

Neuroendocrinology of mast cells: Challenges and controversies

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Abstract

Mast cells (MC) are hemotopoietically derived tissue immune cells that are ubiquitous in the body, including neuroendocrine organs such as the hypothalamus, pineal, pituitary, ovaries, pancreas and uterus where their action is not well understood. Mast cells have historically been associated with allergies because of their rich content of histamine and tryptase, but more recently with regulation of immunity and inflammation due to their synthesis and release of numerous cytokines and chemokines. Mast cells are located perivascularly and express numerous receptors for diverse ligands such as allergens, pathogens, neurotransmitters, neuropeptides and hormones including acetylcholine, calcitonin gene-related peptide (CGRP), corticosteroids, corticotropin-releasing hormone (CRH), β -endorphin, epinephrine, 17β -oestradiol, gonadotrophins, hemokinin-A (HKA), leptin, melatonin, neurotensin (NT), parathyroid hormone (PTH), substance P (SP) and vasoactive intestinal peptide (VIP). Moreover, MC can synthesize and release most of their neurohormonal triggers, including adrenocorticotropin hormone (ACTH), CRH, endorphins, HKA, leptin, melatonin, NT, SP and VIP. Animal experiments have shown that diencephalic MC increase in number during courting in doves, while stimulation of brain and nasal MC leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis. Recent evidence indicates that MC reactivity exhibits diurnal variations, and it is interesting that melatonin appears to regulate MC secretion. However, the way MC change their phenotype or secrete specific molecules selectively at different pathophysiological settings still remains unknown. Mast cells developed over 500 million years ago and may have served as the original prototype neuroimmunoendocrine cell and then evolved into a master regulator of such interactions, especially as most of the known diseases involve neuroinflammation that worsens with stress.

KEYWORDS

allergies, corticotropin-releasing hormone, hypothalamic-pituitary-adrenal axis, melatonin, neuropeptides, neurotransmitters, stress, substance P

1 | INTRODUCTION

There are very few studies on the neuroendocrinology of mast cells (MC), especially in the skin.^[1,2] A neuroimmunoendocrine circuitry of the “brain-skin connection”^[3] has been invoked in many diseases,

especially inflammation,^[s1] because MC can be stimulated by many neuroimmunoendocrine triggers (Figure 1) and can contribute to a local “hypothalamic-pituitary-adrenal axis.”^[4] Mast cells derive from haematopoietic precursors^[5,6] and mature in tissues in response to stem cell factor (SCF), the ligand of the CD117 (KIT) tyrosine kinase

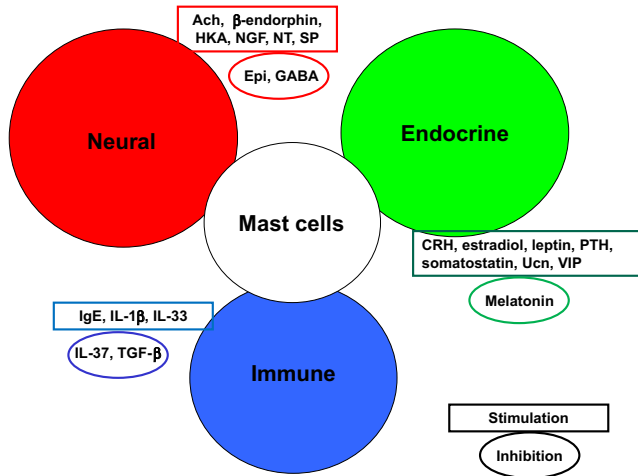


FIGURE 1 Diagrammatic representation of the stimulatory and inhibitory input on mast cells from the neural, endocrine and immune systems

receptor, and local microenvironmental factors^[7] such as IL-4^[8] and nerve growth factor (NGF).^[9] The phenotype of the MC can vary considerably with respect to both their content and its responsiveness to stimulatory or inhibitory signals.^[10]

