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Neurotransmitter and neuropeptide regulation of gut immunity

Calvin Wong and Isaac M. Chiu

It is increasingly clear that the nervous system and immune system share a common molecular dialogue for intersystem communication. One of the key mechanisms of this communication is via neurotransmitters and neuropeptides. Diverse neuronal subtypes interact with various immune cell populations via the release of a wide variety of these neuromodulators that bind to receptors on immune cells. In the gut, this communication occurs via gut-intrinsic enteric neurons, extrinsic sensory and autonomic neurons. Here, we highlight a few key neurotransmitters and neuropeptides that have been shown to play a role in gut inflammation and host defense by acting on immune cells. Aberrations in this communication can lead to disorders including autoimmunity and tissue inflammation. We also discuss the need to better understand the molecular code of neuroimmune communication, which could lead to approaches to improve gut function and health.

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Introduction

Neurotransmitters and neuropeptides are central mediators of cell-to-cell communication in the central nervous system (CNS) and peripheral nervous system (PNS). Beyond the brain, this communication is equally essential for maintaining vital homeostatic functions throughout the body [1–3]. A critical aspect of this body–brain axis is communication between the nervous and immune systems, which orchestrates host defense, tissue repair, and inflammation. Neuromodulators enable neurons to directly communicate with immune cells, which express receptors for these transmitters [1]. Here, we describe mechanisms by which this communication regulates immune activity and explore its implications for tissue immunity.

Historically, neurotransmitters and neuropeptides were identified as substances released by neurons to communicate with other neurons via synaptic signaling [2,3]. Neurotransmitters are small, fast-acting, chemical signaling molecules stored in presynaptic vesicles released upon action potential firing [2]. In contrast, neuropeptides are larger, peptide-based messengers that are more stable and stored in dense core vesicles [3]. Both types of neuromodulators play essential roles in regulating behavior and physiology [2,3].

Distinct immune cells express receptors for specific neurotransmitters and neuropeptides, enabling them to respond to signals from the brain and PNS [1]. Immune cells themselves can also synthesize and secrete certain neuromodulators, facilitating bidirectional communication with neurons [1]. Thus, the nervous and immune systems have co-evolved to share a common molecular language, enabling precise coordination of homeostatic and defense mechanisms.

While neuroimmune interactions occur throughout the body, the gut is a particularly prominent site of such communication. The enteric nervous system (ENS), along with gut-extrinsic neurons, orchestrate immune cell functions in tissue repair, stress responses, and barrier integrity [4,5]. This gut neuroimmune axis also combats foreign threats, including bacterial, viral, fungal, and parasitic pathogens [6]. Disruption of this neuroimmune axis, however, can contribute to gut-related conditions such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) [7].

In this review, we focus on the gut as a hub for neuroimmune communication. We highlight key classes of neuromodulators, their neuronal and immune sources, and how they influence immune cell function (Table 1). While we are unable to comprehensively cover gut neuroimmune mechanisms, we refer readers to other excellent reviews on this topic [8–10].

The neurochemical diversity of neurons innervating the gut

The gastrointestinal (GI) tract receives innervation from diverse neuronal populations classified based on the

