

New aspects of neuroinflammation and neuroimmune crosstalk in the airways



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Neuroimmune interaction has long been discussed in the pathogenesis of allergic airway diseases, such as allergic asthma. Mediators released during inflammation can alter the function of both sensory and parasympathetic neurons innervating the airways. Evidence has been provided that the inflammatory response can be altered by various mediators that are released by sensory and parasympathetic neurons and *vice versa*. Our aim is to demonstrate recent developments in the reciprocal neuroimmune interaction and to include, if available, data from *in vivo* and clinical studies. (J Allergy Clin Immunol 2018;142:1415-22.)

Key words: Allergic asthma, airway innervation, C-fibers, parasympathetic neurons, neurogenic inflammation, vagal ganglia, nucleus of the solitary tract

The development of a single allergic disorder in early life is a strong predisposition for the development of subsequent allergic diseases (ie, the allergic march). Research in the last decades has deciphered the importance of the immune system in the pathogenesis of atopic diseases in various different organs, including the skin, gut, and airways.

Almost all key symptoms, such as itch, sneezing, chronic cough, and airway hyperreactivity (AHR), are largely dependent on central reflex activity and cannot be attributed to activation of immune cells alone. Indeed, evidence suggests a communication between immune cells and the brainstem, the main center that processes signals derived from the lower airways via sensory neurons. Sensory neurons are afferent neurons with their cell bodies located primarily in vagal jugular and nodose ganglia, whereas their peripheral terminals are located in close vicinity to

Abbreviations used

ACh: Acetylcholine
AHR: Airway hyperreactivity
CGRP: Calcitonin gene-related peptide
DC: Dendritic cell
DRG: Dorsal root ganglion
DTX: Diphtheria toxin
IL-31R: IL-31 receptor
MCh: Methacholine
M2R: Muscarinic acetylcholine receptor 2
M3R: Muscarinic acetylcholine receptor 3
NGF: Nerve growth factor
NK1R: Neurokinin 1 receptor
NTS: Nucleus of the solitary tract
RAMP: Receptor activity-modifying protein 1
SP: Substance P
TRPA1: Transient receptor potential ankyrin 1
TRPV1: Transient receptor potential vanilloid 1
TSLP: Thymic stromal lymphopoietin
VIP: Vasoactive intestinal peptide

and within the airway epithelium. Activation of specific receptors and membrane ion channels by a wide variety of exogenous irritants and endogenous inflammatory mediators results in depolarization and subsequent release of neuropeptides in the airways, as well as activation of second-order neurons in the nucleus of the solitary tract (NTS) of the medulla oblongata.¹ Then a desire to cough (“urge to cough”) is elicited, and complex processing is initiated to coordinate cough motor mechanisms by NTS neurons projecting to neurons in the ventrolateral medulla oblongata (Böttinger, pre-Böttinger complex, and rostral ventral respiratory group). In addition, cell bodies of airway-related vagal preganglionic neurons located in the most rostral part of the dorsal motor nucleus of the vagus nerve and the rostral nucleus ambiguus region are activated. The information is passed along preganglionic parasympathetic fibers travelling within the vagus nerve to the intramural ganglia, where it is transferred to secondary (postganglionic) neurons. Postganglionic parasympathetic neurons distribute centrally generated information to effector cells within the airways through acetylcholine (ACh) release.

The aim of this review is to provide an overview of the reciprocal communication between the immune system and sensory and parasympathetic neurons.

AIRWAY INNERVATION

Dense innervation of the airways is required for regulation of breathing. Moreover, it provides the basis for the initiation of

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defense mechanisms in regard to environmental irritants, as well as to viral and bacterial infection. Different populations of neurons innervating the airways can be distinguished, namely sensory and parasympathetic neurons. Most fibers travel within the vagus nerve to the airways.

Investigations regarding the effect of innervation are mostly derived from animal experiments. In human subjects only limited data are available.

The reduction of nerve fibers in the submucosa and airway smooth muscle by means of bronchial thermoplasty is accompanied by clinical benefits, such as reduction of severe exacerbations and oral corticosteroid dose,² pointing to the nervous system as an important player in asthma. However, because autonomic nerve-innervated structures, such as bronchial smooth muscle and submucosal blood vessels, are also reduced by using this technique, the precise role of airway-innervating neurons needs to be addressed in future studies.

