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*Review*

# Mast Cell/Basophil–Nerve Crosstalk: Autonomic Signals and Sensory Circuits

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**Abstract**

Mast cells and basophils both contain basophilic granules and express the high-affinity immunoglobulin E (IgE) receptor FcεRI, but they are functionally distinct immune effectors. Mast cells are key effectors in the immediate phase of IgE-mediated allergy, while basophils contribute to the amplification and maintenance of type 2 inflammation through the production of type 2 cytokines, particularly interleukin-4 (IL-4) and IL-13. Both lineages express receptors for neurotransmitters and neuropeptides, and their activation thresholds and effector profiles are modulated by neuronal mediators. Psychological stress, through autonomic outflow and endocrine axes, increases the secretion of catecholamines and glucocorticoids, which act directly on mast cells and basophils to modulate degranulation, lipid mediator synthesis, and cytokine and chemokine secretion. In addition, mediators released from these cells, including histamine, proteases, lipid mediators, and cytokines, act on peripheral sensory neurons to cause itch and neurogenic inflammation. These bidirectional loops in barrier tissues constitute a neuroimmune interface that integrates environmental stress with immune reactivity. In this review, we synthesize the current evidence regarding mast cell/basophil receptor repertoires for autonomic and sensory mediators, delineate the directionality and kinetics of signaling between nerves and these effector cells, and highlight points of divergence between mast cells and basophils. We conclude with a description of the mechanistic frameworks linking stress, neuroimmune crosstalk, and disease exacerbation, and propose strategies for the development of targeted interventions.

**Keywords:** autonomic nervous system; basophils; mast cells; neuroimmunomodulation; psychological stress; sensory pathways

## 1. Introduction

In recent years, the prevalence of allergic diseases, including bronchial asthma, allergic rhinitis, atopic dermatitis, and food allergy, has increased worldwide. Epidemiological studies based on physician diagnoses have yielded estimates that approximately 10%–30% of the global population is affected by at least one allergic disorder [1]. Specifically, in immunoglobulin E (IgE)-dependent immediate hypersensitivity reactions, re-exposure to allergens leads to the activation of mast cells and basophils, resulting in the rapid release of a wide range of mediators, such as histamine, lipid mediators, proteases, and cytokines. These mediators play pivotal roles in triggering acute symptoms and amplifying inflammatory responses [2,3]. In addition to FcεRI-mediated activation, mast cells and basophils can also integrate selected innate inputs through Toll-like receptor (TLR)- and MyD88-associated pathways [4,5,6]. Such signals can further modulate cellular activation and cytokine output, thereby contributing to allergic inflammation.

Importantly, these immune mediators not only act directly on target cells, including vascular endothelial cells, smooth muscle cells, and epithelial cells, but also stimulate peripheral nerves, such as sensory neurons, autonomic nerves, and the enteric nervous system. This neuroimmune communication has been shown to modulate and amplify diverse symptoms through reflex circuits and local neuronal networks, including cough, pruritus, pain, hypersecretion, and alterations in gastrointestinal motility [7,8,9]. In addition, immune cells themselves express a variety of receptors for neurotransmitters and neuropeptides. Signaling molecules produced by peripheral nerve terminals, including neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP), as well as autonomic neurotransmitters such as norepinephrine and acetylcholine, can profoundly modulate immune cell function [7]. These substances regulate key cellular processes, including degranulation, cytokine production, migration, and the maintenance or alteration of activation states [7,8,9]. Thus, the nervous and immune systems form bidirectional communication circuits, particularly in

barrier tissues, which contribute to host defense. However, excessive or dysregulated activation of these circuits is thought to promote chronic inflammation and exacerbate disease symptoms. In this review, we focus on mast cells, which serve as central effector cells in immediate allergic reactions, and basophils, which have recently gained attention for their roles in amplifying and sustaining type 2 immune responses. We summarize current knowledge regarding the means whereby neuronal factors modulate the signaling pathways in, and the functional properties of, these cells. Furthermore, we discuss how neuroimmune interactions involving mast cells and basophils contribute to the initiation, progression, and exacerbation of various allergic diseases, thereby providing a framework for future mechanistic studies and the identification of potential therapeutic targets.

## 2. Roles of Mast Cells and Basophils in Immune Regulation

Mast cells and basophils were originally described in the late nineteenth century by Paul Ehrlich as granule-containing cells with a strong affinity for basic dyes, and were identified in tissue sections and peripheral blood smears, respectively [10]. Mast cells (first described in 1878) and basophils (described in 1879) share several hallmark features, including the expression of the high-affinity IgE receptor FcεRI and the capacity to respond to IgE–allergen crosslinking by releasing a broad spectrum of inflammatory mediators, such as histamine, lipid mediators, cytokines, and proteases, thereby driving allergic reactions [2]. The overlapping phenotypic features of mast cells and basophils have historically led to their misclassification as closely related or even equivalent cell types. However, research over the past two decades has uncovered lineage-specific properties and functions, and these advances have led to the current view that mast cells and basophils are immunologically distinct cell populations with fundamentally different roles.

### *2.1 Mast Cells*

Mast cells are strategically positioned in barrier tissues that interface with the external environment. They are abundantly distributed in the skin, at the mucosal borders of the airways and gastrointestinal tract, and in close proximity to blood vessels, lymphatics, and peripheral nerve fibers [8,11,12]. This anatomical localization facilitates the rapid sensing of and response to invading allergens, parasites, and other microbes, as well as noxious environmental insults and venoms by mast cells [13]. A hallmark of mast cells is the presence of numerous electron-dense cytoplasmic granules that store preformed effector molecules, including proteases (e.g., tryptases and chymases), histamine, heparin, and other proteoglycans [13].

Canonical mast cell activation is triggered by IgE-dependent crosslinking of the high-affinity IgE receptor FcεRI upon allergen re-exposure [2,14]. Mast cells can also undergo rapid degranulation in response to complement-derived anaphylatoxins binding to C3a and C5a receptors, as well as through IgE-independent activation pathways [15]. IgE-independent activation can be achieved through the Mas-related G protein-coupled receptor X2 (MRGPRX2; murine ortholog MrgprB2), which is a low-affinity receptor that senses a broad range of cationic ligands, including substance P, compound 48/80, and the antimicrobial peptide LL-37 [16]. Activation of these receptors initiates signaling cascades that converge on calcium mobilization and exocytosis, culminating in the extracellular release of granule contents and the initiation of immediate hypersensitivity responses [14,17].

Histamine is one of the best-characterized mast cell mediators, and it drives tissue-level pathological responses following cellular activation. By acting on histamine H1 receptors (H1Rs) on vascular endothelial cells, histamine increases vascular permeability, thereby promoting edema and facilitating the extravasation of plasma proteins, such as albumin, antibodies, and complement components, and the migration of immune cells into tissues [18]. Histamine can also elicit pruritus by activating histamine receptors expressed on pruriceptive sensory neurons, including H1R and H4R [18,19]. In parallel, mast cell proteases, including tryptases and chymases, modulate inflammatory microenvironments by remodeling extracellular matrix components, modulating adhesion and matrix proteins, and activating matrix metalloproteinases (MMPs) [20]. Proteases can also activate protease-activated receptors (PARs), such as PAR2, thereby promoting sensory neuron excitation and sensitization, which contribute to neurogenic inflammation [21]. In addition, mast cell activation induces *de novo* transcriptional programs that drive the production of cytokines and chemokines, including interleukin (IL)-4, IL-5, IL-6, IL-8/C-X-C motif chemokine ligand 8 (CXCL8), IL-13, and tumor necrosis factor-α (TNF-α), with the exact profile being influenced by the nature of the stimulus and the local tissue environment, and these substances collectively support the late-phase inflammatory response [22].

In mice, mast cells are often categorized as connective tissue-type mast cells (CTMCs) or mucosal mast cells (MMCs), which differ in their anatomical distribution and granule protease repertoire [11]. CTMCs typically express carboxypeptidase A3 (CPA3), chymases (e.g., mouse mast cell protease (mMCP)-4 and mMCP-5), and tryptases (e.g., mMCP-6 and mMCP-7) at high levels, although mMCP-7 is not expressed in C57BL/6 mice, because of the presence of a naturally occurring mutation [20]. In contrast, MMCs preferentially express mucosal mast cell proteases, such as murine monocyte chemoattractant protein-1 (mMCP-1) and mMCP-2 [20]. In humans, mast cells are frequently classified as $MC_T$ (tryptase-positive) or $MC_{TC}$ (tryptase- and chymase-positive), which broadly correspond to the mucosal and connective tissue-like phenotypes, respectively

[20,23]. Although their estimated lifespans vary according to the tissue context and inflammatory milieu, rodent CTMC-like populations are generally considered to be survive for a period of months, whereas MMC-like populations are often more transient, and their populations can be expanded by type 2 cytokines such as IL-4 and IL-9 [24,25,26,27].

