

Neural integration and allergic disease

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Changes in neural activity play a key role in many symptoms of allergic disease, including sneezing, coughing, itching, and ocular irritation, among others. The mechanisms underlying allergen-induced changes in neural activity (reflexes) are largely unknown and under active investigation. Allergic inflammation can affect neural activity on a variety of levels, including at the primary afferent sensory nerve, integrative centers of the central nervous system, autonomic ganglia, and autonomic neuroeffector junction. At the level of the afferent sensory nerve, mediators released after allergen exposure either directly or indirectly increase neuronal firing. At the level of sensory ganglia, which contain cell bodies that innervate a variety of organs, changes in neuronal excitability may lead to a generalization of allergic symptoms. In the central nervous system, where afferent inputs from throughout the body converge, allergic inflammation may be associated with central sensitization, leading to the modulation of the neural reflexes. Finally, at the autonomic ganglia and neuroeffector junction, allergic inflammation appears to be associated with enhanced ganglionic transmission and neurotransmitter release, respectively. Mechanisms by which allergen challenge affects neuronal activity at various levels of the nervous system are reviewed, with a primary emphasis on studies of airway physiologic factors. (*J Allergy Clin Immunol* 2000;106:S213-20.)

Key words: Allergic inflammation, central nervous system, excitatory postsynaptic potential, neuroeffector junction, neurogenic inflammation, upper airway

Changes in neural activity lead to many symptoms of allergic disease, including sneezing, coughing, ocular irritation, itching, cutaneous flare reactions, gastrointestinal disorders, excessive secretions, and, arguably, bronchospasm. The mechanism by which allergen exposure leads to perturbations in neuronal control has not been precisely worked out. In general terms, the data are consistent with the concept that allergen exposure leads to the release of various “mediators” that interact with sensory and autonomic nerves, which causes changes in their electrophysiologic and anatomic properties. Most often, allergic inflammation affects the nervous system in a manner that leads to increases in electrical activity and increases in neurotransmitter secretion (Table I).¹⁻²⁶

By affecting the activity of nerves, local allergen exposure can lead to changes in the physiologic features of remote unexposed tissues, which has been directly observed

Abbreviations used

CNS: Central nervous system
EAA: Excitatory amino acids
EPSP: Excitatory postsynaptic potential
NMDA: N-methyl-D-aspartate

in a model of intestinal anaphylaxis.²⁷ With respect to questions concerning the “systemic” aspects of local allergen exposure, it is useful to remember that there are 3 key places in the body where neurons that innervate 1 organ are juxtaposed to neurons that regulate another organ: sensory ganglia, central nervous system (CNS), and autonomic ganglia. This anatomic fact, taken together with observations of neurons that affect the function of neighboring neurons at these sites, provides a mechanism by which allergic inflammation in 1 organ may lead to changes in neuronal function that in turn cause profound physiologic effects on organs and tissues that are unexposed to the allergen.

A straightforward example of the phenomenon of allergen-induced increases in neuronal activity has been observed experimentally in the human nose.^{2,28} Applying an irritant (such as bradykinin) to the nasal mucosa of nonallergic people or to seasonally allergic subjects out of season results in little or no response. If the same dose of bradykinin is applied to the nasal mucosa of subjects during the relevant allergen season or to perennially allergic subjects, it causes excessive sneezing and autonomic reflex-mediated secretions. From these data, it can be concluded that the allergic reaction leads to an increase in reflex neuronal activity.

As illustrated in Fig 1, a simple reflex arc can be segregated into the primary afferent nerve response, the integrative response in the CNS, the response within autonomic ganglia, and the response at the postganglionic autonomic near-effector site within the tissue. In this brief overview, literature pertaining specifically to mechanisms by which allergen challenge affects neuronal activity at each of these levels is reviewed. For the sake of brevity and consistency, the data reviewed have been derived primarily from studies of airway physiologic factors. The general principles discussed, however, are likely to be pertinent to other organs in which allergic inflammation occurs.