Sensory neurons

Cell bodies of sensory neurons innervating the airways are mainly located in the vagal jugular and nodose ganglia and a lower percentage is located in the dorsal root ganglia (DRGs) that predominantly project to the extrapulmonary airways (Fig 1). The nodose ganglion is derived from epibranchial placodes, whereas the origin of the jugular ganglion and the DRGs is the neural crest.

Based on their conduction velocity, afferent neurons can be subdivided into A- and C-fibers. A-fibers conduct action potentials in the A δ and A β range (14–32 m/s) and are myelinated nonpeptidergic mechanoreceptors. Based on their adaption to sustained lung inflation, 2 different A-fiber populations can be distinguished: slowly adapting stretch receptors and rapidly adapting stretch receptors. The activity of rapidly adapting stretch receptors increases with the rate and volume of lung inflation, deflation, or both, whereas slowly adapting stretch receptors terminate inspiration after inflation of the lung (Hering-Breuer reflex).^{3,4} A-fibers are activated by stretch, touch, and other mechanical forces but exhibit a limited sensitivity to chemical mediators and will therefore not be discussed further within this review. In contrast, bronchopulmonary C-fibers represent a distinct neuronal population of slow-conducting (approximately 1 m/s) unmyelinated afferent neurons that express the transient receptor potential vanilloid 1 (TRPV1), the receptor for capsaicin, and can be activated by a wide variety of chemical and thermal stimuli, such as bradykinin, hyperosmolar fluids, cold air, and cigarette smoke.

Compared with neural crest-derived jugular and DRG neurons, nodose C-fibers lack expression of neuropeptides, such as the tachykinin substance P (SP) encoded by alternative splicing from the precursor preprotachykinin A and calcitonin gene-related peptide (CGRP).¹ Neuropeptides are released by nerve terminals and thought to induce neurogenic inflammation (see “Transmitters released from peripheral nerve terminals can influence the inflammatory response” below).

Studying the effect of C-fibers in the setting of allergic asthma is experimentally challenging, and therefore the specific cause/effect relationships are largely unknown. However, improved technical approaches of the last decade allow a more detailed deciphering of their precise role. Thus Tränkner et al⁵ used a mouse model of allergic airway inflammation to study the effect of sensory neurons on AHR.

AHR to methacholine (MCh) was dependent on the presence of inflammation. This finding is supported by data obtained from other experiments in mice⁶ and from an individual clinical study.⁷ Targeted expression of the diphtheria toxin (DTX) receptor in TRPV1-expressing cells and intraperitoneal injection of DTX before allergen sensitization revealed that AHR is additionally largely dependent on the presence of C-fibers.⁵ DTX injection into the vagal ganglia caused a decreased response to MCh, indicating that C-fibers responsible for mediating inflammation-induced AHR are located in the vagal ganglia rather than in DRGs. The other way around, optogenetic activation of vagal neurons in mice that express the light-activatable channelrhodopsin ion channel in TRPV1⁺ neurons caused a profound increase in AHR in a mouse model of allergic airway inflammation.⁵

AHR is measured in the clinical setting by using lung function analysis after inhalation of increasing doses of muscarinic receptor agonists, such as muscarine, ACh, or MCh. In the airways ACh is predominantly released by parasympathetic neurons and acts through muscarinic acetylcholine receptor 3 (M3R) on airway smooth muscle cells. Given those facts, the data obtained by Tränkner et al⁵ need further discussion to be able to link ablation of sensory neurons to decreased smooth muscle contraction in response to administered MCh. Possible explanations involve the observation that MCh causes a substantial reflex contraction of airway smooth muscle mediated by fibers traveling with the vagus nerve. This indicates that a response to MCh represents not only the direct effect on smooth muscle but also points to the possibility of an involvement of vagal sensory afferents. Indeed, our data provide evidence that about 12% of nodose and 6% of jugular C-fibers are directly activated by muscarine through M3R.¹ Because a small population of Mas-related G protein-coupled receptor C11 (MrgprC11)⁺ jugular C-fibers are obviously necessary for the development of AHR in response to MCh,⁸ effects seem to be related to neural crest-derived cells. In addition, indirect mechanisms, such as those caused by bronchoconstriction-mediated mechanical activation of sensory C-fibers, have to be discussed.⁹

Parasympathetic neurons

The parasympathetic nervous system is responsible for mediating the baseline tone of airway smooth muscle and thus airway diameter. Abundant activation is associated with an increased contraction of airway smooth muscle, resulting in limited airflow and increased airway resistance. Airway tone is the final result of the activation of at least 2 distinct subpopulations of parasympathetic neurons exhibiting contrary effects because of the release of different mediators on stimulation.