Table 1

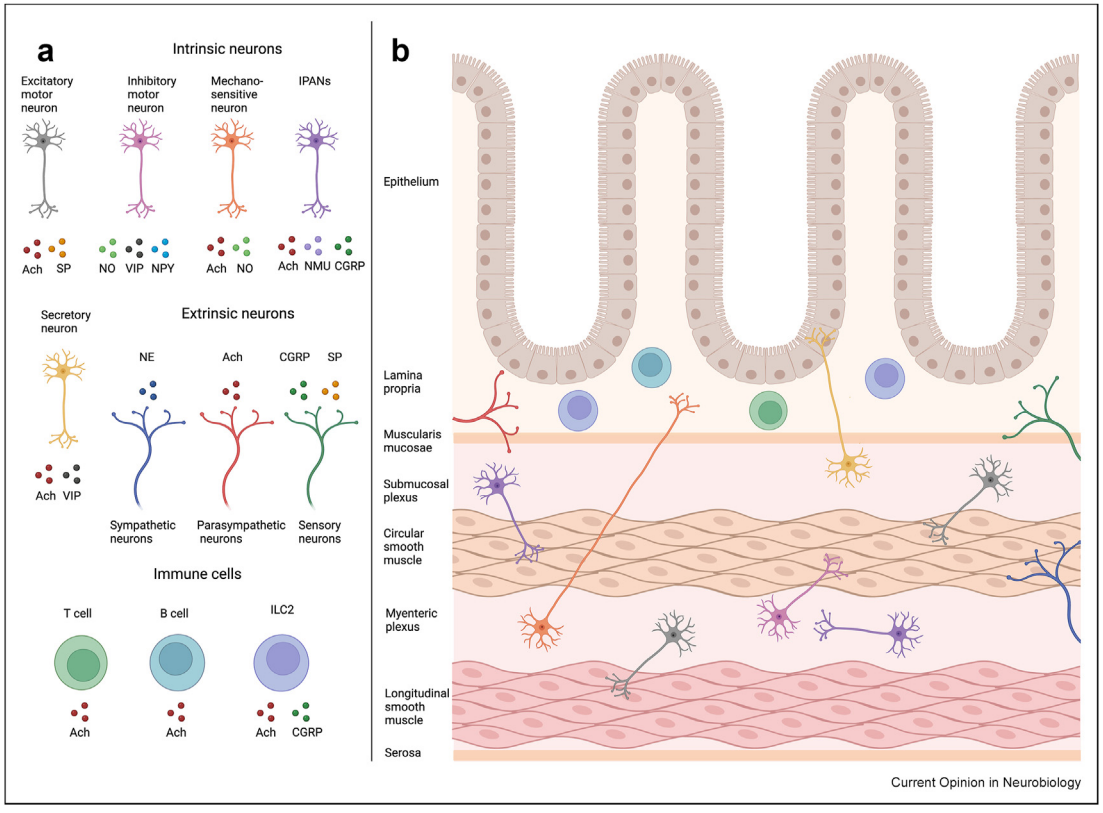
Neurotransmitter and neuropeptide regulation of immune cells in the gut.
Neuronal and immune cellular sources of key neurotransmitters and neuropeptides in the gut are given in the first 3 columns. This is followed by the main receptors activated on immune cells, the cell-type that responds, and overall effects on immunity/inflammation.

Neurotransmitter/ Neuropeptide	Neuronal source	Immune source	Receptor acted on	Immune population acted on	Function
Acetylcholine (ACh)	Parasympathetic neurons, excitatory motor neurons, and IPANs	B and T cells [23], ILC2s [25]	Nicotinic (nAChR) and muscarinic (mAChR)	Mast cells [29], dendritic cells, T cells, B cells, macrophages [23], ILC2s [25]	Promotes resolution of inflammation, suppresses cytokine (e.g. TNF) production
Norepinephrine (NE)	Sympathetic neurons	N/A	α and β adrenergic (AdR)	Mast cells [30], neutrophils, dendritic cells, T cells, B cells, macrophages [31], ILC2s [32]	Promotes tissue protective state and alternatively activated macrophages
Neuromedin U (NMU)	Cholinergic IPANs	N/A	NmUR1 and NmUR2	Eosinophils [33], T cells and ILC2s [12–14,34]	Promotes type 2 immune response and host defense
Vasoactive intestinal peptide (VIP)	IPANs, vagal and DRG sensory neurons	N/A	VPAC1 and VPAC2	T cells, B cells, macrophages [35], ILC2s, ILC3s [36–39]	Modulates lymphocytes, including ILC2 and ILC3 function
Calcitonin-gene related peptide (CGRP)	Myenteric IPANs and DRG sensory neurons	ILC2s [26–28]	Receptor activity modifying protein 1 (RAMP1) and calcitonin receptor-like receptor (CALCRL)	Mast cells, neutrophils, T cells, B cells, dendritic cells, macrophages [40], ILC2s [26–28]	Modulates neutrophil, macrophage and IL2 function
Substance P (SP)	Inhibitory motor IPANs and DRG sensory neurons	N/A	Mas-related G-protein coupled receptor (MRGPRB2) and Neurokinin 1 (NK1R)	Mast cells, dendritic cells, macrophages, T cells [41]	Drives mast cell degranulation and intestinal inflammation