EFFECT OF ALLERGIC INFLAMMATION ON NEURONAL ACTIVITY

Allergic inflammation and primary afferent nerves

The allergic reaction is associated with heightened sensory nerve activity that leads to sneezing, coughing, ocu-

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TABLE I. Examples of neuronal responses associated with antigen challenge

Nerve type	Effect of antigen challenge	Potential consequences	References
Afferent nerves			
Cutaneous sensory nerves	Increase excitability	Itch, vasodilatation, flare responses	1
Airway sensory nerves	Increase excitability, increase neuropeptide synthesis	Cough, sneeze, reflex bronchoconstriction, reflex mucus secretion, neurogenic inflammation	2-9
Central nerves	Phenotypic switch in neuropeptide input from primary afferent nerves	Increase reflex activity (central sensitization)	10-12
Autonomic nerves			
Airway parasympathetic ganglia	Increase in synaptic efficacy, decrease in filtering	Increase parasympathetic tone in airways	13-15
Sympathetic ganglia	Increase synaptic efficacy, decrease filtering	Generalized increase in sympathetic tone	16-18
Postganglionic parasympathetic nerves	Increase acetylcholine secretion	Bronchoconstriction	19-23
Enteric nervous system	Increase activity	Ion flux across epithelium, increase motility, mast cell activation	24-26

Summary of some neuronal effects of antigen challenge seen in various animal models of allergy.

lar irritation, and itching. These symptoms likely are the result of activation of primary afferent nerve endings (neuron A, Fig 1). Early studies have directly demonstrated that allergen challenge leads to activation of primary afferent fibers in the vagus nerves innervating the pulmonary system.³ The “mediators” and mechanism of antigen-induced afferent nerve activation have not been completely worked out. Small-diameter nerve fibers (ie, C-fibers and A-fibers) can be activated by chemical mediators, often in association with allergic inflammation. These mediators include histamine, serotonin, and various eicosanoids.²⁹ Whether the mediators act directly on the nerve endings or act in an indirect fashion is difficult to discern from *in vivo* studies. For example, exposing guinea pigs to histamine leads to the activation of vagal afferent nerve fibers, but this effect is blocked by beta adrenoceptor activation.⁴ This implies that histamine-induced activation of the vagal afferent nerve fibers may have been due to bronchoconstriction. Studies performed *in vitro* are better suited to address questions to discern direct from indirect activity of mediators on nerve endings. In guinea-pig isolated, innervated airway preparations, histamine does not directly activate vagal afferent nerves that innervate the trachea/bronchus.^{5,30} This provides additional support for an indirect mechanism of action concerning histamine-induced vagal afferent activation *in vivo*. In contrast, other mediators (such as bradykinin) are effective in directly stimulating afferent fibers in the airway wall.^{30,31}

In the final analysis, it is likely that allergic mediators stimulate afferent nerves through both direct and indirect mechanisms. A mediator may directly affect the afferent nerve endings without overtly discharging action potentials. In this case, rather than activating the nerve fiber, the mediator is said to have affected the nerve’s excitability. For example, histamine directly depolarizes the membrane potential of guinea pig vagal sensory neurons but, as mentioned earlier, does not overtly lead to action potential discharge.^{32,33} The depolarization of the mem-

brane is due to the inhibition of resting potassium currents. The increase in membrane resistance and small depolarization renders the nerve more excitable such that subthreshold stimuli may be sufficient for activation. Thus, in the *in vivo* setting, although the stimulus for histamine-induced action potential discharge may indeed be the mechanical force caused by bronchoconstriction, histamine may also act directly to increase the excitability of the nerve such that the mechanically-induced action potential discharge is enhanced. This activity has been observed in the dog; although low doses of histamine *per se* had little effect on the action potential discharge of pulmonary vagal afferent fibers, histamine caused a pronounced potentiation of the nerve’s response to mechanical stimulation.³⁴ An effect on afferent nerve excitability has also been noted in the guinea-pig isolated, innervated airway preparation. In this study, antigen challenge did not result in afferent nerve discharge but did lead to a 4-fold increase in the sensitivity of the fiber to subsequent mechanical stimulation.⁵ The mediator responsible for the antigen-induced increase in excitability is not known, but it does not appear to be histamine or an arachidonic acid metabolite. Irrespective of the mechanism (direct vs indirect), mediators that are released at the site of the allergic inflammation will likely lead to enhanced afferent nerve discharge. The CNS receives this enhanced input, which ultimately results in altered reflex activity.