The majority of preganglionic parasympathetic neurons projecting to neurons innervating the tracheal wall and intrapulmonary airways are located in the dorsal motor nucleus of the vagus nerve (Fig 1). Their nerve fibers travel within the vagus nerve to the intramural ganglia, where they project to secondary (postganglionic) neurons. Cholinergic postganglionic parasympathetic neurons release predominantly ACh, which can affect various cell populations through nicotinic and muscarinic ACh receptors. ACh is the predominant bronchoconstrictor in the airways and induces smooth muscle contraction through muscarinic receptors located on the surfaces of smooth muscle cells. Additionally, it also increases secretion from exocrine glands and secretory cells of the epithelium.

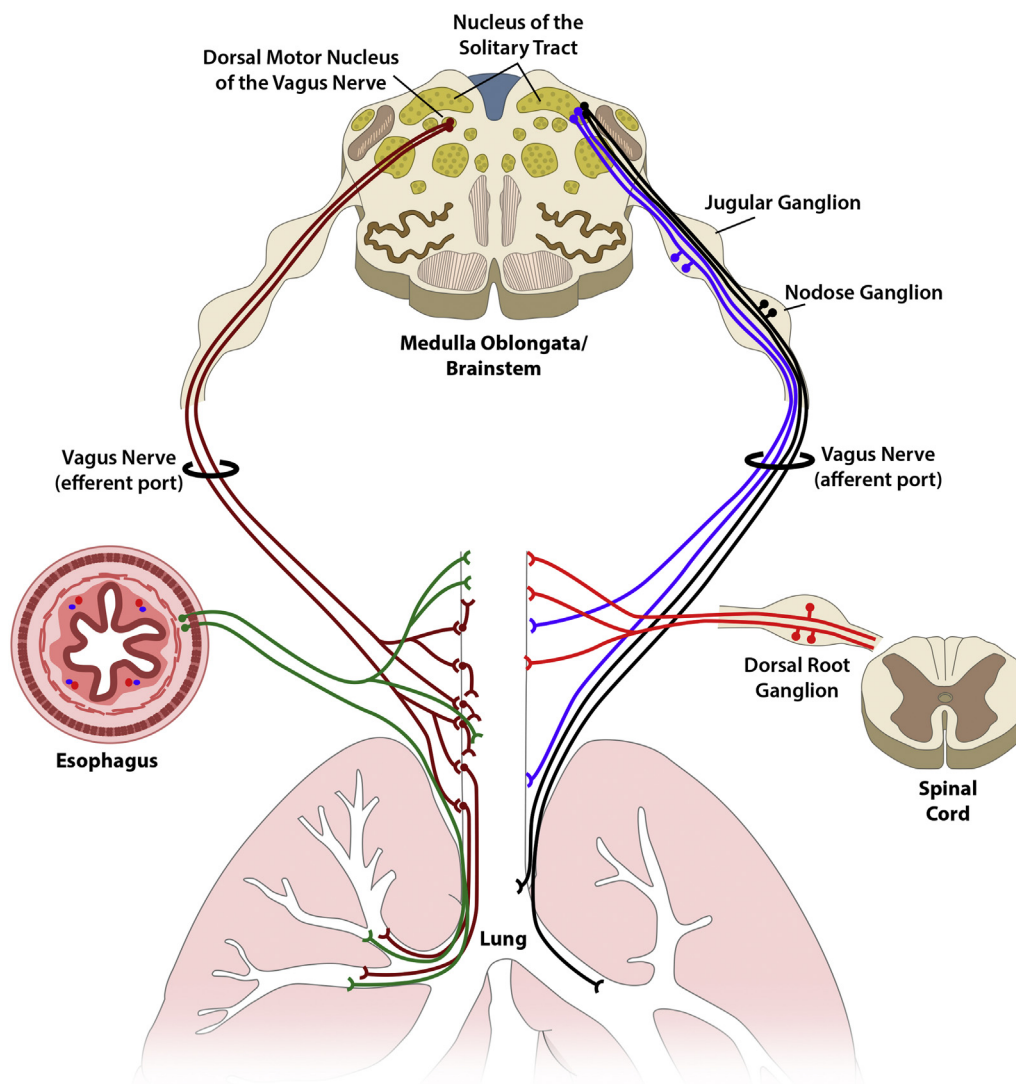


FIG 1. Overview of innervation in the airways. The airways are mainly innervated by sensory neurons located in the jugular nodose complex (nodose neurons are depicted in black, and jugular neurons are depicted in blue) or DRGs (red neurons), respectively, and by parasympathetic neurons. The preganglionic parasympathetic neurons that synapse with cholinergic postganglionic neurons within the airway wall are located in the brainstem (brown neurons), whereas noncholinergic postganglionic neurons originate from the myenteric plexus of the esophagus (green neurons).