Physiologically, mast cells contribute to the host defense against endoparasites, such as *Trichinella spiralis*, and ectoparasites, such as ticks (e.g., *Haemaphysalis longicornis*) [13]. In addition, studies using mast cell-deficient mouse models have demonstrated that these cells can provide critical protection against some venoms, such as bee and snake venoms, in part through granule-associated proteases that degrade or neutralize toxic components [28,29]. Mast cells also serve as major effector cells in IgE-mediated (type I) hypersensitivity reactions, and particularly anaphylaxis, and they can contribute to IgE-associated inflammation in a disease- and tissue-dependent manner, underscoring their dual role in tissue protection and immunopathology [13,30].

### *2.2 Basophils*

Basophils are rare circulating granulocytes, typically accounting for <0.5% of peripheral blood leukocytes, and they have a short lifespan of only 2–3 days. During parasitic infections and allergic inflammation, increases in the concentrations of cytokines, such as IL-3, and epithelial alarmins, including thymic stromal lymphopoietin (TSLP), can drive transient circulating basophilia. Under homeostatic conditions, basophils are generally very rare in tissues; however, inflammatory cues can promote their recruitment into inflamed skin, lung, and intestinal sites, where they contribute to type 2 inflammation and parasite defense.

Basophils express the high-affinity IgE receptor FcεRI and can be activated by IgE-dependent allergen stimulation *via* FcεRI, as well as by complement-derived anaphylatoxins *via* their respective receptors, leading to the release of inflammatory mediators [31,32,33]. Upon their activation, basophils can secrete histamine, generate lipid mediators, and produce cytokines such as IL-4, IL-6, and TNF-α, and thereby modulate local inflammatory responses [34,35]. IL-4 production is a prominent feature of basophils and can be induced by IL-3 or TSLP alone, even in the absence of IgE-dependent stimulation [36,37]. The resulting cytokine-driven responses can be further amplified by innate stimuli and alarmins, including IL-33, IL-18, and lipopolysaccharide (LPS), through specific TLR pathways, as well as by protease allergens such as papain [38,39,40]. With respect to human basophils, IL-3- and/or IL-33-driven activation has also been reported to enhance IL-13 production [41]. In addition, human basophils have been reported to express an IgD receptor complex consisting of galectin-9 and CD44, and the crosslinking of this complex can promote the production of IL-4 and IL-13 by basophils, which suggests that basophils may participate in host defense and humoral immune responses, in addition to allergic inflammation [42].

A key immunological role of basophils is the orchestration and amplification of type 2 immunity. Basophil-derived type 2 cytokines can also modulate immune cell differentiation and tissue microenvironments, thereby influencing the magnitude and quality of downstream responses [43]. In mice, basophils can be recruited to draining lymph nodes in a T cell-derived IL-3-dependent manner during allergic inflammation and parasitic infection [44,45,46]. Moreover, basophils have been reported to acquire peptide–major histocompatibility complex class II (MHC II) complexes from dendritic cells *via* contact-dependent trogocytosis [47]. This acquisition, together with the action of other stimulatory molecules, can enable basophils to promote antigen-specific $CD4^+$ T-cell responses that are biased toward Th2 differentiation [47]. In addition, in mice, basophil-derived IL-4 has been reported to drive the differentiation of inflammatory monocytes toward M2-like macrophages, and the anti-inflammatory functions of these macrophages may contribute to the suppression of allergic inflammation [48].

Physiologically, basophils play important roles in the host defense against parasites, including helminths (e.g., *Nippostrongylus brasiliensis*) and ticks (e.g., *Haemaphysalis longicornis* and *Dermacentor variabilis*), in part through their ability to amplify type 2 immune circuits [49,50,51]. Basophils have also been implicated in the pathogenesis or progression of a range of diseases, including allergic disorders, autoimmunity, and cancer, emphasizing that even a numerically rare leukocyte population can have a substantial biological impact [32,43,52,53,54].

## 3. Major Activating Receptors and Intracellular Signaling Pathways in Mast Cells and Basophils

As described above, the most important activating receptor on mast cells and basophils is the high-affinity IgE receptor, FcεRI. The crosslinking of FcεRI by IgE and allergens is well known to induce degranulation and strong cellular activation. FcεRI consists of three subunits, an α-chain, a β-chain, and a γ-chain. In mast cells and basophils, FcεRI is expressed as a tetrameric complex, αβγ2, which contains two γ-chains [55]. In mice, FcεRI is expressed mainly in mast cells and basophils, but in humans, FcεRI expression is also detected in some antigen-presenting cells, including Langerhans cells and subsets of monocytes and dendritic cells, where it is expressed on the cell surface as a trimeric αγ2 complex, without the β-chain [56]. The α-chain is essential for the cell-surface expression of FcεRI and is responsible for binding to the Fc portion of IgE. The γ-chain contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain that is

essential for signaling, because it recruits spleen tyrosine kinase (SYK) [57]. The β-chain, which also contains an ITAM in its cytoplasmic domain, is known as an atopy-associated candidate protein [58,59]. It is constitutively associated with LYN, and is thought to amplify FcεRI signaling by upregulating ITAM phosphorylation when FcεRI is crosslinked [2]. Most Fc receptors have low affinity for antibodies ($K_d$~$10^{-5}$ to $10^{-7}$ M), and therefore they bind antibodies mainly in the form of immune complexes. In contrast, FcεRI has a very high affinity for IgE ($K_d$ in the $10^{-10}$ M range) and can bind monomeric IgE [55]. Therefore, circulating antigen-specific IgE can bind to FcεRI on mast cells and basophils in the absence of antigen, which results in a "sensitized" state that allows rapid responses upon allergen exposure.

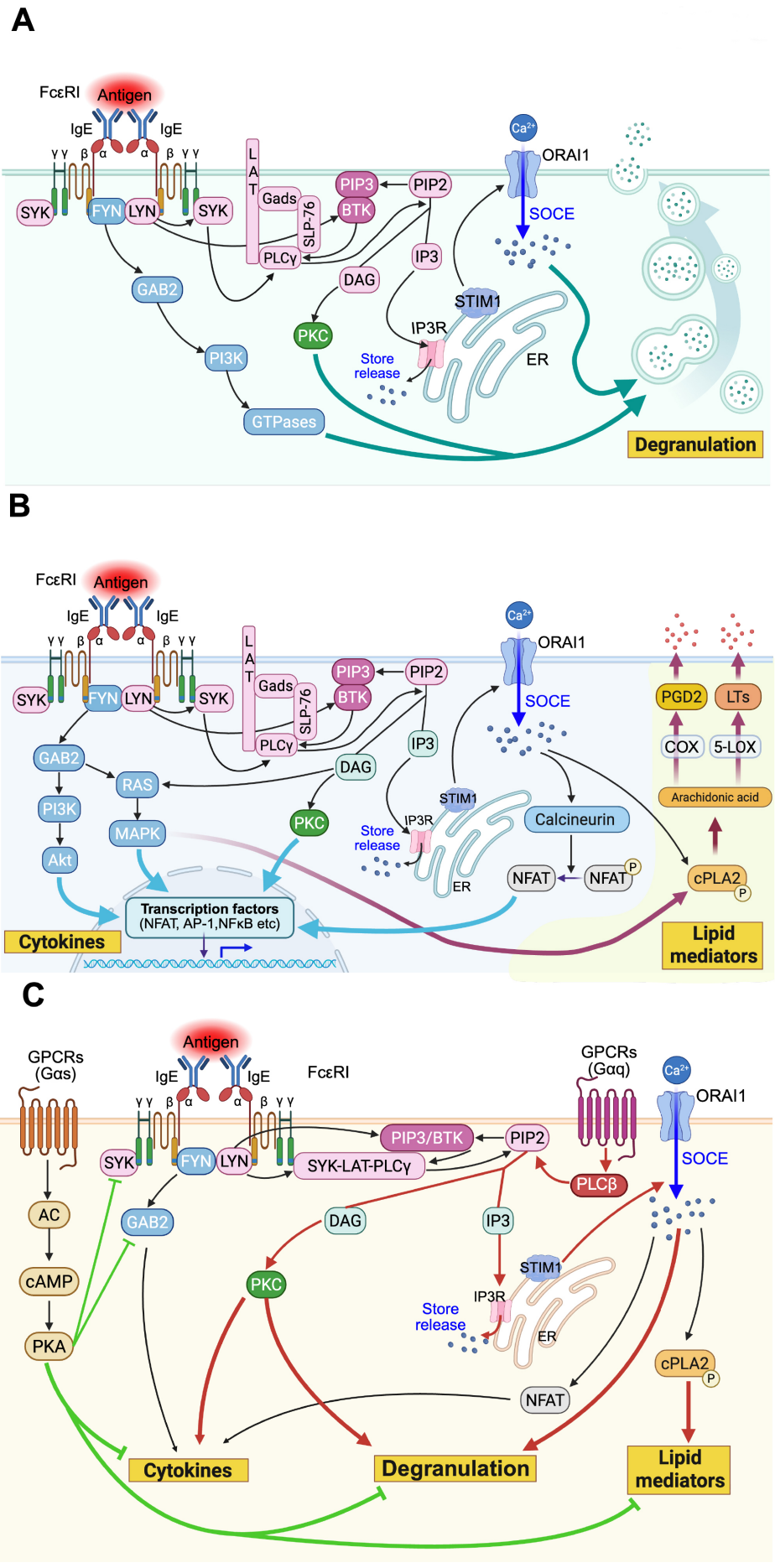
Fig. 1 summarizes shared core signaling pathways downstream of FcεRI and G protein-coupled receptor (GPCR) inputs in mast cells and basophils. To improve clarity, the figure separates the major functional outputs into distinct panels for degranulation, cytokine/eicosanoid production, and GPCR-mediated modulation of FcεRI signaling. When FcεRI is crosslinked by allergen and IgE, the receptor forms microclusters in the plasma membrane and initiates signaling *via* Src family kinases located near the membrane. LYN localizes to the cytoplasmic side of the plasma membrane and is anchored by N-terminal lipid modification. Upon receptor clustering, the spatial proximity and the amplification effect of the β-chain allow LYN to phosphorylate ITAM tyrosines in the β- and γ-chains. Phosphorylated ITAMs in the γ-chain are recognized by the SH2 domains of SYK, leading to its activation. Activated SYK phosphorylates the adaptor molecule linker for activation of T cells (LAT) and promotes formation of the "LAT signalosome", which includes Grb2-related adaptor downstream of Shc (Gads) and SH2 domain-containing leukocyte protein of 76 kDa (SLP-76) [14]. This complex serves as a platform for the recruitment and activation of phospholipase C-γ1/2 (PLCγ1/2). The recruitment of pleckstrin homology (PH) domain-containing proteins, such as Bruton's tyrosine kinase (BTK) further increases PLCγ activity [14]. PLCγ hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to generate inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), and IP3 binds to the IP3 receptor (IP3R) on the endoplasmic reticulum (ER), which induces $Ca^{2+}$ release from ER stores.