location of their cell bodies, and their expression of specific neurotransmitters and neuropeptides (Figure 1). Gut-intrinsic enteric neurons regulate essential functions including motility, secretion, and digestion. Intrinsic primary afferent neurons (IPANs), whose cell bodies reside within the gut wall, primarily detect mechanical stretch and luminal stimuli [8]. In response to these stimuli, IPANs release acetylcholine (ACh) and nitric oxide (NO), facilitating peristalsis [11]. A subset of cholinergic IPANs express neuromedin U (NMU), a neuropeptide that promotes appetite suppression [12–14]. Calcitonin gene-related peptide beta (CGRP-β) is also expressed by IPANs, with roles in both gut motility and immunity [15]. Enteric neurons include excitatory and inhibitory subtypes that regulate smooth muscle contractility. Excitatory neurons promote gut motility via ACh and substance P (SP), while inhibitory enteric neurons release vasoactive intestinal peptide (VIP), NO, and neuropeptide Y (NPY) to mediate smooth muscle relaxation [16]. Secretory enteric neurons innervate the intestinal crypts, regulating water and electrolyte balance via the release of VIP and ACh [8,17].

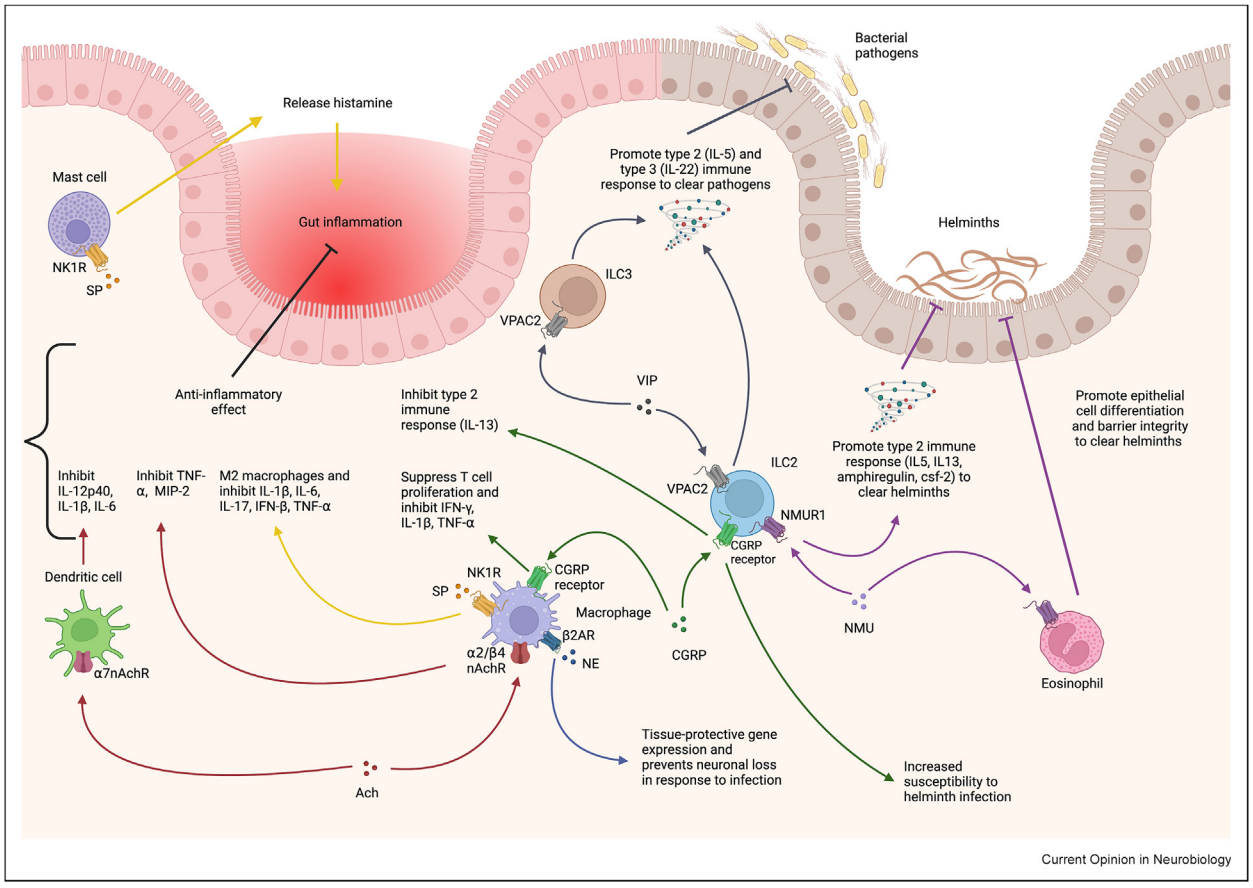
The gut is also innervated by extrinsic sensory, sympathetic, and parasympathetic neurons (Figure 1), which relay signals between the gut and CNS [8]. The cell bodies of extrinsic primary afferent neurons (ExPANs) are located in the dorsal root ganglia (DRG) near spinal vertebrae and in the vagal nodose/jugular ganglia near the brainstem [8]. DRG neurons mediate visceral pain, and are neurochemically heterogeneous, with peptidergic subsets expressing CGRP and SP [18]. Vagal sensory neurons, originating in the nodose and jugular ganglia, play key roles in nutrient detection, appetite/satiety, and nausea [19]. Sympathetic neurons, whose cell bodies reside in prevertebral ganglia (e.g., celiac and