Another subpopulation of postganglionic parasympathetic neurons is also referred to as “noncholinergic” and uses preferentially nitric oxide and vasoactive intestinal peptide (VIP) to elicit airway smooth muscle relaxation.¹⁰ The noncholinergic postganglionic neurons are located either in the myenteric plexus or closely associated with the outer striated longitudinal muscle layer of the esophagus (Fig 1).¹¹ However, the net effect of cholinergic neuronal activity, which increases airway tone, out-balances the effect on noncholinergic neurons, which elicit smooth muscle relaxation. In asthmatic patients cholinergic neuronal activity is pronounced because the phenotype of noncholinergic airway parasympathetic neurons changes to a cholinergic phenotype, an effect that is mimicked by neurotrophin-3, which is released by inflammatory cells.¹²

In conclusion, these data demonstrate that both sensory and parasympathetic neurons can regulate airway tone and therefore

might be critically involved in mediating symptoms that occur in asthmatic patients.

NEUROIMMUNE INTERACTION

Anatomy of neuroimmune interaction

Neuroimmune interaction requires a physically close but not necessarily direct contact between immune cells and neurons, allowing a direct response of immune cells to neuronally released mediators and *vice versa*.

A close relationship of sensory neurons with eosinophils¹³ and type 2 innate lymphoid cells,¹⁴ as well as antigen-presenting dendritic cells (DCs) and T cells, has been observed.^{15,16} Eosinophils can influence the branching of sensory neurons.¹⁷ It remains speculative whether this is due to nerve growth factor (NGF) release.^{18,19} In animals exhibiting allergic airway inflammation,