ER store depletion is sensed by stromal interaction molecule 1 (STIM1) [60]. STIM1 oligomerizes and accumulates near the plasma membrane, causing the opening of the ORAI1 channel (calcium release-activated calcium channel; CRAC), which leads to sustained $Ca^{2+}$ influx from the extracellular space, referred to as store-operated $Ca^{2+}$ entry (SOCE) [60,61]. This $Ca^{2+}$ influx is a trigger for the membrane fusion steps that are required for degranulation and is also essential for transcriptional responses. The increase in $Ca^{2+}$ concentration activates calcineurin through calmodulin, resulting in the dephosphorylation and nuclear translocation of nuclear factor of activated T cells (NFAT). NFAT cooperates with activator protein 1 (AP-1), which is activated by mitogen-activated protein kinase (MAPK) pathways, and with nuclear factor-κB (NF-κB) pathways activated through protein kinase C (PKC), to promote the transcription of cytokine-encoding genes and induce *de novo* cytokine production [14]. DAG generated by the action of PLCγ activates PKC and Ras guanyl-releasing protein (RasGRP), but principally the extracellular signal-regulated kinase (ERK) pathway, which induces AP-1-dependent transcription. In addition, especially for cytokine-encoding mRNAs containing AU-rich elements, post-transcriptional regulation through p38 MAPK-activated protein kinase 2 (MK2) increases mRNA stability and cytokine production [14]. Furthermore, MAPK activation and the increase in $Ca^{2+}$ concentration also promote lipid mediator synthesis.

Arachidonic acid is essential for eicosanoid synthesis. Cytosolic phospholipase A2 (cPLA2) translocates to membranes, which contain its substrates [14,62,63], a process requiring $Ca^{2+}$-dependent membrane association and the MAPK-dependent phosphorylation of cPLA2. The activated enzyme causes the release of arachidonic acid, which is metabolized by cyclooxygenase (COX) pathways (e.g., prostaglandin D2 and PGD2) and 5-lipoxygenase (5-LOX) pathways (e.g., leukotrienes (LTs)), and these mediators are released in parallel with degranulation as acute-phase mediators [14,63]. Therefore, the LYN–SYK–LAT/PLCγ axis, which has $Ca^{2+}$ signaling (IP3–IP3R–STIM1–ORAI1) as a central component, is a common upstream pathway for degranulation, cytokine production, and eicosanoid production.

In addition to signal initiation, LYN is a negative regulator, as shown by analyses of LYN-deficient mice [64]. LYN promotes the recruitment of inhibitory molecules such as Src homology 2-containing inositol phosphatase 1 (SHIP1), particularly when strongly stimulated, and limits excessive activation of degranulation and cytokine-producing programs by suppressing phosphatidylinositol 3,4,5-trisphosphate (PIP3) signaling. Because of this dual function, the phenotype of LYN-deficient cells, including the up- or downregulation of degranulation and downstream responses, can vary according to the antigen dose, crosslinking strength, and genetic background [64,65,66,67,68]. Thus, LYN is considered to initiate FcεRI responses and also to tune the amplitude and duration of responses through negative feedback when there is overstimulation.

FYN is also an Src-family kinase, but in FcεRI signaling it is thought to act in parallel with the core ITAM-dependent pathway centered on LYN/SYK/LAT and to principally contribute to signal amplification through the GAB2–phosphoinositide 3-kinase (PI3K)–PIP3 axis [67]. GAB2 phosphorylated by FYN recruits PI3K, leading


A
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IP3
DAG
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IP3R
Store release
ER
Calcineurin
NFAT
NFAT
P
PGD2
LTs
COX
5-LOX
Arachidonic acid
cPLA2
P
Transcription factors
(NFAT, AP-1,NFκB etc)
Cytokines
Lipid mediators
C
GPCRs
(Gαs)
Antigen
IgE
IgE
FcεRI
SYK
FYN
LYN
PIP3/BTK
PIP2
SYK-LAT-PLCγ
GPCRs
(Gαq)
PLCβ
Ca2+
ORAI1
SOCE
AC
cAMP
PKA
GAB2
DAG
IP3
PKC
STIM1
IP3R
Store release
ER
NFAT
cPLA2
P
Cytokines
Degranulation
Lipid mediators

**Fig. 1. Shared core signaling pathways downstream of FcεRI and G protein-coupled receptor (GPCR) inputs in mast cells and basophils**. This schematic provides a simplified, function-oriented summary of shared core signaling modules in mast cells and basophils. The major functional outputs are separated into distinct panels to facilitate interpretation of degranulation, cytokine/eicosanoid production, and GPCR-mediated modulation of FcεRI signaling. (A) Shared FcεRI signaling pathway to degranulation. Crosslinking of FcεRI by immunoglobulin E (IgE) and antigen initiates proximal signaling events involving LYN and spleen tyrosine kinase (SYK), which lead to the activation of phospholipase Cγ (PLCγ). The activated PLCγ hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to generate diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 binds to IP3 receptors (IP3Rs) on the endoplasmic reticulum (ER), which triggers the release of $Ca^{2+}$ from ER stores into the cytosol. The depletion of $Ca^{2+}$ in the ER is sensed primarily by stromal interaction molecule 1 (STIM1) (and in some settings, STIM2), which activates $Ca^{2+}$ release-activated $Ca^{2+}$ (CRAC) channels at the plasma membrane (including ORAI1), thereby inducing store-operated $Ca^{2+}$ entry (SOCE). This sustained $Ca^{2+}$ influx triggers granule fusion and exocytosis, resulting in degranulation. (B) Shared FcεRI signaling pathways to cytokine and eicosanoid production. In parallel with the signaling cascade described in (A), SOCE promotes the activation of calcineurin, which dephosphorylates nuclear factor of activated T cells (NFAT) and allows its translocation to the nucleus, where it promotes cytokine gene transcription. FcεRI signaling also activates mitogen-activated protein kinase (MAPK) pathways and nuclear factor-κB (NF-κB), which further support cytokine production. In addition, extracellular signal-regulated kinase (ERK) contributes to the activation of cytosolic phospholipase A2 (cPLA2), thereby promoting arachidonic acid mobilization and eicosanoid production. (C) Shared GPCR-mediated activation pathways and inhibitory pathways that modulate FcεRI signaling. Gαq-coupled GPCRs activate phospholipase Cβ (PLCβ) after ligand binding, leading to the production of IP3 and DAG. Through this pathway, Gαq-coupled receptors can induce or enhance degranulation, cytokine production, and eicosanoid synthesis, partly *via* signaling modules that overlap with FcεRI downstream pathways. In contrast, Gαs-coupled GPCRs activate adenylyl cyclase (AC) and increase the intracellular cyclic AMP (cAMP) concentration. cAMP-dependent protein kinase A (PKA) is thought to suppress proximal FcεRI signaling (including Lyn/Syk- and Fyn-associated pathways), as well as downstream MAPK and NF-κB signaling, thereby reducing cytokine production and eicosanoid synthesis, and in many contexts, attenuating degranulation. (A) was created in BioRender.com. Yoshikawa, S. (2026) https://BioRender.com/izzto4h; (B) was created in BioRender. Yoshikawa, S. (2026) https://BioRender.com/y2egdi0; (C) was created in BioRender. Yoshikawa, S. (2026) https://BioRender.com/5nfvd24.

to the activation of Bruton's tyrosine kinase (BTK), 3-phosphoinositide-dependent kinase 1 (PDK1), and protein kinase B (AKT), which increases PLCγ activity and thereby IP3 production, SOCE, and NFAT activation [67]. In addition, PIP3 generated by the action of PI3K promotes the activation of Rho family GTPases and enhances degranulation by increasing the efficiency of granule transport, docking, and membrane fusion through cytoskeletal remodeling [2]. PI3K–AKT signaling also crosstalks with NF-κB and mechanistic target of rapamycin (mTOR) pathways, and increases cytokine production through transcriptional and post-transcriptional mechanisms, as well as through effects on translation and metabolism [69,70]. The PI3K–AKT–mTOR axis is also of therapeutic interest because it integrates signaling programs that regulate immune and inflammatory responses [71,72,73]. Taking these findings together, FcεRI signaling through FYN is thought to complement LYN-dependent signaling and to play a modulatory role in the overall response.

