Mechanisms of allergic diseases

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Mechanisms underlying the neuronal-based symptoms of allergy

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Persons with allergies present with symptoms that often are the result of alterations in the nervous system. Neuronally based symptoms depend on the organ in which the allergic reaction occurs but can include red itchy eyes, sneezing, nasal congestion, rhinorrhea, coughing, bronchoconstriction, airway mucus secretion, dysphagia, altered gastrointestinal motility, and itchy swollen skin. These symptoms occur because mediators released during an allergic reaction can interact with sensory nerves, change processing in the central nervous system, and alter transmission in sympathetic, parasympathetic, and enteric autonomic nerves. In addition, evidence supports the idea that in some subjects this neuromodulation is, for reasons poorly understood, upregulated such that the same degree of nerve stimulus causes a larger effect than seen in healthy subjects. There are distinctions in the mechanisms and nerve types involved in allergen-induced neuromodulation among different organ systems, but general principles have emerged. The products of activated mast cells, other inflammatory cells, and resident cells can overtly stimulate nerve endings, cause long-lasting changes in neuronal excitability, increase synaptic efficacy, and also change gene expression in nerves, resulting in phenotypically altered neurons. A better understanding of these processes might lead to novel therapeutic strategies aimed at limiting the suffering of those with allergies. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

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Abbreviations used

CGRP:	Calcitonin gene–related peptide
CNS:	Central nervous system
GDNF:	Glial-derived growth factor
GFL:	Glial-derived neurotrophic factor family ligand
NGF:	Nerve growth factor
PGD_2:	Prostaglandin D_2
TRK:	Tyrosine kinase receptor
TRP:	Transient receptor potential
TRPA1:	Transient receptor potential ankyrin 1
TRPV1:	Transient receptor potential vanilloid 1

Allergy is the consequence of an IgE-driven overreaction of the immune system to what would otherwise be a relatively innocuous stimulus. Clinically, allergy is characterized by symptoms that, by in large, are secondary to an altered nervous system. The panoply of neuronal symptoms depends on the organ in which the reaction occurs but can include itchy and red eyes; rhinorrhea, nasal congestion, and sneezing; urge to cough, dyspnea, airway mucus secretion, and episodic reflex bronchospasm; dysphagia, altered gastrointestinal motility, and discomfort; and cutaneous itching and flare responses. These events are either *in toto* or in part secondary to changes in neuronal activity. Therefore allergy can be characterized as an immune-neuronal disorder (Fig 1).

Immunologists predominate among those interested in investigating the mechanisms of allergy. Over the past few decades, scientists have made tremendous progress in untangling the complex web comprising the immunologic basis of allergy. This includes both the afferent (sensitization) and efferent (inflammatory cell recruitment and activation) limbs of the response. The outcomes from these investigations are filling pharmaceutical pipelines with rational, clever, and exciting therapeutic strategies aimed at quelling the inflammation associated with the allergic reaction.

However, one might argue that the immune-driven inflammation associated with allergic reactions might in some cases be trivial unless transduced into the neurogenic symptoms of suffering (eg, itch, cough, bronchospasm, motility disturbance, pain, sneeze, skin conditions). Yet although the anti-inflammatory pipeline in allergy therapeutics is teeming with activity, the antineuromodulatory pipeline is largely empty. This might be due to the less than appropriate attention given to the neuronal aspect of this immune-neuronal disorder.

Here we have attempted to review literature that provides a sense of how the nervous system is affected by an allergic

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Terms in boldface and italics are defined in the glossary on page ■■■.

reaction. Space limitations preclude an exhaustive review of this literature, and therefore instead prime examples are selected to reveal some of the more fundamental principles of allergen-induced neuromodulation. We have not reviewed the clinical scientific literature that has investigated neuronal symptoms of allergy nor have we dealt with the issue of the role of higher brain centers (emotion and stress) on the allergic response. We have also largely avoided the related important aspects of mast cell–nerve interactions that occur independently of the immediate hypersensitivity response, as well as the literature that pertains to mechanisms by which the nervous system can modulate the immune response. Rather we have focused here on basic mechanistic investigations of allergy-induced neuromodulation that will give the reader a sense of the peripheral neurologic substrates of allergy.

GENERAL PRINCIPLES OF SENSORY-AUTONOMIC INNERVATION

Sensory (afferent) nerves sense the local tissue environment.[1] Their peripheral nerve terminals are "free" and do not synapse with other nerves. Instead, these peripheral sensory terminals synapse with the local tissue environment. Peripheral sensory terminals express various receptors and ion channels that transduce environmental signals into electrical signals (ie, ***action potentials***). In the visceral and somatosensory systems, these stimuli include touch and other mechanical perturbations, temperature, pH, osmolarity, and various types of chemical stimuli. The action potentials conduct along the axon centrally, past the cell body that resides in a specific peripheral ganglion (either dorsal root ganglia, vagal nodose ganglia, vagal jugular ganglia, or trigeminal ganglia), and into the central nervous system (CNS), where the signal is transposed into ***neurotransmitter*** release at the nerve's synapse with second-order central neurons.