In addition to their sensory function, some primary afferent nerves may serve local efferent functions. Many slow conducting C-fiber neurons contain neuropeptides in their peripheral and central projections. In the CNS, the neuropeptides act as neurotransmitters at the synapse between the primary afferent and secondary neurons (neuron B, Fig 1). In the peripheral tissues, the neuropeptides can be released locally as a consequence of axon reflexes (Fig 1). An axon reflex is said to occur when action potentials are discharged in the afferent nerve ending; then in the process of conduction towards

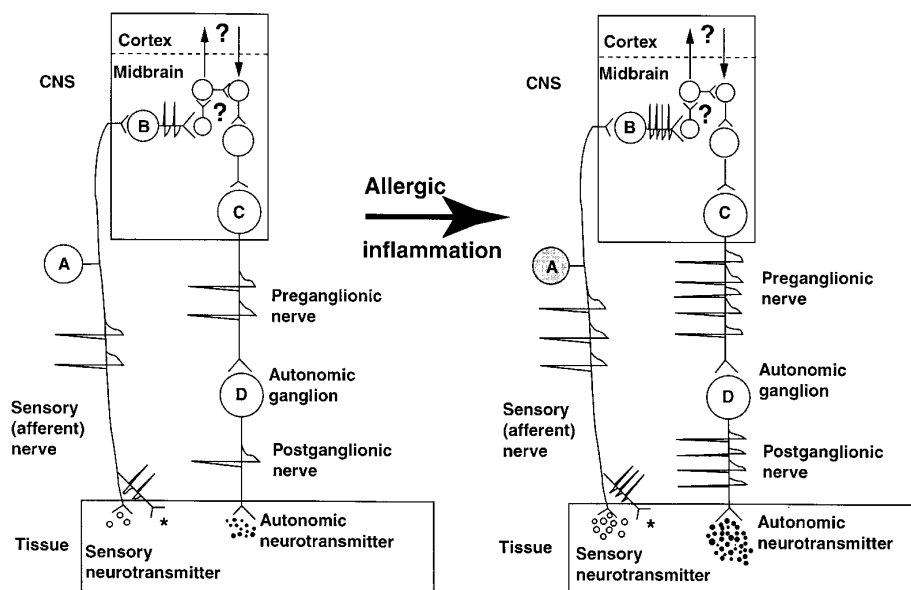


FIG 1. A diagram of a simple reflex arc and how an allergen challenge can affect different neurons in this pathway. **Left**, in the control tissue, a hypothetical response is initiated by the stimulation of a sensory nerve terminal at the asterisk (*) in the tissue; such activation also leads to the so-called "local reflex" (ie, release of sensory neurotransmitter [open circles] within the tissue). The action potentials carried by the sensory nerve, indicated as A, to the CNS release excitatory neurotransmitters that stimulate neuron B, which is located in the midbrain nuclei. The central processing of these signals leads to output from the autonomic (preganglionic) neuron C. Such output from the CNS evokes nicotinic synaptic potentials that may be attenuated by synaptic filtering in the autonomic ganglion D. If an action potential is generated in neuron D, autonomic neurotransmitter (dots) is released, which activates the tissue receptors and the autoreceptors on the postganglionic nerve terminals. During allergic inflammation, **right**, the same stimulus evokes more action potentials and may increase or change the neurotransmitter phenotype in neuron A. Changes in neuron A potentiate synaptic transmission in neuron B, which increases the CNS output by the preganglionic neuron C. Filtering in neuron D is decreased by allergic inflammation, which increases the output from the autonomic ganglia. Finally, mediators that are associated with allergic inflammation affect the postganglionic nerve endings, which causes increased transmitter secretion at the neuroeffector junction.