IL-3 is a major activator of basophils. In mouse basophils, the common β-chain (βc) of the IL-3 receptor has been reported to associate with the FcεRI γ-chain (FcRγ), and signaling through the ITAM of FcRγ is essential for IL-3-induced IL-4 production [74]. In addition, the production of IL-4/IL-13 in response to innate immunity-type stimuli, such as protease allergens, including papain and alarmins such as IL-33, is also much lower in FcRγ-deficient basophils, suggesting that, at least in mice, cytokine production in response to multiple innate immunity-like stimuli can be FcRγ-dependent [36]. However, basophil responses to innate stimuli may not always converge on a single pathway, and the contributions of Syk-dependent pathways and NF-κB-dependent pathways may vary with the type and strength of the stimulus [38]. Although the downstream signaling is not fully understood, IL-3 and some innate stimuli often induce the transcription of cytokine-encoding genes without the massive degranulation that typically occurs after IgE-dependent antigen crosslinking. Interestingly, $Ca^{2+}$ influx from the extracellular space is required for IL-3-induced IL-4 production, but whereas IgE-dependent FcεRI stimulation mainly involves STIM1-dependent SOCE, the stimulation by IL-3 has been reported to be more dependent on STIM2 [75]. These findings suggest that, in basophils, FcRγ-dependent signaling modules may contribute not only to IgE-dependent responses, but also to IL-3-driven and innate-like cytokine responses. They also suggest that switching the mode of $Ca^{2+}$ signaling, such as between STIM1-dominant and STIM2-dominant signaling, may favor cytokine production rather than degranulation.

Many pathways suppress FcεRI signaling, and the inhibitory circuit mediated by GPCRs, adenylyl cyclase (AC), and cyclic AMP (cAMP) has been studied in detail. When a ligand binds to a Gαs-coupled GPCR, AC is activated and catalyzes the synthesis of cAMP, which then

suppresses FcεRI responses at multiple levels, from proximal signaling to downstream effector programs [76,77,78]. cAMP principally activates protein kinase A (PKA), which reduces Src family kinase-dependent signal initiation, including the phosphorylation of ITAMs, thereby dampening signal propagation along the SYK–LAT axis. This also reduces activation of the parallel FYN–Gab2–PI3K pathway and blunts the amplification of FcεRI signaling. In addition, phosphoinositide phosphatases can further attenuate PIP3 signaling, leading to less membrane recruitment and activation of BTK, and lower PLCγ activity, IP3 production, and SOCE. As a result, the amplitude and duration of the increase in $Ca^{2+}$ concentration become insufficient for the membrane fusion and exocytosis that is required for degranulation, and the calcineurin-dependent activation of NFAT is also dampened. PKA also reduces MAPK activation and can reduce NF-κB-dependent transcripts, thereby reducing cytokine production after FcεRI stimulation. Furthermore, the cAMP–PKA axis phosphorylates cAMP response element-binding protein (CREB) and induces repressors such as inducible cAMP early repressor (ICER), which may contribute to the suppression of cytokine gene expression [79].

In contrast to Gαs-coupled GPCRs, GPCRs that signal through the Gαq subunit generally promote mast cell and basophil activation. Upon ligand binding, Gαq activates PLCβ, leading to the hydrolysis of phosphatidylinositol 4,5-bisphosphate and the generation of IP3 and DAG [78,80,81]. Through IP3- and DAG-mediated signaling, Gαq-coupled GPCRs activate $Ca^{2+}$- and PKC-dependent pathways, which substantially overlap with those downstream of FcεRI, leading to mast cell degranulation and cytokine production [76]. Gαq-mediated GPCR signaling integrates with pathways downstream of FcεRI and can either augment FcεRI-dependent responses or act as an alternative activation route, particularly with respect to the IgE-independent mast cell activation that is induced by neuropeptides and basic secretagogues. In this context, Gαq-coupled GPCRs are part of a major activating pathway that complements FcεRI-mediated activation and counterbalances Gαs-dependent inhibitory signaling to regulate mast cell and basophil effector functions.

## 4. Neuroreceptor Expression Profiles in Mast Cells and Basophils

In both mice and humans, the central nervous system (CNS) has been regarded as an immune-privileged site. Under steady state conditions, immune cells are scarce in the CNS parenchyma, with the exception of resident macrophage lineage cells, such as microglia [82,83,84]. Immune cells can also be found in CNS-associated compartments, such as the meninges, choroid plexus, and perivascular spaces [82]. In contrast, in the peripheral nervous system, a broad range of immune cells are present and interact with each other, and this also applies to mast cells and basophils. The peripheral nervous system consists of autonomic, motor, and sensory nerves. Of these, sensory neurons have long been appreciated to reside in close proximity to immune cells in many tissues [12,85]. Specifically, in humans, histological studies have shown that mast cells are located near nerve fibers in the skin, lung, and gastrointestinal tract. Electron microscopy studies have further suggested the possibility that there is direct membrane apposition between mast cells and nerve fibers [86]. In mice, the colocalization of mast cells and nerve fibers has been reported in tissues such as the skin. Moreover, in a model of skin allergy induced by MC903 and OVA, basophils were observed to be in contact with nerve fibers at sites of inflammation [87]. Collectively, these observations raise the possibility that mast cells and basophils release mediators that stimulate nerves. They also suggest that nerve-derived factors may modulate mast cell and basophil responses. Indeed, mast cells and basophils express a variety of receptors that respond to neuronally derived molecules. Many studies have shown that these receptors influence immune cell activation and function (Table 1, Ref. [88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128]).

Neuron-related receptors in mast cells and basophils can be broadly grouped into three categories. The first category comprises receptors that directly activate these cells and induce degranulation and/or cytokine production, such as MRGPRX2 and P2X receptors. The second category comprises receptors that tune immune activation pathways, such as FcεRI signaling. This category includes β2-adrenergic receptor (ADRB2) and cholinergic receptors, which can enhance or suppress FcεRI-driven responses, according to the context. The third category comprises receptors that modulate cell positioning and migration within tissues. This category includes specific purinergic receptors, principally P2Y receptors. Some of these receptors principally regulate a single process, whereas others contribute to the regulation of multiple processes.

## 5. Regulation of Mast Cells and Basophils by Psychological Stress

Psychological stress is widely recognized to contribute to the initiation and exacerbation of various diseases, such as asthma, atopic dermatitis, and some autoimmune diseases [8,129,130]. In the immune system, stress has been shown to influence cellular functions, differentiation states, and the activation thresholds of multiple immune cell types [131]. Psychological stress primarily influences the hypothalamus, which triggers activation of the hypothalamic–pituitary–adrenal (HPA) axis, as well as an increase in activity of the sympathetic nervous system. This neuroendocrine response leads to the release of stress hormones and stress-associated neuromediators that act on peripheral organs to