mesenteric ganglia) and paravertebral ganglia near the thoracolumbar spinal cord, are the primary source of norepinephrine (NE) [8]. NE regulates a variety of functions including gut motility, secretion and cell growth and repair [20,21]. Parasympathetic efferent neurons reside in the brainstem primarily innervate the gut via the efferent vagus nerve and drive gut motility and fluid secretion through release of ACh [19]. Together, sensory afferents and sympathetic and

Figure 1



Cellular sources of neurotransmitters and neuropeptides in the gut.
(a) The neuronal and immune cellular sources of neurotransmitters and neuropeptides expressed in the gut. **(b)** A schematic outlining the different layers of the gut, the types of neurons providing intrinsic and extrinsic innervation and neuromodulation, and resident immune cellular sources of neuropeptides.

Figure 2



Neurotransmitter and neuropeptide modulation of immune cells in the gut.
A schematic depicting specific examples of neurotransmitter and neuropeptide modulation of immune cells in the gut. Acetylcholine acts on macrophages, mast cells and dendritic cells to promote anti-inflammation. Norepinephrine also acts on macrophages to promote tissue protection in response to enteric infections. Vasoactive intestinal peptide acts on ILC2 and ILC3 populations to promote type 2 and type 3 immune responses to combat enteric infections. Similarly, neuromedin U acts on ILC2 and eosinophils to generate a type 2 immune response and mucosal immunity respectively against parasitic helminth infections. Calcitonin gene-related peptide acts on ILC2s and macrophages to suppress pro-inflammation by inhibiting ILC2 and T cell proliferation, respectively. Substance P also acts on macrophages to promote anti-inflammation but promotes pro-inflammation by causing mast cells to release histamine.

parasympathetic efferents coordinate the gut-brain axis and its communication.