Each MC contains as many as 500-1000 secretory granules storing numerous biologically active molecules.^[11] Mast cells are located perivascularly and are typically activated through exposure to allergens that cross-link allergen-specific immunoglobulin E (IgE) bound almost exclusively to high-affinity Fc epsilon receptor 1 (FcεRI).^[s2-s5] IgE may have additional regulatory functions on immunity,^[12] but also on non-immune cells as there is evidence of expression of FcεRI receptors on neurons.^[13] Mast cells also express receptors for additional diverse ligands,^[14] including Toll-like receptors (TLR) that can be activated by bacterial and viral products,^[15] as well as by fungi^[16] and a variety of toxins.^[17] Skin MC can also be stimulated by physical stimuli such as pressure, temperature changes and vibration,^[18] but this mechanism is presently unknown.

Mast cells can also be stimulated by neurotransmitters, neuropeptides and hormones including acetylcholine, calcitonin gene-related peptide (CGRP), corticosteroids, corticotropin-releasing hormone (CRH), β-endorphin, epinephrine, 17β-oestradiol, gonadotrophins, hemokinin-A (HKA), leptin, melatonin, nerve growth factor (NGF), neurotensin (NT), parathyroid hormone (PTH), substance P (SP) and vasoactive intestinal peptide (VIP) (Table 1). Moreover, MC can synthesize and release most of their neurohormonal triggers, including adrenocorticotropin hormone (ACTH), CRH, endorphins, HKA, leptin, melatonin, NT, SP and VIP as discussed later. Mast cell stimulation can be affected by cytokines. For instance, IL-1β triggered selective release of IL-6,^[19] while IL-33 enhanced allergic MC stimulation,^[20] moreover, IL-33 had synergistic action with SP inducing vascular endothelial growth factor (VEGF) release^[21] and acted as “sensors of cell injury,”^[22] and IL-33 has been considered an “alarmin,”^[22] acting through MC to alert the innate immune system.^[23] Other “danger signals” may also stimulate MC.^[24] However, MC activation ultimately results from an

interplay between positive and negative signalling pathways,^[25,26] even though there are few if any innate negative regulators of MC known. Mast cell-derived chondroitin sulphate^[27] and heparin^[28] have been reported to inhibit MC. Recently, spermine was identified in MC secretory granules^[29] and we had reported that it inhibits rat MC secretion.^[30]

MC stimulation leads to secretion of numerous vasoactive, neurosensitizing and pro-inflammatory mediators that include preformed, granule-stored mediators such as heparin, histamine, tryptase and TNF secreted immediately through degranulation. Mast cells also secrete lipid-derived mediators synthesized rapidly from membrane-derived arachidonic acid such as prostaglandin D₂ (PGD₂),^[31] leukotriene C₄ (LTC₄)^[s6,s7] and platelet-activating factor (PAF).^[32] MC also produce newly synthesized cytokines such as numerous interleukins (IL), such as IL-5, IL-6, IL-31 and IL-33, and tumor necrosis factor (TNF), and chemokines such as CCL5 and CXCL8, as well as vascular endothelial growth factor (VEGF) released 6-12 hours after stimulation.^[33,34] The exact mode of secretion of most of these mediators is still little understood. Triggering through cross-linking of the FcεRI leads to compound exocytosis apparently over 60 minutes, while SP results in more rapid secretion (5-10 minutes) of the content of individual granules.^[35] However, this picture may be oversimplified. For instance, we showed that MC can secrete the content of *individual granules*^[36] or *specific mediators*, such as serotonin,^[37] selectively without degranulation.^[38] We later showed that IL-1 can stimulate selective release of IL-6^[19] as does SCF.^[39] We also showed that corticotropin-releasing hormone (CRH) can stimulate selective release of VEGF^[40] as was also reported for PGE_{2α}.^[41]

MC have recently been shown to also have additional means of more rapid and specific communication with other cell types: (i) transgranulation,^[42] (ii) “polarized” exocytosis of proteolytic enzymes at surface sites called “antibody-dependent degranulation synapse,”^[43] (iii) formation of nanotubules^[44,45] and (iv) secretion of nanovesicles (exosomes)^[46] that contain many different biologically active molecules,^[47] in a manner that may be guided by antigens embedded in their phospholipid envelope.^[48] Such exosomes^[s8] could participate in immune^[49] and neuropsychiatric diseases.^[50,51]