the CNS (orthodromic conduction), they reach branch points and revert antidromically down the collateral branch, ultimately invading peripheral neuropeptide-laden varicosities. The biologic activity of the released peptides depends on the tissues of innervation. In most tissues, release of sensory neuropeptides (such as neurokinins) leads to vasodilatation, leukocyte adherence to postcapillary venules, and plasma extravasation, in a process collectively referred to as "neurogenic inflammation."^{6,35} Sensory neuropeptides also directly affect the function of various cell types that are associated with the immune system.^{7,36} In human lungs, neurokinins are potent constrictors of airway smooth muscle and effective pulmonary vasodilators through interactions with neurokinin-2 and neurokinin-1 receptors, respectively.^{37,38} In animal models, evidence supports the hypothesis that stimulation of neurokinin receptors is involved in processes that lead to allergen-induced airway hyperactivity.^{39,40}

It is difficult to design experiments that allow for an accurate assessment of the role of sensory (afferent) neuropeptides in human allergic disease. Perhaps the most

convincing case for sensory neuropeptide involvement in an allergic reaction is the allergen-induced cutaneous flare response. In a regimen that desensitizes cutaneous C-fibers, local capsaicin pretreatment results in a decrease in the vascular flare response and itching sensations that are associated with allergen challenge.⁴¹ However, the wheal response was not affected by capsaicin pretreatment, which suggests that other (or additional) mechanisms are responsible for allergen-induced plasma extravasation. There was also evidence that favored a role for neurogenic inflammation in human upper airway pathophysiology. Thus, stimulation of capsaicin-sensitive nerves leads to plasma extravasation and leukocyte infiltration in the nose.¹ Relevant to the present review, neurogenic inflammatory responses in the human nose are enhanced in the setting of allergic rhinitis.^{1,2}

Allergic inflammation may augment the so-called process of neurogenic inflammation by several mechanisms. As discussed earlier, mediators released after allergen challenge can increase the excitability of primary afferent endings, resulting in an increased frequency of action potential discharge. In addition to eliciting

more action potentials, an allergen challenge can lead to an increase in the amount of neuropeptide secreted per action potential.⁸ Cysteinyl-leukotrienes are particularly potent in the augmentation of action potential-induced neuropeptide secretion. In isolated guinea pig airways, the small amount of cysteinyl-leukotriene in the unstimulated airway is insufficient to cause airway smooth muscle contraction, but it effectively augments neuropeptide secretion.^{42,43} This effect of cysteinyl-leukotrienes appears to be due to a direct effect on the primary afferent nerve; it can lead to an inhibition of resting potassium currents, thereby increasing the electrical resistance of the neuron.⁴³ The enhancement of neuropeptide secretion occurs within minutes of antigen challenge. A longer term effect of allergic inflammation is the elevation in synthesis of neuropeptides in sensory cell bodies.⁴⁴ This is attributed, at least in part, to an increase in the transcription of neuropeptide messenger RNA. Finally, allergic inflammation may lead indirectly to an increase in the processes of neurogenic inflammation by decreasing the metabolism of the released neuropeptide. Neurokinins (such as substance P) are eliminated from the tissue by the action of neutral endopeptidase. In guinea pig airways, allergic inflammation is associated with a decrease in neutral endopeptidase activity, which leads to elevations in substance P content.¹⁰

Allergic inflammation and sensory ganglia

The sensory ganglia represent another level of the nervous system in which an allergen challenge can potentially alter neuronal activity. The cell bodies of vagal afferent nerves are located in the nodose and jugular ganglia situated along the cervical vagus nerves. The cell bodies of spinal afferent nerves are located, for the most part, in the dorsal root ganglia that are situated along the spinal cord. Cell bodies of sensory nerves that innervate the nasal mucosa are located in the trigeminal ganglia.

