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Neuro-immune crosstalk and allergic inflammation

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Introduction

Epithelial barrier cells cover the surface of the entire body. These cells are constantly monitored by tightly regulated immune and neuronal cell networks. Environmental pathogens and allergens trigger the rapid release of proinflammatory cytokines from the epithelial barrier, which leads to the induction of innate immune responses followed by adaptive immune responses. At the same time, neuronal systems sense tissue damage or stimulation and transmit the information to the central nervous system (CNS) or nearby efferent neurons in visceral organs, resulting in various neuronal symptoms, such as itch, sneezing, cough, bronchoconstriction, dysphasia, and altered gastrointestinal motility. These collaborative immune and neuronal responses can contribute to the efficient elimination of infection and noxious stimuli and maintain tissue homeostasis.

Importantly, these immune and neuronal systems are not operating separately. Rather, they closely interact with each other. Activated immune cells produce inflammatory mediators, such as cytokines, lipid mediators, and histamine, which directly stimulate the terminals of peripheral nerves in local tissues. These stimulations not only transmit to the CNS but also enhance neuronal excitability and lower the activation threshold of neurons in response to stimuli, allowing subthreshold or even non-noxious stimuli to evoke neuronal activation and enhance neuronal function in sites of inflammation. In addition, the nerve terminals release various neuropeptides upon neuronal activation, and the released neuropeptides have a significant regulatory effect on multiple immune cells. Early experiments using electrical vagus nerve stimulation demonstrated that vagus nerve–derived acetylcholine suppressed the release of inflammatory cytokines from macrophages and dampened the endotoxin-induced systemic inflammatory response (1). Similarly, sensory nerve terminals contain various neuropeptides, such as substance P, neuropeptide Y, vasoactive intestinal peptide (VIP), and calcitonin gene–related peptide (CGRP), which directly regulate immune cell functions (2). In addition, these neuropeptides also affect endothelial cells and smooth muscle cells, leading to edema, vasodilation, and smooth muscle contraction and relaxation. These changes can further enhance immune cell responses, albeit indirectly. Thus, immune and neuronal systems closely interact with each other with profound effects on immunity, inflammation, and tissue homeostasis.

In recent years, research regarding neuro-immune crosstalk has focused increasingly on the neuro-immune interactions acting locally in tissues. Accumulating evidence has revealed the close anatomical contact and interaction between peripheral neurons and immune cells in peripheral tissues (3, 4). Apart from their systemic effects, various immune cells, including dendritic cells (DCs), macrophages, mast cells, and innate lymphoid cells (ILCs), share anatomical localization with peripheral neurons, and local neuro-immune interactions may have a potent effect on tissue homeostasis and inflammation. Specifically, group 2 innate lymphoid cells (ILC2s) are a recently identified lymphoid cell population that produces type 2 cytokines, including IL-5 and IL-13, in response to epithelial cell–derived cytokines, such as IL-33 and IL-25 (5–7). Neuronal regulation of ILC2s may play an important role in the induction of type 2 inflammation in the context of allergic diseases.

In this article, we first review the general concepts underlying neuro-immune interaction, then introduce recent evidence regarding the influence of local neuro-immune interactions. Lastly, we discuss the influence of neuro-immune interactions in the pathophysiology of asthma.

General neuro-immune interactions

The central nervous system (CNS) and peripheral tissues are connected by the peripheral nervous system (PNS), which transmits...
DCs to decrease Th1 cell differentiation and promote Th2 cell polarization via β-adrenoceptors. Additionally, these neurotransmitters directly act on various immune cells (Figure 1). For example, type 2 cytokines, such as IL-4, IL-5, and IL-13, induce sensory nerve activation and induce chronic itch (16). In addition, thymic stromal lymphopoietin (TSLP) has recently been found to activate TRPA1 by binding to its receptor, TSLPR, on sensory nerves in the skin of atopic dermatitis patients (17). Furthermore, Th2 cell–derived IL-31 activates TRPV1–TRPA1 sensory nerves and induces mast cell–dependent itch (18).