**Table 1. Receptors for neural, neuroendocrine, and endocrine ligands expressed by mast cells and basophils.**

| Target cell | Neural or endocrine source of ligand | | Receptor/pathway | Expression evidence (mRNA/protein/functional) | Ligand(s) | Species | Reported immune-cell effect | References |
|---|---|---|---|---|---|---|---|---|
| Mast cell | Hypothalamic–pituitary–adrenal (HPA)-axis | Hypothalamus | CRHR1/CRHR2 (corticotropin-releasing hormone receptors) | mRNA; Protein; Functional | Corticotropin-releasing hormone (CRH); urocortin | Human; Mouse; Rat | CRH/urocortin can activate mast cells (degranulation, vascular permeability) and promote mediator release such as vascular endothelial growth factor (VEGF); CRHR2 can also limit stress-induced degranulation in some settings | [96,97,98,110] |
| | | Anterior pituitary | Melanocortin receptor (MC1R) | mRNA; Protein; Functional | adrenocorticotropic hormone (ACTH); α-melanocyte-stimulating hormone (α-MSH) | Mouse | MC1R expression reported in mast cells; melanocortin signaling can modulate mediator release depending on model and activation context | [93] |
| | | Adrenal cortex | Glucocorticoid receptor (NR3C1/GR) | Protein; Functional | Glucocorticoids (e.g., cortisol/corticosterone; dexamethasone) | Human; Mouse | Glucocorticoids directly suppress mast-cell activation programs (notably cytokine production, FcεRI expression and interleukin (IL)-33-driven responses) | [88,89,111] |
| | Autonomic nervous systems | Sympathetic nerve; Adrenal medulla | β2 adrenergic receptor (ADRB2) | Protein; Functional | Epinephrine, norepinephrine, isoproterenol (β2-agonists) | Human | Inhibits FcεRI-mediated mediator release (e.g., histamine) | [99] |
| | | Parasympathetic nerve | Muscarinic acetylcholine receptor M3 (CHRM3) | mRNA; Protein; Functional | Acetylcholine, methacholine | Human; Mouse | Induces serotonin (5-HT) release from lung mast cells; contributes to allergic airway responses | [101] |
| | | | Nicotinic acetylcholine receptors (nAChRs) | mRNA; Functional | Acetylcholine, nicotine | Mouse and human | Negative regulation of IgE-mediated degranulation | [102] |
| | | | Vasoactive intestinal peptide receptors (VIP receptor 1/VPAC1, VIPR1; VIP receptor 2/VPAC2, VIPR2) | Protein; Functional | Vasoactive intestinal peptide (VIP) PACAP-38 | Human | Modulates mast cell activation and mediator production Rapid activation/degranulation *via* MRGPRX2 pathway | [105,112] |
| | Central and peripheral nervous systems | Nociceptive sensory neurons (C-fiber) | Mas-related G protein-coupled receptor X2 (MRGPRX2; murine ortholog MrgprB2) | mRNA; Protein; Functional | Substance P, LL-37, compound 48/80 (and other cationic ligands) | Human; Mouse | IgE-independent activation/degranulation; pseudo-allergic reactions; neurogenic inflammation | [113,114] |
| | | | Neurokinin-1 receptor (NK1 receptor); tachykinin receptor 1 (TACR1) | mRNA; Protein; Functional | Substance P | Human | Substance P-induced activation and mediator production | [105,106,107] |
| | | Hypothalamic neurons; enteroendocrine cells; sensory neurons | Putative neuromedin U receptor 1 (NMUR1) (NMU may also act through MrgprB2) | Functional | Neuromedin U (NMU) | Human; Mouse | Direct degranulation/activation of skin mast cells | [108] |
| | | Hypothalamic neurons; intestinal endocrine (N) cells | Neurotensin receptor 1 (NTSR1) | mRNA; Protein; Functional | Neurotensin | Human | Induces mast cell activation and pro-angiogenic mediator release (e.g., VEGF) | [92] |

**Table 1. Continued.**

| Target cell | Neural or endocrine source of ligand | | Receptor/pathway | Expression evidence (mRNA/protein/functional) | Ligand(s) | Species | Reported immune-cell effect | References |
|---|---|---|---|---|---|---|---|---|
| | | Dopaminergic neurons (substantia nigra, ventral tegmental area) | Dopamine receptor (D1-like receptor) | Functional | Dopamine | Mouse | Dopamine can modulate immediate hypersensitivity with mast cell degranulation | [115] |
| | Multiple tissues | Neurons; endothelial cells; immune cells | Adenosine receptor A3 (ADORA3) | mRNA; Protein; Functional | Adenosine | Human; Mouse | Facilitates mast cell degranulation/chemotaxis | [116,117,118,119] |
| | | | Adenosine receptor A2B (ADORA2B) | mRNA; Protein; Functional | Adenosine | Human; Mouse | Drives cytokine production and can potentiate inflammatory outputs | [120,121,122] |
| | | Neurons; epithelial cells; immune cells; damaged cells | P2X purinoceptor 7 (P2RX7) | mRNA; Protein; Functional | Adenosine triphosphate (ATP) | Human; Mouse | ATP amplifies activation of mast cells and promotes chronic allergic inflammation | [123,124] |
| | | | P2Y purinoceptor 14 (P2RY14) | mRNA; Protein; Functional | UDP-glucose (and related UDP-sugars) | Human; Mouse | Modulates mast cell activation and mediator production | [125,126] |
| Basophil | HPA-axis | Hypothalamus | CRHR1/CRHR2 | mRNA; Protein | Urocortin 1–3; CRH | Human (KU812 basophil cell line) | Expression of CRHR1/CRHR2 and urocortins reported in KU812 cells | [94] |
| | | Anterior pituitary | MC1R | Protein; Functional (primary basophils), mRNA; Protein (cell line) | α-MSH; ACTH (melanocortins) | Human | α-MSH can suppress human primary basophil activation responses; MC1R expression also reported in KU812 basophils | [94,95] |
| | | Adrenal cortex | NR3C1/GR | Functional | Glucocorticoids (e.g., cortisol; dexamethasone; hydrocortisone) | Human | Glucocorticoids inhibit IgE-dependent basophil activation, including histamine release and IL-4 production, *via* glucocorticoid receptor-dependent mechanisms | [90,91] |
| | Autonomic nerve | Sympathetic nerve; Adrenal medulla | ADRB2 | Functional | Isoproterenol; β2-agonists (e.g., fenoterol) | Human | Suppresses IgE-mediated basophil mediator release (e.g., histamine) | [100] |
| | | Parasympathetic nerve; Motor neuron | CHRM3 | mRNA; Functional | Acetylcholine | Human; Mouse | Tiotropium (M3 antagonist) suppresses IL-33-driven IL-4 in basophils and reduces allergic inflammation | [103] |
| | | | Nicotinic and muscarinic acetylcholine receptors | Functional | ASM-024 (nicotinic receptor ligand) | Human | Inhibits allergen-induced basophil activation | [104] |
| | Central and peripheral nervous systems | Nociceptive sensory neurons (C-fiber) | Substance P receptor neurokinin-1 receptor (NK1R/TACR1) | Protein; Functional | Substance P | Human | Substance P can activate basophils *via* NK1R, enhancing effector functions | [109] |
| | Multiple tissues | Neurons; endothelial cells; immune cells | A2-type adenosine receptor signaling (cAMP-linked; pharmacologic classification) | Functional | Adenosine | Human | Adenosine inhibits histamine release | [127] |
| | | Neurons; epithelial cells; immune cells; damaged cells | P2X7 | Functional | ATP | Mouse | ATP amplifies activation of basophils and promotes chronic allergic inflammation | [128] |

induce the classic fight-or-flight response, characterized by increases in blood pressure, heart rate, and metabolic activity [132,133]. Importantly, immune cells, including mast cells and basophils, express receptors for many of these stress-associated hormones and neuromediators, which enable direct communication between the nervous, endocrine, and immune systems (Table 1). Through these pathways, psychological stress can modulate immune cell activation and their effector functions, thereby altering inflammatory responses.

### *5.1 HPA Axis-Related Stress Hormones*

#### 5.1.1 Glucocorticoids (GCs)

Of the stress-related hormones, GCs are the best studied in the context of immune regulation. GCs show circadian variation, and under stress their secretion from the adrenal cortex increases, in response to activation of the HPA axis [134,135]. GCs bind to the intracellular glucocorticoid receptor (GR/GRα/NR3C1). After ligand binding, GR translocates to the nucleus and regulates transcription by binding to glucocorticoid response elements (GREs) and interacting with other transcription factors [134,135]. At pharmacological concentrations, GCs can also trigger apoptosis, and because of their strong immunosuppressive activity, they have long been used as anti-inflammatory agents. In mice, corticosterone is the major endogenous GC, because its steroid 17α-hydroxylase activity is minimal, and corticosterone also has effects *via* GR [134,135,136].

In human mast cells, dexamethasone (Dex) has been reported to ameliorate the features of mast cell maturation and to reduce surface FcεRI expression, which is associated with lower cytokine and chemokine production (TNF-α, MCP-1, and GM-CSF) after IgE-dependent stimulation [88,137]. Dex also suppresses IL-33-induced cytokine and chemokine (TNF-α and MCP-1) production, and inhibitory effects on mast cell activation have been described in multiple settings [89]. In contrast, the effects of Dex on histamine release and degranulation are less consistent than its suppressive effects on cytokine production. Both responses and a lack of response to Dex have been reported, and previous studies have not shown a strong suppression of acute histamine release [138,139]. In human basophils, Dex robustly suppresses FcεRI crosslinking-induced IL-4 production and histamine release [90,91,140]. Notably, Dex does not necessarily reduce surface FcεRI expression in basophils, suggesting that its inhibitory effect cannot be explained simply by a reduction in receptor availability [141]. Although the magnitude of the inhibition may also depend on the experimental conditions, these observations imply that additional mechanisms downstream of FcεRI contribute to the GC-mediated suppression of basophil activity. Dex has also been shown to suppress mast cell activation through GR-dependent mechanisms in mouse cells *in vitro*, but there have been few studies of mouse basophils [89,142]. Nevertheless, because systemic GC treatment attenuates basophil-dependent IgE-mediated cutaneous allergic inflammation *in vivo*, it is reasonable to hypothesize that FcεRI-driven basophil responses can also be suppressed by GCs in mice [143].