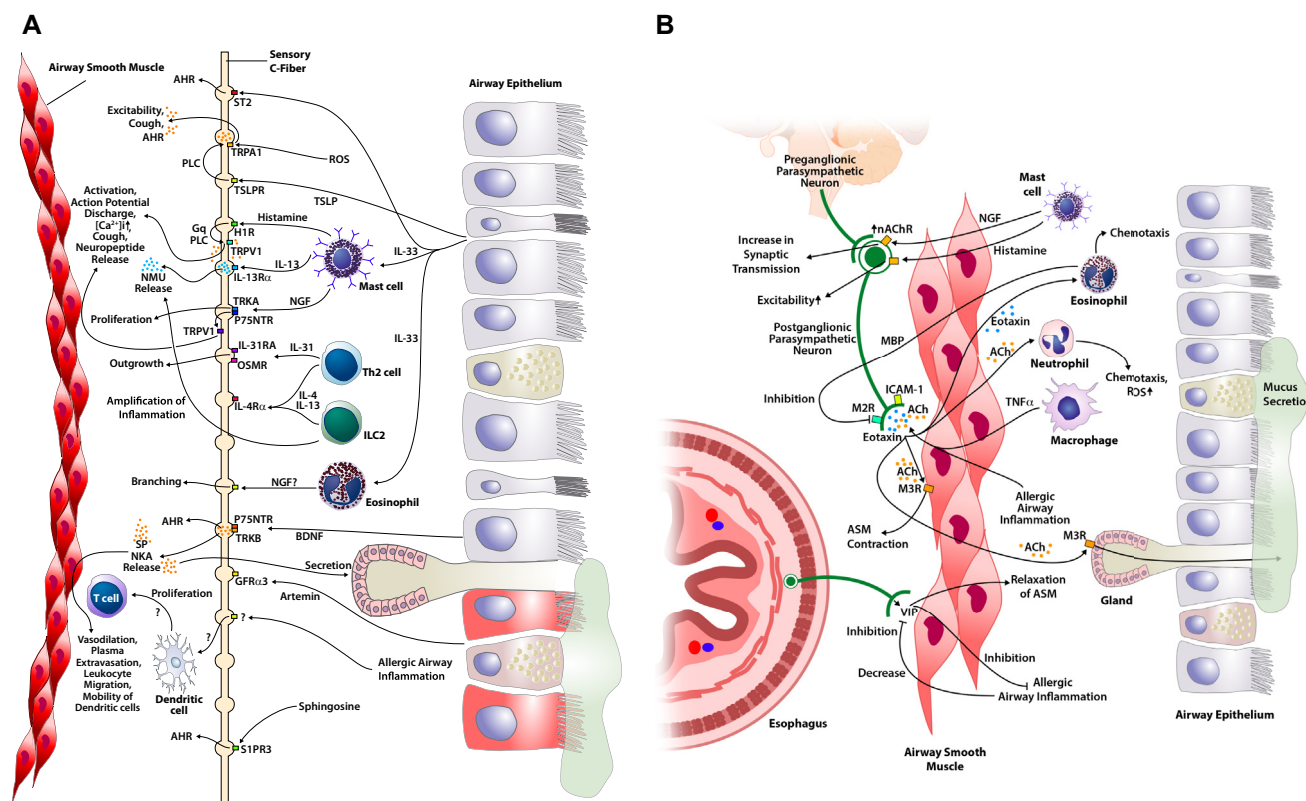


FIG 2. Overview of the reciprocal interaction between neurons and immune cells. **A**, Interaction of sensory neurons and immune cells. **B**, Interaction of parasympathetic neurons and immune cells. Emphasis has been placed on the last decade's new findings. *ASM*, Airway smooth muscle; *BDNF*, brain-derived neurotrophic factor; *GFRα3*, glial cell-derived neurotrophic factor family receptor α3; *ICAM-1*, intercellular adhesion molecule 1; *ILC2*, type 2 innate lymphoid cell; *MBP*, Major basic protein; *nAChR*, nicotinic acetylcholine receptor; *NGF*, nerve growth factor; *NMU*, neuromedin U; *OSMR*, oncostatin M receptor; *PLC*, phospholipase C; *ROS*, reactive oxygen species; *S1PR3*, sphingosine-1-phosphate receptor 3; *TRKA*, tropomyosin receptor kinase A; *TRKB*, tropomyosin receptor kinase B; *TSLPR*, thymic stromal lymphopoietin receptor.

colocalization of DCs and neurons increased proliferation of T cells, which were clustered with nerve-contacting DCs.^{20,21}

Evidence suggests that mast cells are closely associated to bronchial parasympathetic ganglionic neurons in the airways,²² and eosinophils cluster along nerve terminals of parasympathetic postganglionic neurons and infiltrate nerve bundles after allergen challenge,²³ an effect that might be dependent on neuronal release of chemokines, such as eotaxin-1.²⁴

Recent data indicate that neuroimmune interaction can also take place at the level of the vagal sensory ganglia. Thus induction of allergic inflammation causes migration of proliferating DCs.²⁰

Inflammation induces sensitization and plasticity in peripheral nerve fibers innervating the airways

Interaction of inflammatory mediators with sensory neurons. The prerequisite of a sensitization of sensory neurons by inflammatory mediators is expression of the respective receptors on the surfaces of their terminals within the airways. Evidence has been provided that transient receptor potential channels, particularly transient receptor potential ankyrin 1 (TRPA1) and TRPV1, act frequently as a final target for many different immune cell-derived stimuli. This leads to an influx of

cations and then to depolarization of the neurons and enhanced action potential discharge in their respective ganglia, supra-ordinate brain regions, or both.