The sensory ganglia are highly vascularized structures that contain a large number of mast cells. Similar to responses in other tissues, challenging vagal sensory ganglia isolated from actively sensitized guinea pigs results in mast cell activation and mediator release.³³ Mediator release in the ganglia leads to several discrete electrophysiologic events that, together, result in an increase in neuronal excitability.^{32,33} After antigen challenge, the electrical threshold for cell activation is decreased and peak frequency of the action potential discharge is increased. In addition, antigen exposure at the level of sensory ganglia can lead to changes in the chemical responsivity of the neurons. For example, guinea pig nodose neurons are typically unresponsive to neurokinins, but within minutes of allergen exposure, these neurons respond to substance P and neurokinin A with a large membrane depolarization. This effect occurred whether the ganglion was challenged with the antigen *in vitro* or whether the allergen was delivered to the lungs by aerosol, *in vivo*.^{45,46}

The cell bodies located within the vagal sensory ganglia innervate thoracic and abdominal organs. Thus, cell bodies that innervate the airways are juxtaposed to those

that may innervate the esophagus, lower gut, and heart. Changes in excitability of the vagal sensory ganglia will likely be organ-nonspecific and may lead to a generalization of allergic symptoms. It should be kept in mind, however, that, whereas the afferent nerve endings can be affected by local allergen exposure, the sensory somata in the ganglia can only be affected after the allergen has reached the circulation. The extent of sensory ganglionic mast cell activation after inhalation or ingestion of allergens is unknown.

Allergic inflammation and the CNS

Sensory information from the periphery arrives at the CNS encoded as action potentials. Action potentials conducted along the primary afferent fibers communicate with the CNS neurons by chemical synaptic transmission (between neurons A and B, Fig 1). The primary excitatory neurotransmitter at this initial junction appears to be glutamate or related excitatory amino acids (EAAs).⁴⁷ Stimulation of glutaminergic receptors causes excitatory postsynaptic potentials (EPSPs) on the secondary neurons that, on reaching a critical threshold, result in action potentials that are then conducted along the axons to other parts of the CNS, ultimately leading to an "output." With respect to our discussion here, the output is in the form of activation or inhibition of preganglionic autonomic fibers or in conscious irritations leading to scratching, coughing, and sneezing.

In the simplest case, sensory input from an organ leads to reflex output to that same organ. For example, light hitting the retina of the eye leads to an autonomic reflex-mediated constriction of the pupil. More often, however, afferent input from an organ can lead to more generalized output. As Widdicombe and Wells⁴⁸ aptly described it in their introduction to their review of vagal reflexes, "It is almost a truism to say that all motor outputs of the autonomic nervous system will be affected by every sensory input, and certainly a true statement if the latter are strong."

The reflex output from the CNS will depend in large part on the nature of the afferent nerve stimulated and the location in the brain of its central processes. Another variable that regulates the output from the CNS is the frequency and duration of the discharge in the primary afferent neuron. Finally, the nature of the transmitter release from the primary afferent fiber will affect the ultimate output from the CNS. The latter 2 points (the frequency and duration of discharge and nature of neurotransmitter release from the primary afferent nerves) can be affected by allergic inflammation. By increasing the excitability of afferent nerve endings, allergic inflammation can lead to inordinate and excessive stimulation of the primary afferent nerve fibers (Fig 1). This may cause both an increase in the intensity of autonomic output and an increase in the diffuseness of that output. A relevant example of a diffuse output that results from the stimulation of a discrete set of sensory fibers is observed in asthmatic subjects, where activation of temperature-sensitive nerve endings in the nasal mucosa leads to reflex cholinergic bronchial contractions.⁴⁹