#### 5.1.2 Adrenocorticotropic Hormone (ACTH)

ACTH, a pituitary peptide hormone that drives GC production, has also been reported to act on mast cells and basophils. The canonical ACTH receptor for adrenal steroidogenesis is melanocortin receptor 2 (MC2R), but immune cells do not typically express MC2R at high levels [144]. Instead, mast cells and basophils have been reported to express melanocortin receptor 1 (MC1R) [92,93,94,95,145]. In mouse mast cells, MC1R expression is under the control of microphthalmia-associated transcription factor (MITF), as shown by analyses in MITF-deficient models [145]. MC1R is best known as a receptor for α-melanocyte-stimulating hormone (α-MSH), but ACTH can also bind to MC1R as a noncanonical ligand [146]. In mouse mast cells, α-MSH has been shown to suppress IgE/antigen-induced histamine release and cytokine production through MC1R [93]. In contrast, direct functional evidence for effects of ACTH in primary human or mouse mast cells is limited. Because MC1R is a Gαs-coupled receptor that activates AC and increases the intracellular cAMP concentration, ACTH would be expected to have similar effects to α-MSH and to cause suppression rather than acute activation. In human basophils, MC1R expression has also been demonstrated at the protein level. In functional assays, α-MSH has been shown to suppress the upregulation of the degranulation-associated marker CD63 and to reduce IgE/antigen-, fMLP-, or PMA-stimulated IL-4 and IL-13 production [94,95].

#### 5.1.3 Corticotropin-Releasing Hormone (CRH)

CRH, which lies upstream of ACTH, is released by hypothalamic neurons, but is also produced in peripheral tissues, including barrier tissues such as skin and hair follicles, as well as by certain immune cells [147]. CRH receptors are seven-transmembrane GPCRs, and two subtypes, CRHR1 and CRHR2, have been identified. CRHRs are classically described as Gαs-coupled receptors that increase the intracellular cAMP concentration after ligand binding [147]. However, it has been reported that CRHR signaling does not necessarily only negatively regulate mast cell activation.

Depending on the experimental system, both CRHR1 and CRHR2 expression has been reported in human and rodent mast cells [96,97]. *In vivo*, intradermal CRH administration in mice or rats increases vascular permeability in a mast cell- and CRHR1-dependent manner, and histamine has been suggested to contribute to this response [98]. In contrast, *in vitro* studies have shown that CRH or urocortin stimulation alone does not potently induce mast cell degranulation, but does increase vascular endothelial

growth factor (VEGF) production in a cAMP-dependent manner [96]. Because VEGF promotes vascular leakage and amplifies inflammatory responses, CRH signaling may increase susceptibility to local allergic reactions *via* mast cell CRH receptors [148,149]. Genetic studies have further supported distinct roles of CRHR1 and CRHR2 in the modulation of FcεRI-driven effector function. IgE-mediated systemic anaphylaxis is attenuated in mast cell-deficient *Kit*$^{W\text{-}sh/W\text{-}sh}$ mice that have been transplanted with CRHR1-deficient bone marrow-derived mast cells (BMMCs), and these CRHR1-deficient BMMCs exhibit lower SOCE and less degranulation after IgE/allergen stimulation [150]. In contrast, IgE-mediated systemic anaphylaxis is upregulated in CRHR2-deficient mice, and CRHR2-deficient BMMCs show higher expression of SOCE-related molecules (including STIM1 and ORAI1), more SOCE, and greater degranulation upon IgE/allergen stimulation [97]. Together, these observations support a model in which CRHR1 enhances, whereas CRHR2 suppresses, FcεRI-dependent mast cell activation, thereby fine-tuning downstream effector responses.

In basophils, the current evidence is limited to the detection of CRH receptor transcripts in the human basophil-like cell line KU812, and therefore the functional relevance of CRHR signaling in basophils remains unknown [94].

### *5.2 Autonomic Nervous System*

#### 5.2.1 Catecholamines (Epinephrine and Norepinephrine)

Epinephrine and norepinephrine bind to members of the same receptor families. Their receptors are seven-transmembrane GPCRs of five subtypes: the α-adrenergic receptors α1 and α2, and the β-adrenergic receptors (β1, β2, and β3) [151]. In general, α1-adrenergic receptors couple to Gαq, activate PLC, and promote intracellular $Ca^{2+}$ mobilization, whereas α2-adrenergic receptors couple to Gαi and reduce the intracellular cAMP concentration [151,152]. In contrast, β-adrenergic receptors couple to Gαs and increase the intracellular cAMP concentration [151,153].

The expression of the β2-adrenergic receptor (ADRB2) in mast cells has been reported, and functional studies have been performed, in particular using human lung-derived mast cells [99,154,155,156,157,158]. Pharmacological analyses using β-agonists have indicated that ADRB2 signaling suppresses the IgE/antigen-induced release of mediators, including histamine, cytokines (TNF-α), and lipid mediators (prostaglandin D2, PGD2, and cysteinyl leukotrienes (cysLTs)), and this suppression is associated with an increase in intracellular cAMP concentration [99]. In contrast, β1- or β3-selective agonists do not induce clear suppression of mediator release, suggesting that there are low or insignificant levels of β1 and β3 signaling in mast cells under these conditions [157]. Interestingly, mouse mast cells deficient in Adrb2 show less IgE/antigen-induced SOCE, which is accompanied by less degranulation and cytokine production, even in the absence of exogenous β-agonists [159]. Because the ligand-independent modulation of ADRB2 signaling has been described in other cell types [160,161,162], such as cardiomyocytes, these findings may imply that ADRB2 can modulate FcεRI signaling in mouse mast cells in a ligand-independent manner.

In human basophils, ADRB2 signaling has also been reported to suppress IgE/antigen-induced histamine release and cytokine production (IL-4 and IL-13), in association with an increase in intracellular cAMP concentration, although in one study, the β2-agonist salbutamol did not show a clear inhibitory effect under the experimental conditions used [100,163,164].

#### 5.2.2 Acetylcholine

Acetylcholine is a classical neurotransmitter that is principally produced by motor neurons and enteric neurons, as well as by preganglionic sympathetic neurons and parasympathetic neurons (both preganglionic and postganglionic). In the body, acetylcholine is rapidly hydrolyzed by abundant cholinesterases, including acetylcholinesterase, and therefore it has a short half-life in extracellular spaces [165]. Acetylcholine receptors are broadly classified into muscarinic receptors (mAChRs) and nicotinic receptors (nAChRs). Five muscarinic receptor subtypes (M1 to M5) have been identified, whereas nAChRs are assembled as pentamers from 17 subunits (α1–α10, β1–β4, δ, ε, and γ), which permits a wide variety of receptor compositions and functional diversity [166].

The expression of muscarinic receptor M3 (CHRM3) has been reported in mouse lung mast cells and in the human mast cell line LAD2 [101]. Methacholine induces calcium influx in these cells and promotes degranulation, resulting in serotonin release, which has been implicated in house dust mite (HDM)-induced airway obstruction *in vivo* [101]. In addition, mouse mast cells have been reported to express the nAChR α7 subunit (CHRNA7). Acetylcholine, nicotine, and α7-selective agonists can suppress IgE/antigen-induced degranulation, assessed by measuring β-hexosaminidase release [102]. In addition, in rat basophilic leukemia (RBL) cells, which are a widely used mast cell model, nicotine suppresses IgE/antigen-induced cytokine production (TNF-α and IL-1β) and lipid mediator generation (LTC4), whereas its effects on degranulation (β-hexosaminidase and histamine release) are limited. Knockdown analyses have suggested the involvement of the nAChR subunits α7, α9, and α10 in these inhibitory effects [167].

High CHRM3 expression has also been reported in mouse basophils. Treatment with tiotropium bromide, a long-acting M3 antagonist, reduces the IL-33-induced production of IL-4, suggesting that CHRM3 signaling may facilitate basophil activation [103]. However, it remained unclear in this study whether an endogenous CHRM3 agonist was required under the tested conditions [103]. In hu-

man peripheral blood basophils, the expression of several nicotinic receptor subunits, including α4 and α7, as well as α1/α3/α5-related subunits, has been reported [104]. In addition, the nicotinic agonist ASM-024 suppresses FcεRI crosslinking-induced histamine release [104]. Taken together, these findings suggest that, even for the same ligand, acetylcholine-related signals can have markedly different effects in mast cells and basophils, depending on the receptor subtype engaged [101,102,103,104,167].