An overview of inflammatory mediators with sensory neurons is provided in Fig 2, A. Classical mediators of the inflammatory environment interacting with sensory neurons include histamine and neurotrophins. On release of histamine from mast cells during the allergic early-phase reaction, H1 activation leads subsequently to activation of transient receptor potential channels, especially TRPV1, through Gq and phospholipase C.²¹

The neurotrophins NGF and brain-derived neurotrophic factor are mediators released from local resident cells, as well as infiltrating immune cells, after allergen challenge both in animal models and human subjects.¹ The multiple functions of neurotrophins on sensory neurons include the increase in the density of tachykinin-containing nerve fibers¹⁹ associated with enhanced release of tachykinins during airway inflammation,²⁵ the increase in TRPV1 membrane expression,²⁶ and the *de novo* synthesis of neuropeptides in sensory nerve fibers, which lack neuropeptide expression under noninflammatory conditions.²⁷

Jugular and nodose C-fibers differ in their expression of purinergic and neurotrophic factor receptors. Neural crest-derived (jugular and DRG) C-fibers are peptidergic and express

tropomyosin receptor kinase A, the high-affinity receptor for NGF, and glial cell-derived neurotrophic factor family receptor $\alpha 3$, a coreceptor for artemin. Tropomyosin receptor kinase B, the high-affinity receptor for brain-derived neurotrophic factor and neurotrophin-4, and the purinergic receptor P2X2 are predominantly expressed in placodal (nodose) C-fibers. These data indicate that neural crest- and placode-derived C-fibers respond to different endogenous inflammatory signals²⁸ and might have different effects in asthmatic patients.

IL-31 and IL-33 play crucial roles in mediating itch in patients with atopic dermatitis. In patients with asthma, serum levels of both cytokines are increased.²⁹

IL-31 is synthesized by T_H2 cells and mediates its effects by binding to its receptor composed of IL-31 receptor (IL-31R) and oncostatin M receptor. IL-31 is known to promote outgrowth of TRPV1⁺ and TRPA1⁺ small-diameter nerve fibers through IL-31R α , thus leading to hyperinnervation and activation.^{29,30} First clinical studies indicate that long-term treatment with nemolizumab, an anti-IL-31R α mAb, improves the symptoms of allergic disease. However, because IL-31 signaling is not limited to neurons, it remains unclear how these effects relate to neurons.³¹

IL-33, together with other mediators, such as thymic stromal lymphopoietin (TSLP), belongs to the group of epithelial cell-derived cytokines called “alarmins” that regulate T_H2 cytokine-associated inflammation. IL-33 induces AHR in a mouse model of allergic airway inflammation involving ST2³² and might also affect eosinophil function.³³ IL-33 can stimulate sensory neurons directly through ST2 expressed in small-diameter sensory neurons³⁴; however, evidence is also provided that this effect was dependent on IL-33-induced IL-13 release from mast cells.³⁵ A small population of sensory neurons expresses IL-13R $\alpha 1$ and can be activated by a TRPA1- and TRPV1-channel dependent calcium influx.³⁶ Evidence has been provided that neuromedin U is upregulated by IL-13 in sensory neurons. Neuromedin U is able to amplify type 2 innate lymphoid cell-driven allergic lung inflammation.¹⁴

Similarly, TSLP activates a subset of TRPV1⁺ and TRPA1⁺ sensory neurons, whereas TRPA1 channels mediate TSLP-evoked neuronal excitability through a phospholipase C-dependent communication between the TSLP receptor and TRPA1.³⁷

Lately, sphingosine 1 has been discussed as an important player in neuroimmune interaction in asthmatic patients. Sphingosine 1 levels are dramatically increased in a murine model of allergic inflammation. Sphingosine-1-phosphate receptor 3 expression is restricted to TRPV1⁺ cells in the vagal ganglion complex. Treatment with the sphingosine-1-phosphate receptor 3 agonist (FTY720) can trigger AHR in the absence of allergic inflammation.⁵

Interaction of inflammatory mediators with parasympathetic neurons. Both parasympathetic ganglia and postganglionic neurons are located within the airways. Early studies suggest that classical mediators of allergen-induced inflammation, such as histamine, can induce excitability of bronchial parasympathetic ganglion neurons.²² Recent evidence suggests that NGF increases synaptic transmission because of interactions with ionotropic nicotinic ACh receptor located on postganglionic neurons.³⁸