Notably, the terminals of nociceptors contain neuropeptides, such as CGRP, substance P, and VIP, which are rapidly released in response to noxious stimuli and inflammation. These neuropeptides directly act on various immune cells (Figure 1). Substance P is known to be a proinflammatory neuropeptide that activates multiple immune cells, including T cells, macrophages, DCs, mast cells, eosinophils, and neutrophils (19–21). The functions of VIP and CGRP skew toward a Th2 cytokine-like phenotype. Moreover, VIP suppresses inflammatory cytokines derived from DCs and macrophages, whereas it promotes Th2 cell differentiation, survival, and migration (22–24), and CGRP induces mast cell degranulation and shifts Langerhans cells to promote Th2 differentiation (25). These neuropeptides also affect nonimmune cells and increase vascular permeability, which is involved in the further recruitment of immune cells.

Thus, neuropeptides and neurotransmitters have a wide range of regulatory effects on multiple immune cells, and immune cell–derived mediators induce neuronal activation, which leads to a further release of neuropeptides in a positive-feedback loop. In addition, many observations suggest that these effects are modified by the local environment. Therefore, there has been a recent increased interest in studying the local effect of neuro-immune communications.

**Local neuro-immune interaction in peripheral tissues**

Although neuropeptides and neurotransmitters have multiple regulatory functions in the immune system, recent studies have...
emphasized the importance of the anatomical relationship between neurons and immune cells in the peripheral tissues, including skin, lungs, and intestine, and accumulating evidence suggests that various immune cells and neurons directly interact with each other in these sites (refs. 3, 4, and Figure 2).

Neuronal regulation of granulocyte responses. Many reports have shown that mast cells closely localize with sensory nerves in the gastrointestinal tract, urinary bladder, and skin (26–28). This anatomic colocalization between mast cells and nerves becomes more prevalent in the context of inflammation such as atopic dermatitis (29). The epidermis and papillary dermis of an atopic dermatitis lesion is hyperinnervated with increased substance P–positive nerve fibers, with increased mast cells expressing substance P’s receptor (NK-1R) compared with nonlesional skin. This finding implies that innervation and neuropeptides play a role in the pathogenesis of AD (30–32). Sensory nerve–derived substance P induces mast cell degranulation and release of histamine, TNF-α, leukotriene B4, and vascular endothelial growth factor (VEGF) (ref. 33 and Figure 2). VEGF further promotes endothelial cell proliferation and vascularization, facilitating the inflammatory process. Notably, mast cell–derived histamine acts on the histamine receptors on sensory nerve endings and evokes further release of neuropeptides, which establishes a positive-feedback loop between mast cells and sensory nerves in

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Figure 2. Neuro-immune interactions in different tissues. Immune cells and neurons colocalize and interact with each other in local tissues. The effects of the interaction differ depending on the tissue. A detailed explanation can be found in the main text. LCs, Langerhans cells; LTB4, leukotriene B4; MBP, major basic protein; M2AChR, muscarinic 2 acetylcholine receptor; NA, noradrenaline.
tissues (ref. 34 and Figure 2). Mast cells also release neurotrophic factors that promote local nerve elongation (35). Furthermore, substance P–mast cell pathways induce itch, and the administration of an NK-1R antagonist decreases scratching behavior in mice (36). Collectively, these findings suggest that the close interaction between mast cells and neurons in tissues affects inflammatory responses.