#### 5.2.3 Vasoactive Intestinal Peptide (VIP)

VIP is abundantly expressed in peripheral neurons, including enteric neurons and parasympathetic postganglionic fibers, and it can also be produced in some non-neuronal compartments. Three common, closely related receptors are involved in VIP and PACAP signaling, namely VPAC1, VPAC2, and PAC1 [168]. VPAC2 expression has been reported in human mast cells, including primary cells and mast cell lines. Previous studies have shown that VIP alone can induce degranulation (β-hexosaminidase release and histamine release) and promote cytokine (TNF-α, IL-3, and GM-CSF) and chemokine (IP-10, RANTES, IL-8, MCP-1, and MIG) production [105,169]. Recent findings suggest that VIP-induced degranulation is confined to a subset of human mast cells expressing MRGPRX2 (MrgprB2), raising the possibility that MRGPRX2 may also serve as a functional receptor for VIP in mast cells [169]. In contrast, there have been few studies of VIP in basophils, and the nature of its receptor expression and effects have not been well defined.

Overall, autonomic nervous system-related neurotransmitters and neuropeptides often modulate mast cell and basophil responses, and are frequently inhibitory, although acetylcholine and VIP can also increase the level of activation of these cells, depending on which receptor subtype is engaged. Therefore, these mediator systems may contribute to the adjustment of immune responses according to the psychological state and the presence or absence of specific environmental factors.

## 6. Bidirectional Crosstalk Between Mast Cells/Basophils and Sensory Neurons

### *6.1 Regulation of Mast Cells and Basophils by Sensory Neurons*

Sensory neurons can release a range of neuropeptides, including substance P, neurokinin A (NKA), neuromedin U (NMU), CGRP, and neuropeptide Y (NPY), although NPY is more important in the context of sympathetic neurotransmission. Many of these mediators have been reported to activate mast cells, and similar effects on basophils have been shown in a limited number of studies [170].

Among the receptors implicated in neuropeptide-induced mast cell activation, MRGPRX2 (MrgprB2) is widely recognized to be a GPCR with broad ligand responsiveness [17]. Upon ligand binding, MRGPRX2 couples to Gαq/11, activates PLC, and induces intracellular $Ca^{2+}$ mobilization and entry, thereby triggering substantial degranulation [17,76]. Substance P is a potent stimulus for degranulation in this context, and MRGPRX2-dependent induction of cytokine (TNF-α, GM-CSF, and IL-3) and chemokine (e.g., MCP-1, IL-8/CXCL8, and RANTES) production has also been reported [105,106,107]. In parallel, several studies have shown that classical receptors, such as the substance P receptor neurokinin-1 receptor (NK1R/TACR1), the NMU receptor NMUR1, and VIP receptors (VPAC1/VPAC2), may contribute to mast cell activation, and in some settings, degranulation [105,171]. Because the outcome depends on the cell type, agonist concentration, and experimental setup, the relative contribution of each pathway has yet to be fully resolved. This issue may be addressed by evaluating the responses in receptor-targeting knockdown systems and in relevant knockout models. It is also worth noting that BMMCs, which are frequently used in mouse studies, represent relatively immature mast cells. One study has shown that MrgprB2 expression is much lower in BMMCs than in mature CTMCs, which can make BMMCs less responsive to substance P or NMU under certain conditions [108]. These observations support the idea that MrgprB2 expression is acquired or increases during mast cell maturation in tissues [108].

The situation for CGRP appears to differ from those for the neuropeptides discussed above. The canonical CGRP receptor is composed of the calcitonin receptor-like receptor (CLR/CALCRL) and receptor activity-modifying protein 1 (RAMP1), and is generally referred to as a Gαs-coupled GPCR [172]. *In vivo* studies have shown the close apposition of CGRP-positive nerve fibers and mast cells, and suggested that exogenous CGRP can induce mast cell degranulation and vasodilation, depending on the experimental conditions [173]. In contrast, direct *in vitro* evidence that CGRP alone robustly activates mast cells is limited and appears to depend on the mast cell subtype and experimental conditions. Although CGRP has been reported to induce degranulation or mediator release from murine mucosal mast cells, other studies have observed little or no degranulation following CGRP stimulation alone [105,174]. Thus, although further work is needed, CGRP may contribute to neurogenic inflammation through both direct and indirect mechanisms. However, its direct effects on mast cells appear to be less consistent and may differ from the robust activation induced by substance P.

Studies of transcriptomic resources, such as the Immunological Genome Project, has suggested that *MrgprB2* expression is extremely low in mouse basophils. In contrast, MRGPRX2 expression has been detected in a subset of human peripheral blood basophils, and its expression has been reported to increase after allergen or IL-3 stimulation. Consistent with this, ciprofloxacin increases the cell surface expression of CD63, suggesting that functional MRGPRX2 responses may occur in human basophils [175]. Moreover,

in patients with chronic spontaneous urticaria (CSU), the increase in the fraction of peripheral blood basophils has been reported to be associated with the expression of substance P and NK1R, and substance P has been shown to induce histamine release under these experimental conditions [109]. Similar findings have also been made in sensitized mouse models, in which NK1R expression in basophils appears to be induced in the presence of sensitization, potentially enabling these cells to respond to substance P and undergo degranulation [176]. There is little primary evidence available regarding the functional significance of other sensory neuropeptides in basophils.

### *6.2 Effects of Mast Cell- and Basophil-Derived Mediators on Sensory Neurons*

For decades, immune cell-derived mediators have been considered to be key drivers of inflammatory symptoms, such as cough, itch, pain, mucus hypersecretion, and greater vascular permeability, in part through direct actions on peripheral neurons. In line with this concept, sensory neurons express receptors for multiple immune mediators [12,177]. In addition to causing pruritus and pain-like sensory outputs, the histamine, lipid mediators, and proteases released by mast cells and basophils influence afferent nerves in the airways and gastrointestinal tract, modulating reflex responses and local neurovascular reactions, including cough and vasodilation [87,177,178,179]. With the advent of genetically engineered mice and improvements in analytical methods, these neuroimmune mechanisms are being defined more clearly. Of the various immune effector cells, mast cells and basophils are central players in allergic responses and are closely linked to pruritus (Fig. 2).

Itch is detected by specialized sensory neurons whose cell bodies reside in the dorsal root ganglion (DRG) and trigeminal ganglion (TG). Recently developed transcriptomic approaches have begun to delineate pruriceptor subsets. A classical reference is the mouse DRG single-cell RNA-seq study by Usoskin and colleagues [19], in which they proposed that non-peptidergic (NP) clusters, including NP1 (Mrgprd$^{+}$ non-peptidergic neurons), NP2 (MrgprA3$^{+}$ pruriceptors, chloroquine-responsive), and NP3 (Sst$^{+}$ pruriceptor-like neurons) are the mediators of itch transmission. The classification of human pruriceptors has been debated, but in a recent study, Yu and colleagues [180] analyzed neuronal somatic transcriptomes obtained by laser capture microdissection from frozen sections using Smart-seq2, and proposed the pruriceptor-related categories hNP1 (MRGPRX1$^{high}$, HRH1$^{high}$), hNP2 (MRGPRX1$^{high}$, HRH1$^{high}$, with an MRGPRX4$^{+}$ subset), and hSST (SST$^{+}$, corresponding to mouse/macaque NP3). In general terms, NP1-like neurons can function as nociceptors and may also participate in itch, depending on experimental conditions, whereas NP2-like neurons are often regarded as canonical pruriceptors, which detect chemical itch [19]. Multiple cytokines and lipid mediators that have been implicated in allergy can act on these neuronal subsets. NP2 neurons have been reported to express receptors for TSLP and type 2 cytokines, such as IL-4 and IL-13, and can transmit itch evoked by these cytokines, as well as by pruritogens such as chloroquine [19,181,182]. NP3/hSST neurons are thought to contribute to inflammatory or chronic itch and have been shown to be associated with receptors for IL-31 and leukotrienes (e.g., CysLT2R) [19,87,183,184]. TSLP and IL-31 can directly activate defined neuronal populations and induce acute itch [37,183,185,186]. In contrast, IL-4 and IL-13 are well known to sensitize sensory neurons. When these cytokines act directly on neurons, JAK1-dependent signaling increases itch responsiveness and promotes a “sensitized” state, and the pharmacological or genetic inhibition of neuronal JAK signaling has been reported to markedly ameliorate atopic dermatitis-associated itch in mice and humans [182].

Basophils have been identified in the inflamed skin lesions associated with atopic dermatitis [187] and are potent producers of IL-4 (and, depending on the conditions, IL-13). These features support the idea that basophils can contribute to itch by modulating the local cytokine milieu [177,182,188]. In addition, basophil-derived LTC4 has been reported to evoke itch by activating pruriceptive sensory neurons *via* CysLT2R in the MC903-induced model of allergic skin inflammation in mice [87]. Basophil-derived IL-4 can also promote the expression of M2-like macrophage programs and amplify Th2 differentiation [48]. Because these downstream cell types have been reported to produce IL-31 [189], basophils may also indirectly influence IL-31-dependent itch. Mast cells and basophils store histamine in cytoplasmic granules, and when it is released upon FcεRI crosslinking or the activation of IgE-independent pathways such as MRGPRX2 signaling, histamine directly activates H1R-expressing sensory neurons, induces $Ca^{2+}$ influx, and triggers itch [190,191,192]. Histamine is a canonical mast cell/basophil-derived pruritogen. However, in inflamed skin, the activation of non-histaminergic pathways can predominate, and itch exacerbations may be maintained by cytokines and lipid mediators, rather than by histamine alone [177,193]. In addition, mast cell proteases such as tryptase may activate protease-activated receptors (e.g., PAR2) on sensory neurons, leading to neuronal excitation and potentially contributing to itch transmission [194].