Consequently, counting the number of intact and degranulated MC, as it typically reported in disease, may be a gross misrepresentation of their potential involvement. Instead, it would be more relevant to investigate the extent of MC mediator release even though MC may otherwise look intact in numbers and degree of degranulation.^[52,53]

2 | HYPOTHALAMIC HORMONES

Stress contributes to pathological outcomes in various tissues, including skin diseases.^[54-57,57,57-61,s9-s11] In fact, stress can worsen allergies,^[s12] asthma,^[s13] cardiovascular disease^[s14] and multiple sclerosis.^[s15] Emotional stress is the most common trigger of symptoms in patients with systemic mastocytosis, characterized by increased number and degree of activation of MC.^[62] Severe stress worsened urticaria pigmentosa and led to increased number of skin

TABLE 1 Mast cell neurohormonal triggers

Trigger	Effect
Circadian hormones	
Melatonin	↓
Growth factors	
BDNF	↑
Insulin-like growth factor-1	↑
Neurotrophin-3	↑
NGF	↑
PDGF	↑
SCF	↑
Metabolic hormones	
Leptin	↑
Neuropeptides	
Adrenomedullin	↑
CGRP	↑
Hemokinin-A	↑
Neurotensin	↑
PACAP	↑
PTH	↑
Somatostatin	↓
SP	↑
Neurotransmitters	
Acetylcholine	↑
Dopamine	?
Epinephrine	↓
GABA	↓
Histamine	↓
Norepinephrine	↓
Serotonin	?
Pheromones	
Oxytocin	?
Pain peptides	
Enkephalins	↑
β-Endorphin	↑
Sex hormones	
Oestrogen	↑
Gonadotrophins	↑
Progesterone	↓
Testosterone	↓
Stress hormones	
ACTH	?
CRH	↑
Cortisone	↓
Urocortin	↑
Vascular peptides	
Endothelin	↑
VEGF	?
VIP	↑

ACTH, adrenocorticotrophic hormone; BDNF, brain-derived neurotrophic factor; CGRP, calcitonin gene-related peptide; CRH, corticotropin-releasing hormone; GABA, γ -aminobutyric acid; NGF, nerve growth factor; PACAP, pituitary adenylate cyclase-activating polypeptide; PDGF, platelet-derived growth factor; PTH, parathyroid hormone; SP, substance P; VIP, vasoactive intestinal peptide; VEGF, vascular endothelial growth factor.

MC expressing CRH receptor-1 (CRHR-1).^[63] The possible role of CRH in cutaneous inflammatory diseases has also been reviewed.^[64,65] Psychological stress worsened symptoms in a patient with systemic mastocytosis, who had increased serum CRH levels and whose bone marrow MC also expressed CRHR-1.^[66] We also reported a case of stress-induced anaphylaxis.^[67] It is important to note that patients with mastocytosis experience neuropsychiatric problems,^[516-518] which patients have termed “mastopsychosis.”

Symptoms of both psoriasis (Ps) and atopic dermatitis (AD) worsen with stress.^[68,69] These chronic inflammatory skin disorders^[64,70,71] are characterized by severe pruritus,^[519-520] implicating MC in both Ps^[72-74] and AD.^[75-77] It is interesting that maternal psychological problems increase the risk of childhood AD.^[78] A number of reports indicate more frequent allergies in children with autism spectrum disorder (ASD)^[79,80] with food allergies being the most prevalent complaint, often in the absence of elevated serum IgE or positive skin tests.^[521-523] Large epidemiological studies reported that eczema was strongly associated with ASD and attention-deficit/hyperactivity disorder (ADHD)^[81] and atopy was associated with risk of both ASD and ADHD.^[82] Moreover, a large case-control study reported that allergies, asthma and autoimmune disorders, especially Ps, were diagnosed more frequently in patients with ASD than controls.^[83] An experimental study actually reported that a mouse model of food allergy was characterized by autistic-like behaviour.^[84]