In addition to mast cells, other granulocytes are less clearly colocalized with neurons at a steady state. However, eosinophils localize with airway cholinergic nerves after allergen challenges. It has been suggested that eosinophils adhere to cholinergic nerves via vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1) (ref. 37 and Figure 2). The terminals of cholinergic nerves express the M2 muscarinic acetylcholine receptor, and stimulation of the receptor limits further release of acetylcholine in a negative-feedback pathway. Eosinophil-derived major basic protein acts as an antagonist of M2 muscarinic receptors. Therefore, eosinophil-derived major basic protein inhibits the negative-feedback loop and potentiates overproduction of acetylcholine, which enhances acetylcholine–induced bronchoconstriction in the airway (ref. 38 and Figure 2). In addition, it is also reported that sensory nerve–derived neuropeptides such as substance P, CGRP, secretoneurin, VIP, and secretin promote the constriction in the airway (39), which play a role in increasing sensory nerve responsiveness, stimulating nerve growth, and increasing neuropeptide expression in the context of inflammation (40). Therefore, the interactions between eosinophils and neurons may accelerate inflammation.

**Neuro-immune interactions with myeloid cells.** Recent studies have revealed a previously unrecognized local neuro-immune interaction between macrophages and neurons in the intestine and adipose tissues. Enteric neurons produce colony-stimulating factor 1 (CSF1), a growth factor required for the development of MHC class II+ CX3CR1+ macrophages in the intestinal muscularis externa. These muscularis macrophages regulate peristaltic activity, a muscular contraction that moves food down the intestine, through the production of bone morphogenetic protein 2 (BMP2). Macrophage-derived BMP2 stimulates BMP receptor (BMPR) on enteric neurons to induce CSF1 secretion, which leads to the further growth of macrophages in a positive-feedback loop. Therefore, these interactions between enteric neurons and macrophages play an important role in the homeostasis of the intestine (ref. 41 and Figure 2). Data indicate that this neuro-macrophage crosstalk is further enhanced by the microbiome. In contrast, intestinal pathogenic bacterial infections stimulate enteric sympathetic neurons to produce noradrenaline. The noradrenaline directly stimulates muscularis macrophages via β2-adrenergic receptors (β2ARs) and promotes a tissue-protective function (ref. 42 and Figure 2). Furthermore, a recent study demonstrated that macrophages mediate noradrenaline clearance via the noradrenaline transporter and production of noradrenaline degradation enzymes in adipose tissue. The sympathetic nervous system also plays an essential role in the regulation of metabolic homeostasis (43–45). Loss of function of the noradrenaline transporter on macrophages increases noradrenaline’s effects, which promotes increases in brown adipose tissue (BAT) content. Elevated BAT levels enhance thermogenesis and lead to weight loss in obese mice (46). Another study demonstrated that BAT-resident macrophages are related to the maintenance of sympathetic innervation in BAT (44). Thus, the interaction between sympathetic neurons and macrophages is involved in metabolic regulation in adipose tissues (Figure 2). Taken together, the interaction between neurons and macrophages has multiple effects depending on the tissue microenvironment.

**DCs** are also affected by neuropeptides and are in close contact with sensory neurons in the airway and skin (47, 48). Sensory nerve–derived CGRP inhibits DC maturation, which leads to suppression of T cell activation. Another study showed that adoptive transfer of CGRP-treated DCs diminishes allergic airway inflammation in vivo, which was associated with reduced eosinophilia and elevated levels of IL-10 in bronchoalveolar lavage fluid (49). These findings suggest that sensory neuron–derived CGRP has a suppressive effect on DCs in the lung (Figure 2). Again, however, the neuronal regulatory effects are variable depending on the tissue. In the skin, DCs are in close contact with TRPV1+ sensory neurons (48). CGRP derived from TRPV1+ neurons drives IL-23 production from CD301b+ DCs, leading to secretion of γδT cell–derived IL-17A, which inhibits cutaneous *Candida albicans* infection (ref. 50 and Figure 2). Furthermore, Langerhans cells, a population of DCs in the epidermis of the skin, are also very closely associated with epidermal sensory nerves (51). CGRP and VIP enhance Langerhans cell antigen presentation on Th2 cells while inhibiting presentation to Th1 cells (refs. 51, 52, and Figure 2). In contrast, substance P enhances Langerhans cell migration and antigen presentation, leading to the generation of Th1-type immune response (ref. 53 and Figure 2). Together, these studies indicate that DCs are closely interacting with sensory neurons in the lungs and skin, and their regulatory effects depend on the tissue microenvironment.