However, because eosinophils are clustered around parasympathetic nerve fibers in the airways, the interactions between them have been extensively examined. Eosinophils are actively

recruited to airway parasympathetic neurons by means of IL-4- and IL-13-dependent neural expression of intercellular adhesion molecule 1 and eotaxin.^{24,39} Eosinophils release eosinophil major basic protein, which blocks autoregulatory prejunctional muscarinic acetylcholine receptor 2 (M2R), leading to enhanced ACh release and finally enhanced smooth muscle contraction (Fig 2, B).⁴⁰

Inflammation causes plasticity of second-order neurons in the brainstem

NTS neurons, the second-order neurons in the brainstem, undergo neuronal plasticity after peripheral nerve sensitization in different animal models of allergic asthma. It is hypothesized that this is associated with long-lasting pathophysiologic modifications in their neural functions and an enhanced central reflex activity. Thus it has been demonstrated that inhaled antigen in a nonhuman primate model of asthma causes an intrinsic increase in excitability⁴¹ and increases the NTS neural firing response to intratracheal capsaicin application in rats.⁴² Additionally, c-Fos and the endocannabinoid anandamide, which exerts proinflammatory properties and is a ligand of TRPV1, are upregulated.^{42,43} c-Fos expression in rat NTS neurons can be reversed by corticosteroid treatment, indicating that it is induced by inflammation.⁴³ The mechanism through which plasticity of NTS neurons is modulated remains unclear. It has been discussed that altered levels of transmitters or neuropeptides released by peripheral neurons projecting to NTS neurons might play an important role. Another plausible alternative is that proinflammatory cytokines cross the (deficient) blood-brain barrier directly or stimulate endothelial cells of the blood-brain barrier, which give rise to secondary paracrine signals by specific transporters or through circumventricular organs.⁴⁴

Transmitters released from peripheral nerve terminals can influence the inflammatory response

Transmitters released by sensory neurons affect airway inflammation. The relevance of sensory C-fibers to drive inflammation has been demonstrated by Talbot et al.⁴⁵ Ablating Nav1.8⁺ sensory neurons or silencing them with QX-314, a charged sodium-channel inhibitor that enters through large-pore ion channels to specifically block nociceptors, substantially reduced ovalbumin- or house dust mite-induced airway inflammation. It is thought that on stimulation, sensory neurons, in particular neural crest-derived C-fibers, release neuropeptides, including CGRP and the tachykinins SP and neurokinin A, from their peripheral terminals (Fig 2, A). These peptides activate their specific receptors (neurokinin 1 receptor [NK1R], neurokinin 2 receptor, and neurokinin 3 receptor for tachykinins and receptor activity-modifying protein [RAMP] 1, RAMP2, and RAMP-3 for CGRP) located on mucosal blood vessels, smooth muscle cells, and submucosal glands, which lead to vasodilation and plasma extravasation, bronchoconstriction and mucus production, respectively.^{46,47} They influence diverse physiologic processes involving integrins, including leukocyte-mediated migration.⁴⁸ The effects on lymphocytes, eosinophils, and neutrophils can be induced by NK1R and CGRP receptor signaling but also secondary effects caused by an SP-induced tachykinin receptor-independent mast cell degranulation have been discussed.⁴⁹⁻⁵¹ Furthermore, neuropeptides alter the motility of

TABLE I. Overview of clinical studies using specific NK receptor antagonists or combinations thereof

Antagonist	Selectivity	Outcome	Reference
SR48968 (saredutant)	NK2R antagonist	● Inhibits bronchoconstriction induced by neurokinin A ● Does not inhibit AMP-induced bronchoconstriction	56 57
MEN11420 (nepadutant)	NK2R antagonist	● Inhibits bronchoconstriction induced by neurokinin A	58
AVE5883	Dual NK1R/NK2R antagonist	● No effect on AHR and airway inflammation ● Enhanced allergen-induced airway responses ● Inhibits bronchoconstriction induced by neurokinin A	55
FK344	Dual NK1R/NK2R antagonist	● No effect on baseline lung function ● No protection against NKA-induced bronchoconstriction	59
DNK333	Dual NK1R/NK2R antagonist	● Inhibits bronchoconstriction induced by neurokinin A	60
CS-003	Triple NK1R/NK2R/NK3R antagonist	● Inhibits bronchoconstriction induced by neurokinin A	61

NKA, Neurokinin A; NK2R, neurokinin 2 receptor; NK3R, neurokinin 3 receptor.

airway DCs,⁵² guide immature DCs to peripheral nerve fibers, and are known to directly activate mast cells.⁵³ This process has previously been referred to as “neurogenic inflammation.”