Taking these findings together, mast cells and basophils represent major sources of pruritogenic mediators and of cytokines that can sensitize sensory neurons. Through these mediator-to-neuron pathways, mast cells and basophils link allergic inflammation to neural output, thereby shaping host defense-related behaviors and disease symptoms at the organismal level. However, the contexts in which these two cell types influence sensory neurons may not be identical. Mast cells are tissue-resident and often positioned close to peripheral nerve fibers, which makes

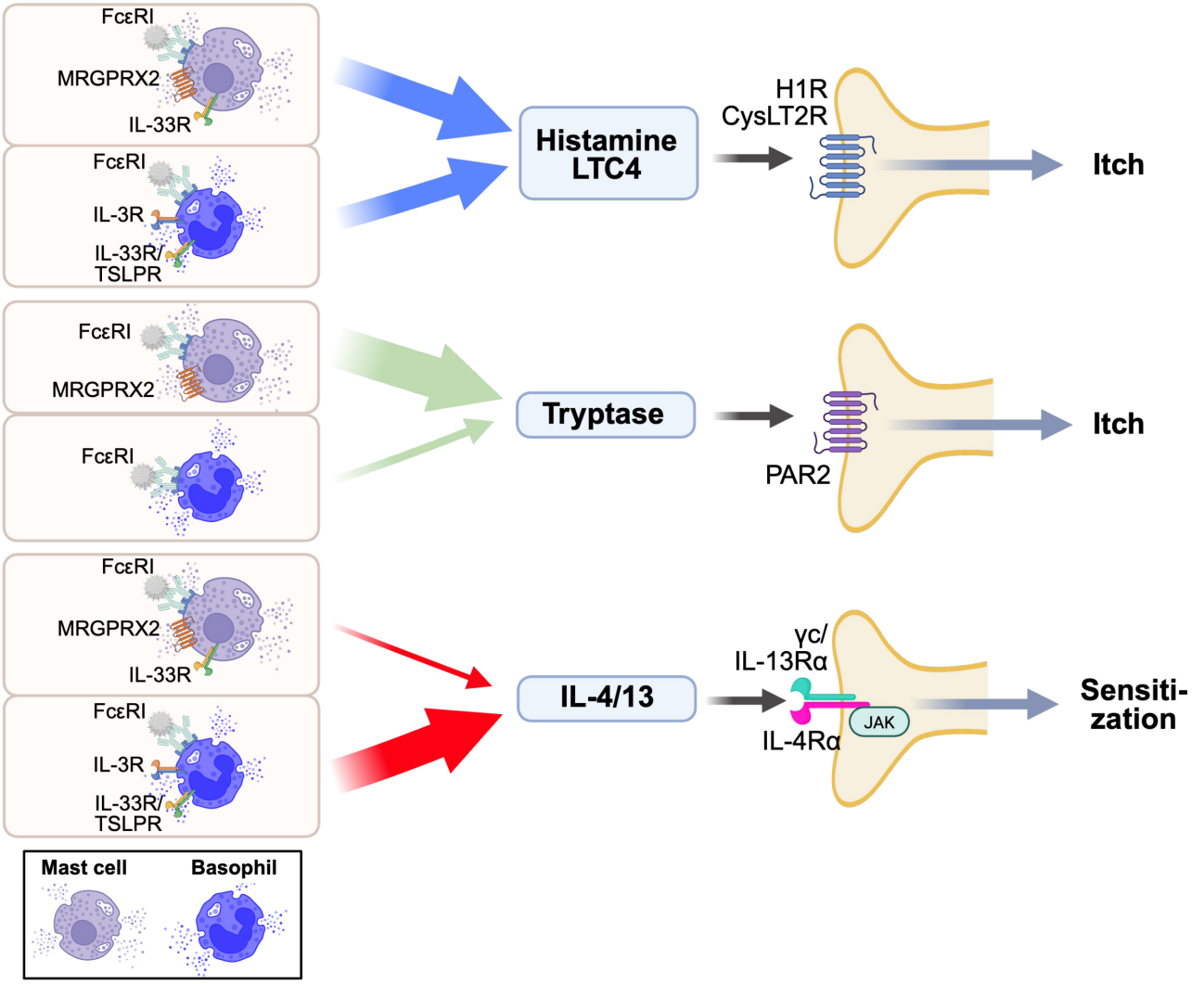


**Fig. 2. Activation and sensitization of pruriceptive sensory neurons by mast cells and basophils**. When mast cells are activated through FcεRI, Mas-related G protein-coupled receptor X2 (MRGPRX2), or the IL-33 receptor (IL-33R), and when basophils are activated through FcεRI, IL-3 receptor (IL-3R), IL-33R, or thymic stromal lymphopoietin receptor (TSLPR), they produce or increase their release of mediators such as histamine and leukotriene C4 (LTC4). Histamine and LTC4 act *via* histamine H1 receptor (H1R) and cysteinyl leukotriene receptor 2 (CysLT2R), respectively, on pruriceptive sensory neurons, thereby contributing to itch transmission. In addition, the activation of mast cells through FcεRI or MRGPRX2, and the activation of basophils through FcεRI, can induce the degranulation and release of granule-associated mediators, including proteases (in particular, mast cell tryptase). Tryptase is thought to promote itch signaling, at least in part through protease-activated receptor 2 (PAR2) on sensory neurons. Furthermore, the activation of mast cells (*via* FcεRI, MRGPRX2, or IL-33R) or basophils (*via* FcεRI, IL-3R, IL-33R, or TSLPR) induces the production of type 2 cytokines, such as IL-4 and IL-13. These cytokines act on IL-4 and IL-13 receptor pathways in pruriceptive neurons and promote neuronal sensitization, thereby lowering the itch threshold and amplifying itch responses to pruritogenic stimuli. Created with BioRender.com. Yoshikawa, S. (2026) https://BioRender.com/endnwwv.

them well suited for rapid local neuroimmune communication. By contrast, basophils are recruited to inflamed tissues and may progressively accumulate as inflammation evolves, thereby exerting greater effects during sustained or chronic type 2 inflammation through the production of cytokines and lipid mediators. This difference in tissue localization and kinetics may help explain why basophil-dependent neuron-directed effects have been more readily observed in some models of persistent allergic inflammation [79,107].

## 7. Conclusion

Neuroimmune interactions are now recognized to be bidirectional processes in which neural mediators modulate immune cell function, and conversely, immune cell-derived

signals modify neuronal activity. Mast cells and basophils are central effectors in allergic inflammation, and their responses are tuned by neurotransmitters, neuropeptides, and stress-related hormones through a defined set of receptors and intracellular signaling pathways. These concepts provide a useful framework to link immune activation to tissue-level symptoms, including itch, cough, pain, secretion, and changes in smooth muscle tone.

In this review, we have summarized the current evidence regarding the neurogenic regulation of mast cells and basophils, with emphasis on the main activating receptors and intracellular signaling programs that determine effector outputs. However, several gaps in knowledge remain. First, compared with "neuron-to-immune" regulation, mechanistic analyses of "immune-to-neuron" regulation have been limited to date, particularly at the level of defined mediators, receptors, and downstream neuronal circuits. Second, the neural pathways that modulate allergic responses at the organism level, including circuits involving the brain, remain incompletely mapped. In addition, much of the current mechanistic literature, particularly for mast cells, is based on animal studies, and some findings may not be directly transferable to human biology.

Future work should integrate analyses of molecular signaling with circuit- and tissue-level physiology, using approaches that can connect specific receptor pathways to defined symptoms and disease phases. We hope that this review will help organize the field and support efforts to identify new therapeutic targets relevant to neuroimmune communication in allergic diseases.

## Author Contributions

SY developed the overall manuscript structure. SY and KN drafted the manuscript. SY, KN, ZH, and AY prepared the figures. SY, KN, and ST organized the literature and drafted the review. MT and KT contributed to the conception and scope of the review, interpreted the relevant literature, and helped refine the scientific content and organization of the manuscript. They also critically revised the manuscript for important intellectual content. All the authors critically reviewed the manuscript, contributed to its revision, read and approved the final version for publication. Each author contributed sufficiently to the work and is accountable for all aspects of the study.

## Ethics Approval and Consent to Participate

Not applicable.


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## Conflicts of Interest

The authors declare no conflicts of interest.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) solely to assist with English grammar and typographical corrections. The manuscript's scientific content, the data interpretation, and the conclusions were entirely the work of the authors. The authors have carefully reviewed and edited the entire manuscript and take full responsibility for the content of the work.

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