**Neuro-immune interactions with ILCs.** ILCs are a recently discovered lymphoid cell population that lack rearranged antigen receptors and produce a variety of cytokines. ILCs are classified into three groups on the basis of transcriptional factors and production of cytokines: ILC1s (expressing T-bet, producing IFN-γ), ILC2s (expressing GATA3, producing IL-5 and IL-13), and ILC3s (expressing RORγt, producing IL-17 and/or IL-22) (54).

Recent studies shed light on the new mechanisms of neuronal regulation of ILC2s. These cells produce type 2 cytokines in response to epithelial cell–derived cytokines, including TSLP, IL-33, and IL-25, and play a critical role in eosinophilic inflammation of allergic diseases (55). A series of seminal studies have demonstrated that tuft cells, chemosensory cells that express TRPM5 to sense bitter and sweet taste, are the dominant sources of IL-25 in the respiratory tract and intestine (56–59). ILC2s are predominantly tissue-resident cells and reside in various tissues at a steady state. Recent studies have revealed that ILC2s are closely associated with neurons in the intestine and that neuropeptides and neurotransmitters directly activate or suppress ILC2 function. For example, ILC2s colocalize with neuromedin U–expressing (NMU-expressing) neurons, most of which are enteric cholinergic neurons in the intestine (Figure 2). ILC2s selectively express NMU receptor 1 (NMUR1), and NMU has a potent effect of inducing the proliferation of ILC2s as well as inducing their production of the cytokines IL-5, IL-9, IL-13, and AREG (60–62). NMU enhances type 2 inflammation via the activation of ILC2s...
Neuronal regulation in asthma

Classically, neuronal systems, especially sympathetic and parasympathetic nerves, were thought to affect smooth muscle cells and contribute to the symptoms of asthma. However, as evidence of neuro-immune interactions in tissues accumulates, it has been suggested that neuronal systems directly affect immune responses in asthma. The immune responses in asthma mainly divide into two distinct cascades: allergen-specific and allergen-nonspecific responses. In allergen-specific responses, allergens are captured by antigen-presenting cells like DCs that induce antigen-specific Th2 cells in the lymph nodes. Then, allergens activate antigen-specific Th2 cells, which leads to the production of type 2 cytokines such as IL-4, IL-5, and IL-13. IL-4 stimulates B cells to synthesize IgE antibodies, IL-5 induces eosinophilic inflammation, and IL-13 promotes mucin overproduction and tissue remodeling. Moreover, IgE causes antigen-specific activation of mast cells and basophils, which results in the release of inflammatory mediators. On the other hand, some allergens directly induce the release of cytokines such as IL-33 and IL-25 from epithelial cells, and these cytokines directly activate ILC2s independent of antigen-specificity. Activated ILC2s produce type 2 cytokines like IL-5 and IL-13 and cause eosinophilic inflammation without acquired immunity. Subsequently, ILC2s promote the induction of antigen-specific Th2 cells. Although neuronal systems modify both allergen-specific and allergen-nonspecific immune responses in multidimensional ways, recent studies demonstrated that they might have more impact on ILC2-mediated allergen-nonspecific immune responses.