There is strong evidence of the existence of a cutaneous neuroendocrine system,^[4] involved in skin pathology^[524] through interactions among biogenic amines, catecholamines, melatonin, proopiomelanocortin, adrenocorticotrophic hormone (ACTH), β -endorphin and melanin-stimulating hormone (MSH), as well as CRH and related peptides.^[57,85] The role of CRH in the skin has been increasingly discussed.^[64,65,86] CRH is typically secreted from the hypothalamus under stress and activates the hypothalamic-pituitary-adrenal (HPA) axis.^[87] CRH^[525-527] and CRHR^[88] gene expression has been documented in rodent and human skin^[89] and has been shown to contribute to a local HPA axis.^[90-92] CRH can be released outside the brain from nerve endings,^[87,88] but it is also synthesized by skin cells,^[93] immune cells^[94] and MC.^[95] Amazingly, even corticosterone has been localized inside MC secretory granules.^[96]

MC are juxtaposed to CRH-positive nerve endings in the median eminence,^[97] as well as during hair follicle formation.^[98] There is hair follicle-dependent expression of CRH and CRHR in murine skin.^[99] In fact, CRH can promote MC maturation from local hair follicle-associated progenitor cells.^[100,101]

Acute stress induces local release of CRH in the skin and increases skin vascular permeability^[102] through MC^[103] activation by CRH.^[104] CRHR-1 gene is expressed in a subpopulation of skin MC,^[99] and human MC express mRNA and protein for CRHR-1.^[40,105] We further showed that skin MC can express CRHR-1, as well as human cultured MC, activation of which induced production of VEGF.^[40] Stress has also been reported to induce selective release of VEGF,^[106] an effect that is absent in MC-deficient mice.^[107] Acute stress and locally secreted CRH^[103] activate MC^[68,103] leading to neurogenic inflammation with subsequent chronic nerve sensitization^[108] in a “brain-skin” connection.^[3]

In fact, MC have also been implicated in the regulation of HPA axis both in the skin^[528,109] and in the brain.^[86,110-112] In particular, histamine was shown to activate the HPA,^[113] as did MC-derived IL-6^[114] and CRH.^[95] Interestingly, unlike its inhibitory effect on other secretory cells, somatostatin triggers MC secretion.^[115,116]

Mast cells immunoreactive for gonadotrophin-releasing hormone (GRH) increased during courting in the habenula of doves (equivalent to the median eminence in humans).^[117,118] MC are absent from the thalamus during pro-oestrus, but are present in the hypothalamus only during the oestrous phase.^[119] MC in ovarian, uterine and brain tissues change their histamine content throughout the rat oestrous cycle; moreover, brain MC appear to respond to chemosensory cues and are activated during oestrous induction.^[120]

3 | PITUITARY HORMONES

Oxytocin receptors are expressed by MC in the uterus where their activation prevented serotonin uptake.^[121] Mast cells are also activated by pituitary adenylate cyclase-activating peptide (PACAP), a response augmented by SCF,^[122] which is an important skin vascular regulator.^[123]

Mast cells are found in the pituitary^[124] and thyroid^[125] glands and can regulate thyroid function. Moreover, the incidence of thyroid disease is higher in patients with chronic urticaria.^[126]

It is interesting that PTH is a potent trigger of MC.^[127]

4 | DIURNAL PEPTIDES

Mast cell numbers and reactivity have been reported to undergo daily rhythmic variations in the rat thyroid gland.^[128] Moreover, the reactivity of individual MC was further shown to follow a "circadian clock."^[129] In this context, it is of interest that MC are present within the pineal gland and melatonin appears to inhibit MC proliferation.^[130,131]

5 | NEUROTRANSMITTERS

Mast cells have the ability to take up, store and secrete all known neurotransmitters, especially dopamine^[132,133] and serotonin.^[134,135] Acetylcholine (ACh) at 10^{-12} M was reported to stimulate skin MC.^[136]

Epinephrine can inhibit TNF release from MC.^[137] Beta-receptor agonists were shown to be better inhibitors of PGD₂ release than cromolyn.^[138] Such beta-agonists also inhibited IgE-induced histamine release from human gastric MC.^[139] However, such drugs do not appear to inhibit chronic inflammation in asthma.^[140]