TABLE II. The phenotypic switch in substance P–producing neurons that project to guinea pig airways

Treatment	Substance P-immunoreactivity in large diameter nodose ganglion neurons that project to the trachea*	
	Control	1 Day after treatment
Antigen (ovalbumin)	3/1261	98/938
Inhalation (0.01-0.1%)	Approx 0.2%	Approx 10%
Nerve growth factor	7/666	52/492
Instillation into trachea	Approx 1%	Approx 10%

Data from Lilly CM, Kobzik L, Hall AE, Drazen JM. Effects of chronic airway inflammation on the activity and enzymatic inactivation of neuropeptides in guinea pig lungs. *J Clin Invest* 1994;93:2667-74; and from Hunter D, Myers A, Undem BJ. Nerve growth factor-induced phenotypic switch in tachykinergic neurons innervating airways. *Am J Respir Crit Care Med* 2000;161:1985-90.

*Capsaicin and bradykinin-insensitive neurons that are sensitive to mechanical stimulation.^{31,35}

Allergen challenge can also affect the type and amount of neurotransmitters in sensory nerves. Within 1 day of exposing the lungs of a sensitized guinea pig to allergen, there is an elevation in the production of neuropeptides (substance P and calcitonin gene-related peptide) in the primary afferent neurons (Fig 1).⁴⁴ In visceral tissues, including the airways, substance P is found almost exclusively in afferent neurons with thin unmyelinated axons (C-fibers). In the airways, these fibers respond to capsaicin and inflammatory mediators (such as bradykinin) but typically are difficult to stimulate with physiologic stimuli.^{29,50}

In the somatosensory system, C-fibers are often termed *nociceptive fibers*. Importantly, the induction of neuropeptide production by allergen inhalation was found to occur in fast-conducting, capsaicin-insensitive afferent nodose ganglion neurons that were not producing the peptides before allergen challenge (Table II).^{10-12,31,35,44} In other words, the allergen challenge caused a phenotypic switch in the nature of afferent nerves that use neuropeptides as their transmitter. Although these neurons are unresponsive to chemical mediators (such as capsaicin and bradykinin), they are sensitive to mechanical stimulation.⁵ If the neuropeptide is transported to the central terminals, allergic inflammation could have substantive effects on the input-output relationship between the primary afferent nerve and the reflex activity by a process often referred to as “central sensitization.”

In the present context, central sensitization refers to the increased efficacy of synaptic transmission in the CNS that occurs as a result of the concerted action of convergent presynaptic inputs (synapse between neurons A and B, Fig 1). This process has been most rigorously studied in the dorsal horn of the spinal cord, where it has been suggested to play a key role in the development of hyperalgesia associated with inflammation.⁵¹ In this case, the converging presynaptic nerves contain neuropeptides or EAAs as their transmitters. It is envisaged that stimulating myelinated primary afferents leads to the release of EAA into the synaptic cleft. The EAAs subsequently activate primarily non-N-methyl-D-aspartate (NMDA) receptors on the postsynaptic membrane. Most NMDA receptors are not activated because, at the resting membrane potential of the postsynaptic neuron, their

function is blocked by magnesium. Activation of the non-NMDA receptors results in transient, graded EPSPs. When inflammation is present, converging C-fiber afferent nerves are activated, which results in the release of neurokinins into the synapse. Neurokinins stimulate neurokinin receptors on the postsynaptic membrane, causing postsynaptic slow and long-lasting membrane depolarization. The long-lasting depolarization increases the function of the NMDA receptors, thereby increasing synaptic transmission and associated hyperalgesia.⁵¹ In the case where there is a phenotypic switch in the neuropeptide-containing neurons (eg, fast-conducting A fibers producing substance P), it can be envisaged that this type of central sensitization occurs physiologically, independently of nociceptive C-fiber activation.⁵²

