and antiviral activities	
	Defensin Alpha 1, 4, 5, 6 Beta 1, 4A, 108B, 119; Granulysin; Lysozyme

Table 1 (continued)

Symptoms	Potential mediators
Inducing cytokine production	High Mobility Group Box 1
Enhances all basic T-cell responses to a foreign antigen	Inducible T Cell Costimulator
Key part of the innate immune response with potent antiviral, antiproliferative and immunomodulatory properties	Interferon Alpha 1, Beta 1, Gamma, Lambda 1-3
Immunoregulation	Interleukin (IL)-1 Alpha, 1 Beta, Interleukin-1 Receptor Antagonist, IL 2-7, 9-11, 12B, 13, 15, 16, 17A, 17C, 17D, 17F, 18, 22, 23 Subunit Alpha, 24, 25, 27, 31, 32, 37
An important component of the non-specific immune system with an antimicrobial activity	Lactotransferrin
Tumor progression/regression by MCA	
Progression	
Important role in tumor progression due to its effect on mRNA production and angiogenesis	Angiogenin
Has been implicated in tumor invasion and metastasis	Cathepsin B, F
Expressed in a significant fraction of human breast cancers, where it could contribute to tumor invasiveness	Cathepsin K
Stimulates the motility of tumor cells and has angiogenic properties, and its expression is upregulated in several kinds of carcinomas	Ectonucleotide Pyrophosphatase/Phosphodiesterase 2
Involved in the growth and proliferation of tumor cells by inducing vasculogenesis	Epidermal Growth Factor-Like Domain Multiple 7
Promotes cancer invasion and metastasis	Kallikrein Related Peptidase 7
Elevated expression of this protein may be associated with cancer cachexia	Inhibin Subunit Beta A
Regression	
Can prevent metastasis by inhibiting vascular growth and tumor cell invasion due to its role as an apoptosis survival factor for vascular endothelial cells	Angiopoietin Like 4
Tumor suppression by stimulation of autophagy and inflammation and an inhibition of angiogenesis and tumorigenesis	Decorin
Inhibits the proliferation of tumor cell	Oncostatin M

the MC by secretion of exosomes and vesicles (Savage et al. 2023), some of them containing KIT (Pfeiffer et al. 2022); (3) formation of nanotubes with exchange of intracellular material which seems to be involved in inducing apoptosis in cancer cells (Ahani et al. 2022); and (4) formation of MC extracellular traps (Möllerherm et al. 2016; Table 4). These four mechanisms, by which MCs can use almost any molecule as a mediator, underline the extraordinary role of these cells in our immune system. At the same time, this creates an almost insurmountable hurdle for precisely attributing specific clinical symptoms to specific messenger substances. This problem of assigning (a) certain MC mediator(s) to symptoms is further complicated by the fact that released MC mediators can maintain and enhance MC activation in autocrine and paracrine manners (Fig. 1), and additionally by the possibility of MCs taking up substances from their immediate environment and then re-releasing them. In this context, it has to be noted that MCs are able to survive even complete degranulation followed by regranulation (Iskarpotyoti et al. 2022). Interestingly, MCs have altered granule contents and structure after regranulation, likely depending on the trigger that had induced

the degranulation (Friend et al. 1996; Iskarpotyoti et al. 2022, further references therein).

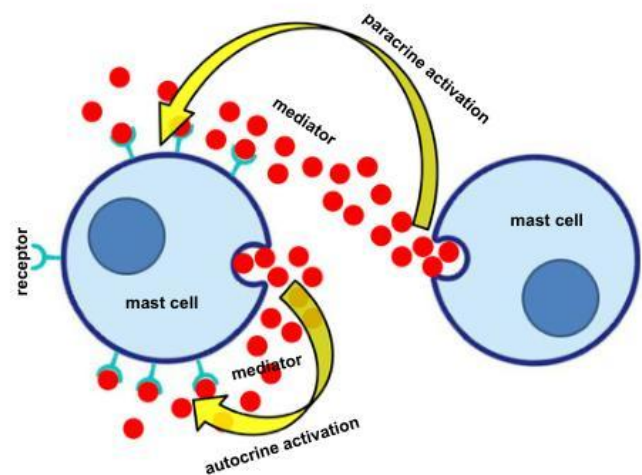


Fig. 1 Mast cell activation after mediator (red circles) exocytosis by autocrine and paracrine stimulation of mast cell receptors for this specific released mediator