6 | OTHER NEUROPEPTIDES

A new human G-protein-coupled receptor MRGPRX2 was recently shown to be activated by cationic drugs and peptides, including SP at high concentrations.^[141] Nevertheless, SP^[21,142-144] and other

neuropeptides^[34] such as NT^[105,145-147] and NGF^[148,149] also stimulate MC apparently also through specific receptors. In particular, SP can have pro-inflammatory actions acting through its specific NK-1.^[529,150]

Psoriasis is also associated with increased skin level of SP, TNF and VEGF. An increased number of contacts between SP-positive nerves and MC have been observed in Ps.^[55] Moreover, Ps patients with pruritus had increased SP-containing nerve fibre areas and increased number of perivascular degranulated MC compared to Ps patients without pruritus.^[151] Increased nerve-MC contacts were also reported in the skin of AD patients.^[152] NT, a brain peptide involved in inflammation,^[153] stimulates rodent MC through NTR^[154,155] to secrete histamine and elevates histamine plasma levels.^[156] NT administration increases vascular permeability in isolated rat skin^[157] and in skin blisters in a MC-dependent manner.^[158] NT is increased in the skin following acute stress, stimulates skin MC and increases vascular permeability.^[159] It is interesting that NT,^[160] HKA^[161] and NGF^[9] can be synthesized and released from MC.^[91] NT increases expression of CRHR-1 receptor,^[162] activation of which by CRH increases allergic stimulation of human MC.^[163,164]

It should be stressed, however, that there is great tissue variability in MC^[165] with papers reporting that human skin MC apparently do not degranulate in response to neuropeptides,^[166] even though their secretion is augmented by specific cytokines such as IL-4 and IL-33.

7 | SEX HORMONES

Oestrogens and oestrogen receptors^[530] have been implicated in skin pathophysiology as skin disorders are known to worsen during the menstrual cycle.^[531] Human MC express oestrogen receptors^[167] activation of which increase MC stimulation.^[67,168] Oestrogen receptors are also expressed on MC found in bladder^[169-171] and in lung.^[172,173] Oestrogen may activate MC via a non-genomic oestrogen receptor.^[167] Oestradiol also induced MC migration into the uterus and their degranulation.^[174] Treatment of mice with luteinizing hormone (LH), follicle-stimulating hormone (FSH) or oestradiol increased the number and extent of MC degranulation in the ovaries.^[175] Human MC also express progesterone^[176,177] and testosterone^[178] receptors, but their activation appears to have an inhibitory effect.

Mast cells are present in the human penis,^[179,180] prostate^[181-183] uterus,^[184-187] vagina^[184] and placenta.^[188] Uterine MC increase during pregnancy and may be important for reproductive processes.^[532] IgE-independent MC activation has been reported to augment contractility of guinea pig,^[189] mouse^[190] and human^[191] myometrium. Activation of MC also leads to angiogenesis in the rat uterine cervix during pregnancy.^[192]

The decidua of women with high levels of stress^[533] and aborted decidua^[193] contained high number of tryptase-positive MC. We reported high levels of CRH and tryptase in products of conception from women with habitual spontaneous abortions.^[194] Endometriosis tissue has also been associated with high number of activated MC.^[195-197] Mast cells were also increased in response to stress that exacerbated endometriosis in a rat model.^[198] In fact, targeting MC has been proposed as way to treat endometriosis.^[199] Mast cells have also been implicated in fibrosis, whether it is present in endometriosis or in Hodgkin's lymphoma.^[200]

TABLE 2 Main messages

MC may have functioned as a primitive neuroimmunoendocrine organ
MC are found in all tissues, including the brain and endocrine glands
MC can synthesize, take up, store and secrete most hormones and neurotransmitters
MC are affected by most known hormones and neurotransmitters
MC secrete proteases that can either activate pro-peptides or degrade them
MC can release mediators selectively through different secretory pathways
MC mediators can have autocrine and paracrine effects
MC regulate allergic, autoimmune, immune and inflammatory processes
MC participate in many diseases affected by stress