Immune cell sources of neurotransmitters and neuropeptides

The majority of the body's immune cells reside in the gut, where they play critical roles in maintaining homeostasis and responding to infectious and injurious challenges [22]. Interestingly, some immune cells are capable of synthesizing and releasing neuromodulators (Table 1). Choline acetyltransferase (ChAT), the enzyme that catalyzes the biosynthesis of acetylcholine, is expressed in a subset of T cells and B cells after stimulation by antigen presenting cells [23]. $ChAT^{+}$ T cells play roles in modulating splenic macrophage activation and memory responses in viral infection [24]. $ChAT^{+}$ B cells modulate adaptive immunity by both autocrine and paracrine signaling [23]. ChAT is also expressed by activated group 2 innate lymphoid cells (ILC2s), which drive protective type 2 immune responses via ACh during intestinal helminth infection [25]. The neuropeptide CGRPα can also be expressed by activated ILC2s, which in turn dampens type 2 immune responses during allergic airway inflammation and helminth infection [26–28]. Given the mobility of immune cells, their expression of neurotransmitters and neuropeptides could facilitate delivery of these mediators to different tissues.

Neurotransmitter effects on immune cells in the gut

In the following section, we discuss how immune cells functionally respond to neurotransmitters to impact gut inflammation and host defense.

Acetylcholine

Acetylcholine in the gut primarily originates from parasympathetic efferents and enteric neurons. ACh exerts its effects through nicotinic (nAChR) and muscarinic (mAChR) receptors, which are expressed on various immune cells including macrophages, dendritic cells (DCs), T cells, B cells and ILCs (Table 1). This cholinergic signaling plays a key immunomodulatory role by suppressing proinflammatory cytokine production through a cholinergic anti-inflammatory pathway (Figure 2) [23,29]. In macrophages, stimulation of α2- and β4-nAChR inhibits TNF-α, and MIP-2 induction in a model of zymosan-induced inflammation [42]. Similarly, stimulation of α7-nAChR on DCs using the cholinergic agonist galantamine inhibited colitis-associated cytokines IL-12-p40, IL-1β and IL-6 [43]. These findings demonstrate the role of ACh in preventing excessive tissue inflammation.

The therapeutic potential of this pathway is demonstrated in models of colitis, where stimulating cholinergic signaling alleviates inflammation and weight loss induced by dextran sodium sulfate (DSS) and 2,4-dinitrobenzenesulfonic acid (DNBS) [43]. Beyond its effects on macrophages and DCs, cholinergic signaling also regulates type 2 immunity. *Nippostrongylus brasiliensis* infection has been shown to induce ACh production by ChAT $^{+}$ ILC2s. ACh acts in an autocrine manner to enhance type 2 immune responses, as measured by enhanced IL-5 and IL-13 levels, to promote anti-helminth immunity [25].

Norepinephrine

The sympathetic nervous system is the predominant local source of NE, a regulator of gut homeostasis that becomes amplified during stress signaling. NE acts through adrenergic receptors (AR), of which β_2-AR is most widely expressed on immune cell-types (Table 1). Adrenergic signaling has been shown to play crucial roles in response to enteric infections [44]. Infection with the enteric pathogen *Salmonella typhimurium* leads to activation of catecholaminergic neurons in superior mesenteric and celiac ganglia, as indicated by cFos staining, and release NE [44]. NE subsequently signals through β_2-AR on muscularis macrophages (MMs), inducing expression of *Arg1* and *Chi3l3*, genes characteristic of an alternatively activated, tissue-protective macrophage (Figure 2) [44]. This sympathetic neuron-to-macrophage pathway was critical to infection-induced death of enteric neurons [45]. It was shown that multiple pathogens can trigger the death of intrinsic enteric-associated neurons in mice via non-canonical inflammasome signaling through Nlrp6 and caspase-11 [45]. Sympathetic neurons and their polarization of the MMs to induce *Arg1* expression led to production of neuroprotective amines that suppressed Nlrp6-driven neuronal cell death [45].