Sensory nerves are heterogeneous with respect to sensitivity to stimuli (ie, receptor expression), size, myelination, conduction velocity, and neuropeptide and neurotransmitter content. In general, however, sensory nerves fall into 2 main categories: those that have been specifically adapted to detect routine physiologic stimuli (eg, touch, hearing, smell, mild temperature, changes in blood pressure, and osmolarity) and those that detect noxious or potentially noxious stimuli, such as physical damage, chemical irritants, and strong changes in pH.

Sherrington[2] was the first to specifically describe these latter types of nerves in his famous book, *The Integrative Action of*

GLOSSARY

ACTION POTENTIAL: A mammalian nerve fiber at rest is in a state of electronegativity because of concentration gradients of ions and membrane permeability for particular ions. An action potential involves brisk changes in the membrane potential that spread rapidly down the length of the nerve fiber membrane. A normal resting negative membrane potential changes suddenly (within a few 10,000ths of a second) to a positive potential (depolarization) and then back to a negative potential (repolarization). Events that cause an increase in the membrane potential from electronegativity toward the zero level trigger voltage-gated sodium channels to begin opening, causing a further increase in the membrane potential and more opening of voltage-gated sodium channels until all channels have been opened. Potassium-gated channels then begin to open and sodium channels close, leading to termination of the action potential.

CYSTEINYL LEUKOTRIENE D_4 (LTD_4): LTD_4 binds to cysteinyl leukotriene receptor (CysLT) 1 and CysLT2. CysLT1 promotes bronchial smooth muscle contraction and regulates various aspects of the immune system. Montelukast antagonizes CysLT1.

EICOSANOID FAMILY: A class of lipids derived from polyunsaturated fatty acids (eg, arachidonic acid) that mediate inflammation.

ENTERIC: A nervous system exclusive to the gastrointestinal tract. The enteric system contains approximately 100 million neurons, which is comparable to the number of neurons in the spinal cord. It contains an outer (myenteric) plexus and an inner (submucosal) plexus. Sympathetic and parasympathetic nerves connect with these 2 plexuses. Enteric nerves secrete a variety of neurotransmitters, including acetylcholine, norepinephrine, serotonin, dopamine, substance P, and vasoactive intestinal polypeptide.

MECHANOSENSORS: A sensory receptor that detects mechanical compression or stretching of the receptor or adjacent tissues. Respiratory muscle mechanosensors provide afferent input to neurons in the medulla, as well as the sensory cortex.

MYELINATED: Nerve fibers with axons surrounded by a myelin sheath. Schwann cells envelop axons and rotate around the axon many times, creating layers of membrane containing the lipid substance sphingomyelin. Sphingomyelin acts as an electrical insulator and is capable of decreasing ion flow through the membrane approximately 5000-fold. Uninsulated junctions between Schwann cells are termed the node of Ranvier. Action potentials "jump" from node to node to increase the velocity of nerve transmission in myelinated fibers.

NEUROTRANSMITTER: A chemical substance secreted by neurons that causes signal transmission in CNS synapses. Most synapses involved in CNS signal transmission are chemical synapses. The neurotransmitter binds to membrane receptor proteins of the next neuron to excite, inhibit, or modify the sensitivity of the neuron. There are more than 40 neurotransmitters, including acetylcholine, norepinephrine, histamine, serotonin, and gamma-aminobutyric acid.

PARASYMPATHETIC: Nerve fibers of the autonomic nervous system that leave the CNS through cranial nerves III, VII, IX, and X, as well as spinal sacral nerves. Most parasympathetic nerves are in the vagus nerves (cranial nerve X). Parasympathetic nerves also contain preganglionic and postganglionic neurons. Most parasympathetic postganglionic neurons are cholinergic.

REACTIVE OXYGEN SPECIES (ROS): Substances typically generated at a low frequency during oxidative phosphorylation in the mitochondria, as well as in a variety of other cellular reactions. ROS can exert cellular damage by reacting with intracellular constituents, such as DNA and membrane lipids.

SYMPATHETIC: Nerve fibers of the autonomic nervous system that originate in the spinal cord between T1 and L2. They pass first into paravertebral chains of ganglia and then to tissues and organs. Each sympathetic nerve is composed of a preganglionic neuron and a postganglionic neuron. Preganglionic nerves can synapse in a paravertebral ganglion or a peripheral sympathetic ganglion (eg, celiac ganglion). Preganglionic nerves in both the sympathetic and parasympathetic systems are cholinergic (ie, secrete acetylcholine). Most sympathetic postganglionic neurons are adrenergic (ie, secrete norepinephrine).

TACHYKININS: A class of neuropeptides, which includes the sensory afferent neurotransmitter substance P.

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