8 | METABOLIC HORMONES

Mast cells have been implicated in the metabolic syndrome^[s34] and in atherosclerosis.^[201,202] Obesity is considered an inflammatory state^[203] and been associated activation of MC.^[202,s35] Moreover, MC secrete leptin,^[204] which is increased in obesity,^[s36] which is increasingly considered an inflammatory disease. Leptin deficiency switches MC to an anti-inflammatory phenotype.^[205] Insulin and insulin-like growth factor-1 promote MC survival,^[206] and MC stabilization has been proposed as a means to treat obesity and diabetes.^[s37] Skin MC were recently shown to be degranulated in type I diabetes, but to be necessary for healing of diabetic wound ulcers.^[207]

9 | CONCLUSION

MC have been retained throughout the phylogenetic tree^[208] and may be necessary for survival of the species^[s38] by (a) protecting the organism against external triggers,^[s4] (b) fighting pathogens,^[15,16] (c) inactivating venoms,^[17] and (d) regulating immunity,^[209-211] (e) inflammation,^[212] (f) the HPA axis^[110-112,213,214] and (g) the gut-brain axis.^[215,216,s39] Some of the key “take-home” messages are listed in Table 2.

The potential role of MC in immunity^[217] or autoimmunity^[218] has occasionally been challenged^[219] based mostly on the use of certain MC-deficient mice^[220] that do not necessarily reflect especially inflammatory human conditions.^[221] It is therefore of critical importance to establish conditions where primary human MC may be cultured together with other cell types, such as human skin fibroblasts,^[222] to study the development of specific phenotypes.^[223]

It is reasonable to wonder what is the physiological function of MC.^[s40,s41] For instance, even though MC bind IgE almost exclusively, it was not known how they do so as IgE circulates and MC develop expression of their FcεRI receptors in the tissues; similarly, MC is the exclusive source of heparin, but MC do not circulate to make heparin available for blood thinning. It was recently shown that perivascular MC extend cell processes through endothelial cell gaps and “capture” circulating IgE,^[224] this mechanism may also allow them to secrete heparin

in the systemic circulation. In this context, it is relevant that endothelin has been shown to stimulate MC, which subsequently degrade it.^[s42]

The ability of MC to respond to so many diverse triggers, especially neurohormonal triggers (Table 1), and secrete numerous biologically powerful mediators by utilizing different means of secretion^[s43] permits them to participate in many pathophysiological processes such as allergic diseases,^[s44-s46] especially in the skin,^[s47] but also in the lungs,^[s48] innate immunity,^[7,s49-s52] autoimmunity,^[s53,s54] and inflammation.^[34,68,151,214,225,s55] A case in point is mast cell disorders, especially mastocytosis where patients experience multiple symptoms stemming from the effect of numerous MC-derived mediators affecting many organs.^[34]

10 | REMAINING ISSUES

Many questions remain unanswered, especially the way MC change their phenotype or secrete specific molecules selectively at different pathophysiological settings. Other questions include (a) the specific content of human MC secretory granules, (b) the regulation of selective MC mediator secretion, (c) the identification of innate MC inhibitory molecules, (d) the role of MC within endocrine glands, (e) the pathophysiology of uterine MC, (f) the ability of MC to sense odours through the expression of olfactory receptors and (g) the ability of MC to acquire a different phenotype. The latter possibility may permit the use of autologous blood-derived MC progenitors or basophils, or fat or skin-derived MC, to be “transplanted” in the pancreas or substantia nigra for the treatment of type I diabetes or Parkinson’s disease, respectively. Mast cells developed over 500 million years ago and may have served as the original prototype neuroimmunoendocrine cell and then evolved into a master regulator of such interactions, especially as most of the known diseases involve neuroinflammation that worsens with stress.

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CONFLICT OF INTEREST

The authors have declared no conflicting interests.

TCT has been awarded the following US and EU patents on the regulation of MC: US 8,268,365; 9,050,725; 9,176,146. EPO 0618796; 0748217

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DATA S1. Supplemental References.

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