Neuronal regulation in asthma by sympathetic nerves. Sympathetic nerve–derived noradrenaline is known to be involved in bronchial muscle relaxation via β2AR on airway smooth muscle cells, and agonists of β2AR are used for the treatment of asthma and chronic obstructive pulmonary disease (COPD) as a bronchodilator. However, some studies report that this neuronal regulation is modified by immune cells. Mast cells infiltrate in airway smooth muscles of patients with asthma (68), and mast cell–derived TGF-β induces phosphorylation of β2AR on smooth muscle cells, which results in a reduced response to a β2AR agonist (69). In addition, noradrenaline can directly suppress proinflammatory cytokine production from immune cells through β2AR, and β2AR-deficient mice have more severe type 2 airway inflammation in allergen-nonspecific asthma mouse models. Specifically, β2AR agonists dampen IL-33– and Alternaria–induced airway inflammation via suppression of ILC2s (64). Thus, β2AR agonists might have a beneficial effect on asthma via not only smooth muscle cells but also immune cells (Figure 3). However, it is still unclear whether β2AR agonists can suppress human ILC2s and suppress ILC2-mediated inflammation in patients with asthma, although it is reported that human lung ILC2s express β2AR (64).

Neuronal regulation in asthma by parasympathetic nerves. Parasympathetic nerve–derived acetylcholine induces airway smooth muscle contraction and mucus secretion mainly via muscarinic M3 receptors. Therefore, inhalation of selective M3 receptor antagonists, which act as bronchodilators, is currently used for the treatment of asthma and COPD (70). Patients with asthma have increased pulmonary cholinergic nerve activity and hypersensitivity to cholinergic agonists. As described earlier, eosinophil–derived major basic protein mediates the dysfunction of the muscarinic M2 receptor, which might contribute to this increased cholinergic neuron activity (38). On the immune side, vagal nerve stimulation suppresses the inflammatory response
while vagal denervation worsens lung infection, inflammation, and injury with increased proinflammatory cytokines (71). These effects are caused by acetylcholine via \( \alpha_7nAChR \), and a recent study showed that \( \alpha_7nAChR \) agonists directly suppressed ILC2s, resulting in decreased type 2 inflammation in IL-33– and Alternaria–induced airway inflammation (63). Therefore, acetylcholine has a beneficial effect on type 2 inflammation in asthma via \( \alpha_7nAChR \), although it causes bronchoconstriction via muscarinic M3 receptors. Thus, parasympathetic neurons have multiple functions in the pathophysiology of asthma that vary depending on their receptors (Figure 3). Further studies are needed to clarify the clinical relevance of the interaction between cholinergic neurons and the immune system in asthma.

Sensory nerves and neuroendocrine cells regulate asthma pathophysiology. Recent studies have shown that sensory nerves also play a critical role in the pathophysiology of asthma (72, 73). Sensory nerves contain various neuropeptides, including substance P, VIP, and CGRP, and allergen provocation induces neuropeptide release. Indeed, it is reported that the levels of substance P in induced sputum are increased and correlated with airway obstruction in asthmatic patients (74). Furthermore, CGRP is elevated in the bronchoalveolar lavage fluid of asthmatics during the late-phase reactions provoked by allergen inhalation (75). In recent years, several studies in mice demonstrated that blocking sensory nerves ameliorates type 2 inflammation in the airways. For example, genetic ablation of TRP-expressing sensory nerves by diphtheria toxin suppresses type 2 inflammation in IL-33– and Alternaria–induced airway inflammation (73). These studies suggest that allergen provocation induces the release of neuropeptides from sensory nerves and these neuropeptides directly affect immune cells. Specifically, ILC2- and CD4+ T cell–derived IL-5 directly stimulates pulmonary nociceptors to release VIP, and VIP activates ILC2s and CD4+ T cells to further enhance type 2 inflammation. IL-5 activates the terminals of sensory neurons and induces the further release of VIP. NMU also directly activates ILC2s, leading to type 2 inflammation. Blocking the activation of sensory neurons using QX-314, a voltage-gated sodium channel blocker, inhibits the release of neuropeptides and attenuates type 2 inflammation. PNECs also produce CGRP and GABA, thereby activating ILC2s and directly inducing goblet cell hyperplasia in the airway. TRPs, transient receptor potential channels.