The peripheral effects of neuropeptide release from primary afferent nerve endings have been given significantly more attention in the allergy literature than has central sensitization. However, it is tempting to speculate that, by affecting synaptic transmission in the brain stem, sensory neuropeptides released from the central end of the afferent nerve may play a larger role in allergic symptoms than those released peripherally. Although the mediators responsible for allergen-induced phenotypic switch of afferent neuropeptide innervation are not known, this response can be mimicked by nerve growth factor, a neurotrophin molecule known to be produced by mast cells.^{10,12,31,35}

Allergic inflammation and autonomic ganglia

Afferent input to the CNS induced by allergen exposure ultimately leads to conscious and subconscious outputs from the CNS. The conscious outputs include dyspnea, upper airway irritation, and itching among others, whereas the subconscious outputs include changes in autonomic nerve activity. The CNS regulates autonomic tone by setting the activity (action potential discharge) in preganglionic neurons. The autonomic preganglionic neurons (neuron C, Fig 1) leave the CNS and synapse with secondary neurons (neuron D, Fig 1) located in either sympathetic or parasympathetic ganglia. Regardless of the nature of the autonomic ganglia, action potentials that arise at the synapse cause the release of acetylcholine from the preganglionic terminals. Acetylcholine

acts on nicotinic receptors on the dendrites and soma of the postganglionic neuron. Similar to the effect of EAA transmitters released from primary afferent nerve in the CNS, acetylcholine causes a transient, fast-EPSP in the postganglionic nerve. If the EPSPs are of sufficient amplitude, action potentials are elicited and conducted along the postganglionic axons to effector cells within the various organs and tissues. The EPSPs often fail to reach the action potential threshold; in this case, the transmission is terminated, and the autonomic ganglia are said to have acted as a filter.⁵³

The filtering capacity of autonomic ganglia neurons is an important regulator of autonomic tone in visceral tissues. Allergic inflammation may enhance autonomic tone by inhibiting the filtering capacity of the autonomic ganglia neurons (neuron D, Fig 1). This has been directly observed in the allergen-sensitized guinea pig model. Like sensory ganglia, sympathetic ganglia have large numbers of mast cells that can be activated by antigen challenge.⁵⁴ Activation of these mast cells leads to mediator release that affects the electrophysiologic features of both the preganglionic terminals and the postganglionic membranes. These effects lead to a profound and long-lasting increase in the synaptic efficacy of the ganglia. That is, antigen challenge leads to a substantial decrease in the filtering capacity of the ganglia. In isolated superior cervical ganglia of guinea pig, the increase in synaptic efficacy after antigen exposure is long lasting and has been termed *antigen-induced long-term potentiation*.¹⁶⁻¹⁸ That transmission through sympathetic ganglia participates in the allergic response is supported by findings in the rat, where decentralization of the superior cervical ganglia protected against the antigen-induced pulmonary inflammation during the late-phase response.⁵⁵ In addition, because neurons located in sympathetic ganglia innervate diverse tissues, modulation of the preganglionic input-postganglionic output relationship is another mechanism by which local allergen-induced activation of mast cells can lead to generalized physiologic effects.

Antigen challenge also affects synaptic transmission through parasympathetic ganglia (ie, between neurons C and D, Fig 1). Parasympathetic ganglia contain far fewer neurons than sympathetic ganglia and are typically situated within or in close proximity to the organ of innervation. In the airways, parasympathetic ganglia are clusters of relatively few neurons located along and within the airway wall.⁵³ Exposing sensitized airways to antigen causes an increase in the excitability of the airway parasympathetic neurons and decreases the filtering capacity of the ganglia.¹³⁻¹⁵ As a consequence, substantial increases in parasympathetic activity at the level of effector cells (eg, smooth muscle, glands) within the airways would be expected.