However, the pathophysiologic relevance of tachykinin release is still inconclusive in human subjects, as seen by nonsatisfactory outcomes in clinical studies using specific or combinations of different NK receptor antagonists (Table I).⁵⁴⁻⁶¹ The lack of effect remains unclear. Boot et al⁵⁵ hypothesize that the dual NK1R/neurokinin 2 receptor antagonist used in their study either showed (1) that neurokinin A and SP do not play an important role in allergen-induced bronchoconstriction and airway inflammation, even though evidence has been provided for this observation in several animal models of asthma; (2) the NK antagonist might not have been potent enough to offer protection against allergen-induced airway response and inflammation; or (3) that greater and longer-lasting treatment and more frequent dosing might be required to warrant adequate drug concentrations within the airways.

The effect of CGRP-dependent signaling has not been investigated in clinical asthma studies; however, different CGRP receptor antagonists and humanized mAbs are currently being tested for the treatment of migraine in clinical studies. The results from the first phase 3 trial showed a trial agent-induced liver injury in a few patients; however, none were considered by the investigators as serious, and none led to discontinuation of the trial.⁶²

Transmitters released by parasympathetic neurons affect airway inflammation. ACh is the dominant transmitter in postganglionic parasympathetic neurons within the airways and an autocrine/paracrine-secreted hormone from nonneuronal origins, including inflammatory cells and airway structural cells, such as epithelial cells. In contrast to neuronal ACh, the release of nonneuronal ACh is nonquantal and not altered in a mouse model of allergic airway inflammation (own unpublished observations). Therefore increased release of ACh in the airways of asthmatic patients, which induces bronchoconstriction and mucus secretion through M3R, is probably attributed to neurons. In an animal model of asthma, treatment with anticholinergic drugs inhibits both airway inflammation and airway remodeling.⁶³ The proinflammatory effects, such as increased chemotaxis of neutrophils and cellular release of reactive oxygen species, are probably mediated by M3R rather than M2R because the selective M3R antagonists inhibit this response, whereas no effect of an M2R antagonist is observed.⁶⁴ However, the majority of proinflammatory effects can be explained by M3R-expressing (not further

characterized) structural cells rather than bone marrow-derived immune cells,⁶⁵ even though the latter express also M3R.⁶⁶

VIP is a neuropeptide originally isolated from porcine intestines. VIPergic parasympathetic nerve fibers are associated with smooth muscle of the trachea, bronchi, and pulmonary vessels.⁶⁷ VIP expression is often colocalized with pituitary adenylate cyclase-activating peptide. Both mediators facilitate vasodilation and bronchodilation.^{68,69} In addition, mast cells and T_H2 lymphocytes synthesize VIP (reviewed by Groneberg et al⁷⁰), whereas the expression in eosinophils is contradictory.⁷¹⁻⁷⁴ VIP regulates the immune response in an anti-inflammatory manner. Supportively, VIP is decreased in the lungs of asthmatic patients, and VIP-deficient mice exhibit a spontaneous airway inflammation and AHR, highlighting the importance of VIP in allergic asthma.⁷⁰ Therefore efforts are being made to develop a VIP aerosol for asthma treatment.¹⁷ Allergic airway inflammation evoked in a rat model was attenuated by intratracheal pretreatment with a VIP analog and led to a 70% reduction of recruited inflammatory cells in bronchoalveolar lavage fluid.

CONCLUSION

Neuroimmune interaction has long been discussed in the pathogenesis of allergic asthma. Because of the lack of clinical studies, it is not possible to clearly define the effect of neuroimmune interaction in patients with asthma. However, the presented data obtained from animal experiments show the diversity and plurality of possible interaction sites between the nervous and immune systems. Establishment of new techniques that allow selective silencing or activation of individual neuronal subpopulations provides the urgently needed proof of concept in various animal models that was past due.

Imagining asthma as a reflex initiated by activation of sensory neurons and resulting in smooth muscle contraction through release of mediators from parasympathetic neurons, there is emerging evidence that neuroimmune interaction takes place at multiple levels. The effect of individual levels needs to be addressed in further studies. This will be the basis for the setup of new clinical studies that are designed to target neuroimmune interaction and therefore neuroinflammation.

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