In addition, sensory nerve endings express a variety of ion channels. Capsaicin, a selective TRPV1 agonist, activates lung nociceptors to enhance OVA-induced lung inflammation via the release of neuropeptides (73). However, TRPV1 deficiency does not affect the phenotype of asthma mouse models (72, 76). On the other hand, TRPA1-deficient mice or treatment with HC-030031, a selective TRPA1 channel antagonist, showed a remarkable reduction in bronchial hyperresponsiveness and a pronounced inhibition of type 2 inflammation. The activation of TRPA1 induces the release of the neuropeptides CGRP, substance P, and neurokinin A from sensory nerve terminals, and OVA-induced release of neuropeptides is inhibited in TRPA1-deficient mice (76). Therefore, TRPA1 is considered to be associated with antigen-induced neuronal activation and neuropeptide release, which results in the type 2 airway inflammation that characterizes asthma.

A recent study suggested that PNECs are also important sources of neuropeptides, especially CGRP, in the lungs. ILC2s colocalize with PNECs in the lungs, and PNEC-derived CGRP directly promotes ILC2 activation. Moreover, PNECs produce the neurotransmitter GABA, which directly stimulates epithelial cells to induce goblet cell hyperplasia. Accordingly, PNEC-deficient mice exhibit less severe inflammation than control mice in HDM- and OVA-induced asthma models (ref. 65 and Figure 3).
Recent evidence also indicates that enteric cholinergic neuron–derived NMU has a potent activating effect on ILC2s that induces type 2 inflammation in the intestine (60–62). Unlike in the intestine, the population of NMU-expressing neurons in the lungs still remains unclear, and one study showed that NMU is expressed in the neurons of the thoracic dorsal root ganglia, which contain afferent sensory innervating the lungs (61). NMU stimulates lung ILC2s to induce type 2 airway inflammation, and HDM-induced and N. brasiliensis–induced lung inflammation was suppressed in NMUR1-deficient mice. These data suggest that neuron-derived NMU also has a role in ILC2-mediated lung inflammation.

Collectively, the conclusions of recent studies indicate that various neurotransmitters and neuropeptides directly affect immune cells, especially Th2 cells and ILC2s, and have a potent effect on type 2 inflammation in the pathophysiology of asthma.

Summary and future directions

Building on seminal studies conducted decades ago, the study of neuro-immune crosstalk has become an active research area in the field of both immunology and neurobiology. The positive-feedback loop between the neuronal and immune systems in local tissues appears to be an amplification mechanism to induce potent immune reactions. However, excess inflammation might cause health problems, such as allergic and inflammatory diseases. Therefore, the regulation of neuro-immune interaction is a potential therapeutic target for these conditions.

To expand this research area in the future, it could be beneficial to define the activation mechanisms of peripheral neurons in the context of allergy, inflammation, and infection, test the influence of neuropeptides and neurotransmitters on the immune systems, and examine the different roles of neuro-immune crosstalk in various tissues and the context of inflammation.

Regarding the potential of therapeutically targeting neuro-immune pathways, recent studies have shown that an anti–IL-31 receptor antibody, nemolizumab, successfully improves pruritus in patients with atopic dermatitis (77). Furthermore, ion channels play an essential role in the activation of sensory nerves, and TRP channel inhibitors are also promising candidates for various neuron-related symptoms and diseases (78). Neuropeptides, neurotransmitters, or their receptors are also potential targets for neuro-immune interaction, including VIP, CGRP, substance P, NMU, β2AR, and nAChR. However, we have to interpret the results of rodent-based studies carefully because of species differences in these pathways. For example, substance P activates mast cells and induces skin inflammation in mice, but the results of clinical studies using substance P receptor (NK-1R) antagonists were equivocal in human studies (79). Notwithstanding these challenges, future translational efforts to study the effects of local neuro-immune interactions in human health and disease are certainly warranted.

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