In addition to directly affecting synaptic transmission, allergic inflammation may also affect ganglionic transmission by increasing peripheral reflex activity. A peripheral reflex occurs when stimulation of primary

afferent nerves leads directly to an activation of autonomic ganglion neurons. Some primary afferent nerve fibers send collateral branches to autonomic ganglia and the CNS. This has been most extensively studied in the gastrointestinal system but also occurs in the airways. Thus, neurokinin-containing afferent fibers are found to be closely associated with parasympathetic ganglia in airways of several mammals, including guinea pigs,^{56,57} equids,⁵⁸ ferrets,⁵⁹ and human beings.⁶⁰ Stimulation of these afferent nerves results in the activation of neurokinin receptors (neurokinin 1 and neurokinin 3) on ganglion neurons, which results in slow EPSPs.⁶¹ In some cases, the slow EPSPs reach an action potential threshold and a peripheral reflex ensues;⁶² in other cases the slow EPSPs may serve to amplify cholinergic synaptic transmission by a mechanism analogous to the aforementioned central sensitization. Allergic inflammation may enhance peripheral reflexes by increasing the activity of the primary afferent fibers or increasing neuropeptide synthesis in these fibers.

Allergic inflammation and the neuroeffector junction

The final location in the reflex pathway that is affected by allergic inflammation is the autonomic neuroeffector junction. Action potentials conducted along postganglionic axons (neuron D, Fig 1) invade neurotransmitter-laden varicosities, which leads to calcium-dependent secretion of the autonomic neurotransmitter (in tissue, Fig 1). The action potential-dependent secretion of autonomic transmitters can be enhanced by allergic inflammation. A good example of this is antigen-induced potentiation of acetylcholine release from postganglionic parasympathetic nerves in the airways. When the number and frequency of action potentials are held constant, exposure of the airways to allergen increases the amount of acetylcholine release from postganglionic cholinergic nerves and increases cholinergic-mediated bronchoconstriction. This is attributed, in part, to allergen-induced inhibition of the cholinergic muscarinic M2 receptor function.^{19,20} Acetylcholine-mediated activation of muscarinic M2 receptors located on the postganglionic cholinergic nerves leads to the inhibition of further acetylcholine release.²¹ By inhibiting this negative feedback loop, allergic inflammation can lead to an increase in cholinergic neurotransmission.

Antibody to major basic protein inhibits the effect of allergen challenge on muscarinic M2 function in the airways, thereby affecting the role of activated eosinophils in this process.⁶³ Several autacoids that are associated with allergic inflammation also amplify acetylcholine release from airway cholinergic nerves.^{22,23} The mechanisms that underlie autacoid-induced potentiation of acetylcholine release have not yet been ascertained. Effects of allergic inflammation on neuroeffector interactions can also be seen in the enteric nervous system, in which allergen challenge is associated with the increased activity of myenteric nerves and changes in gastrointestinal physiologic features.²⁴⁻²⁶

SUMMARY

Studies with various animal models and clinical studies with humans have provided direct evidence that allergen challenge leads to substantial changes in neuronal function. This is not surprising, given that the key symptoms of allergy are neuronal in nature. In any given tissue, neuronal regulation occurs by way of reflex loops. In simplest terms, the reflex is initiated by the activation of primary afferent (sensory) nerve fibers that leads to activation or inhibition of secondary neurons located in the CNS. This, in turn, leads to additional transmission and integration in the CNS that ultimately elicit changes in the reflex output along conscious and autonomic pathways. Laboratory studies have revealed several mechanisms by which allergen challenge can lead to alterations in reflex activity by affecting each of these sites along the reflex pathway. Neuronal reflexes locally initiated in 1 site of the body can profoundly influence the physiologic factors of other sites. By affecting reflex neurophysiologic features, allergen exposure can therefore lead to both local and systemic symptoms. Unfortunately, knowledge about the mediators and electrophysiologic mechanisms of allergen-induced alterations of neuronal activity must be considered rudimentary at best. More detailed knowledge of the complex allergen-induced modulation of reflex neurophysiologic factors is an important prerequisite to the ultimate understanding of the mechanisms that underlie the symptoms of allergic disease.

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