However, β_2-AR signaling in ILC2 cells has been shown to be detrimental in *N. brasiliensis* infection, and β_2-AR knockout mice had reduced worm burden [32]. NE also plays tissue-protective effects during stress through the hypothalamic-pituitary-adrenal (HPA) axis, which can decrease gut oxidative stress, proinflammatory cytokines, and attenuate tissue apoptosis to promote tissue integrity [46]. Thus, adrenergic signaling plays a critical role in both mitigating inflammation and cell damage during tissue infection and injury.

Neuropeptide effects on immune cells in the gut

Unlike neurotransmitters, neuropeptides are larger, more stable messengers capable of traveling greater distances; As a result, neuropeptides often elicit longer-lasting responses compared to neurotransmitters [2,3].

Vasoactive intestinal peptide

VIP is a neuropeptide with emerging roles in immunoregulation. It signals through two main receptors: VPAC1 and VPAC2, the latter of which is expressed on innate lymphoid cells including ILC2s and ILC3s (Table 1) [47].

VIP release is induced by food consumption, where it acts as an appetite suppressant [47]. ILCs expressing VPAC2 are found localized proximal to VIP^{+} enteric neurons, suggesting a coordinated mechanism linking food consumption and immunity. One study demonstrated that VIP enhanced ILC2 and ILC3 responses by increasing IL-5 and IL-22 production, respectively, through VPAC2-dependent signaling [39]. Mice with conditional deletion of the *VPAC2* gene in ILC2 and ILC3 populations showed increased worm burden and bacterial load when infected with *Trichuris muris*, *Citrobacter rodentium* and *Escherichia coli* (Figure 2) [36].

By contrast, another study found that chemogenetic activation of VIP^{+} neurons suppressed ILC3 activation, indicated by reduced IL-22 levels, which diminished protection against intestinal infections [38]. The discrepancy regarding the effects of VIP on ILC3 function may arise from differences in study design, microbiome composition, and timing of experiments. VIP also plays an important role in supporting postnatal recruitment and development via ILC3 in the gut, which is necessary to combat enteric infections in later life [37]. Thus, VIP plays a powerful role in regulating innate lymphocyte function and host defense.

Neuromedin U

NMU, known for its role in appetite suppression, plays a critical role in driving type 2 immune responses [48]. NMU signals through two receptors, NmUR1 and NmUR2, with NmUR1 expressed on ILC2s and

eosinophils (Table 1). In the gut, NMU activates ILC2s via NMmUR1, leading to elevated levels of IL5, IL13, amphiregulin, and colony stimulating factor 2 [12,13]. This NmUR1-mediated ILC2 activation was essential for driving protective type 2 immunity during *N. brasiliensis* infection [12,13]. NmUR1 deficient mice exhibited an impaired type 2 immune response and increased parasite loads [12,13]. NMU plays similar roles in the lungs by activating ILC2s and exacerbates house dust mite driven allergic airway inflammation by synergizing with alarmin signaling [14]. Recent work also indicates that NMU regulates eosinophil function. NmUR1 signaling maintains eosinophil homeostasis, including cell numbers and degranulation [33]. Mice with conditional deletion of NmUR1 in eosinophils showed impaired goblet cell differentiation and mucus secretion, associated with increased worm burden when infected with *N. brasiliensis* [33]. Adoptive transfer of bone marrow-derived eosinophils with functional NmUR1 signaling rescued gut epithelial cell defects and reduced worm burden [33]. Thus, NMU plays critical roles in regulating type 2 immunity by signaling to ILCs and eosinophils (Figure 2).

Calcitonin gene-related peptide

CGRP is a neuropeptide traditionally associated with headache and migraine, where it contributes to peripheral and central pain sensitization [18]. CGRP also exhibits potent anti-inflammatory and tissue-repair functions, particularly through its action on immune cells such as neutrophils and macrophages [49—51]. In the gut, CGRP is sourced from DRG and enteric neurons, with the CGRPα (Calca) isoform mainly expressed in extrinsic neurons, and CGRPβ (Calcb) isoform primarily produced by intrinsic ENS neurons (Table 1). CGRP promotes anti-inflammatory phenotypes in the gut. For example, reduced levels of CGRP are associated with increased severity of IBD and ulcerative colitis in humans and animal models, while CGRP blockade delays ulcerative colitis recovery in mice [52,53]. CGRP may prevent inflammation and alleviate colitis by acting on macrophages to suppress T cell proliferation and induce T cell apoptosis [52]. In addition, CGRP promotes TGF-β expression in macrophages, which is essential for inflammation resolution. In DSS-induced colitis, TGF-β-deficient mice had elevated levels of proinflammatory cytokines IFN-γ, IL-1β, and TNF-α [52].

CGRP also regulates type 2 inflammation by inhibiting ILC2 activity [28]. In animal models of IL25 and OVA-induced allergic inflammation, ILC2s produced α-CGRP, which acted via autocrine signaling to repress CGRP receptor expression and IL-13 production [28]. Complementary studies showed that CGRP inhibited ILC2 activity in the lungs and gut, leading to decreased type 2 immune responses in allergic airway inflammation and helminth infection [26,27]. DRG nociceptors have also been shown to regulate host defense against *Salmonella* infection and promote mucus production through CGRP signaling to intestinal M cells and goblet cells [4,54]. Therefore, CGRP plays a strong role in modulating innate immune cell activation and regulating inflammation in the GI tract (Figure 2).

Substance P

SP, which is sourced from both DRG and enteric neurons, is also traditionally thought to promote pain by inducing sensitization of neurons [18]. SP powerfully induces mast cell degranulation via activation of the MRGPRB2 in mice and MRGPRX2 in humans [55,56]. In the gut, substance P levels has been correlated with mast cell activation in patients with IBD and Crohn's disease [57]. SP can also induce anti-inflammatory actions via the neurokinin receptor NK1R to inhibit macrophage infiltration, promote an M2-like macrophage state, and accumulation of regulatory T cells to alleviate DSS-induced damage [58,59].

SP administration during DSS-induced colitis in mice reduced levels of cytokines including IL-1β, IL-6, IL-17, IFN-β and TNF-α [58,59]. SP was also shown to modulate gut microbiome composition, and its deficiency exacerbates colitis pathogenesis [60]. Therefore, SP can play both pro- and anti-inflammatory effects depending on the receptor signaling pathway and context of inflammation (Figure 2).

Functional implications and remaining questions

Immune cells are central in maintaining gastrointestinal homeostasis by regulating cell growth, barrier function, host defense and inflammation. These cells operate within a dynamic and complex environment shaped by the gut microbiome, epithelial cells, and the nervous system. Neurotransmitters and neuropeptides play a pivotal role in regulating immune cell function, mediating both gut-brain and enteric neuron-immune communication. Despite significant advancements, several key questions remain on this topic.

1. What are the distinct effects of neurotransmitter and neuropeptide signaling on immune cell transcription, antigen presentation, and trafficking?
2. Are there conserved transcriptional cell states due to activation by neuromodulators that are shared between certain immune populations?
3. How do neuropeptides and neurotransmitters interact with cytokines to modulate immune cell function?
4. How do neuroimmune interactions in the gut influence other organ systems, such as the skin and brain?
5. Can manipulating neuromodulator expression affect the composition and activity of the gut microbiome?

Beyond neurotransmitters and neuropeptides, neurons can also release cytokines, lipid mediators, chemokines, and growth factors that affect immune function and

activity [61]. How these molecular mediators and their release is coordinate with neuromodulators, and their combinatory action on immune cells requires further investigation. It is important to note that gut microbes have also been found to produce neurotransmitters, adding further complexity to neuron-immune-microbe interactions.

Few studies have investigated how neuromodulators affect specific lymphoid and myeloid cells in the gut, such as B cells, natural killer cells, basophils and neutrophils. Future research in this area holds promise in uncovering cellular and molecular mechanisms governing gastrointestinal physiology and inflammation. These insights may provide opportunities to target neurotransmitter and neuropeptide signaling to treat GI disorders.

Author contributions

Calvin Wong: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Isaac M. Chiu: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing, Funding acquisition.

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Data availability

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