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Mediators of allergic rhinitis

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Although histamine is the principal mediator of the immediate allergic reaction, other inflammatory mediators as well as neuropeptides also contribute to rhinorrhea and nasal congestion. Within minutes of exposure to allergen, mast cells produce histamine, leukotriene C_4, and prostaglandin D_2. A concomitant increase occurs in neuropeptides and bradykinin. In vitro mast cell activation also leads to the release of tumor necrosis factor–α, several interleukins, and granulocyte-macrophage colony—stimulating factor. Because all these various mediators and neuropeptides may play a role in producing rhinorrhea and congestion, antihistamines alone cannot control all of the symptoms of allergic rhinitis. However, the combination of antihistamines with topical corticosteroids can inhibit the generation, release, and activity of most if not all of the mediators potentially involved in the allergic response. (J ALLERGY CLIN IMMUNOL 1992;90:699-704.)

Key words: *Allergic rhinitis, mast cells, mediator release, nasal mucosa, neuropeptides*

Allergic rhinitis is the most common immunologic disease and the most common chronic disease experienced by humans. It affects approximately 10% to 20% of the American population. More than 1 billion dollars are spent yearly on over-the-counter and prescription allergy preparations. In addition, allergic rhinitis accounts for 2.5% of all physician visits for all diseases, and another 0.5% of all visits are for receiving allergy immunotherapy.[1]

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To understand the pathophysiology of allergic rhinitis, it is first necessary to be knowledgeable about nasal anatomy. (See the box "Anatomy of the nasal mucosa" that appears later in this article.)

MEDIATORS OF ALLERGIC RHINITIS

To assess which mediators are important in inducing the symptoms of allergic rhinitis, it is important to know which mediators are released during an allergic reaction. Mast cell activation after antigen challenge is well described. In electron micrographic studies of resting mast cells, the ubiquitous, densely stained, secretory granules are roughly spherical, and most are 0.25 to 0.5 μm in diameter. Most granules comprise a dense, amorphous matrix with embedded or interspersed crystalline constituents in the form of scrolls, gratings, or lattices. Scrolls are found most commonly in cells undergoing degranulation. It should be noted

Abbreviations used

LTC_4, LTD_4, LTE_4:	Leukotrienes C_4, D_4, and E_4
PGD_2:	Prostaglandin D_2
CGRP:	Calcitonin gene-related peptide
SP:	Substance P
VIP:	Vasoactive intestinal peptide
TNF-α:	Tumor necrosis factor–α
IL:	Interleukin
GM-CSF:	Granulocyte-macrophage colony–stimulating factor
PAF:	Platelet-activating factor
MC_T:	Mast cells that contain only tryptase
NKA:	Neurokinin A
GRP:	Gastrin-releasing peptide

that even in experimentally unstimulated nasal tissue, variable numbers of degranulating mast cells are present. In unstimulated nasal epithelium, one third of mast cells may be degranulated, and the percentage progressively increases from the lamina propria to the mucosal surface.

Early events after IgE-mediated stimulation of human lung mast cells include granule swelling with loss of stainable matrix, an increase in the proportion of granules demonstrating the scroll pattern, and the appearance of electron-dense clumps in the granules. Granules progressively become more ropelike, and granule contents eventually become soluble. In nasal and lung mast cells, extruded granules are never observed intact in the external environment of the degranulated nasal mast cell. Over a few-minute period, the degranulating mast cell may discharge the solubilized contents from 1000 secretory granules into the surrounding interstitial fluid.[2]

Within minutes of exposure to allergen, the mast cell products histamine, LTC_4, and PGD_2 can be measured in nasal washings.[3] Mast cells are found near superficial postcapillary venules (which respond with increased vascular permeability), near sensory nerves (which respond by initiating the itch sensation and so eliciting the sneeze reflex), and near glands that respond by secretion. Many of the effects associated with acute allergic rhinitis can be reproduced by histamine challenge,[4] and antihistamines prevent many of the symptoms of allergic rhinitis.[5] Thus histamine challenge to the nose leads to pruritus, sneezing, nasal congestion that is induced by vasodilation, increased vascular permeability, and reflex cholinergic stimulation of glandular secretion in both the ipsilateral and contralateral nares. Activation of mast cells also leads to the generation of the 5-lipoxygenase products, LTC_4, LTD_4, and LTE_4, which can induce vascular permeability, vasodilation, and mucous secretion.

Concomitant with the increase in mast cell mediators, an increase in the neuropeptides CGRP, SP, and VIP[6] and in bradykinin[7] can also be observed. In addition, mast cell activation in vitro leads to the transcription and/or translation and release of a number of cytokines including TNF-α, IL-1, -3, -4, -5, and -6, and GM-CSF.[8-11] During an allergic response, the nose also contains many inflammatory cells that may contribute cytokines to the allergic response. Lymphocytes comprise most of the cells in the nasal submucosa. After allergen challenge, lymphocytes in the mucosa of allergic individuals transcribe message for the TH-2 products, IL-4 and IL-5, as well as for GM-CSF[12] and IL-3. Only scant data are available on cytokines recovered in lavages after antigen challenge; however, IL-1, -2, -3, -4, and -5 and GM-CSF have been recovered,[13-17] IL-1 and IL-2 during the first 30 minutes, and all of them during the ensuing 10 hours.

SYMPTOMS OF ALLERGIC RHINITIS AND RESPONSIBLE MEDIATORS

The cardinal symptoms of allergic rhinitis include pruritus, sneezing, rhinorrhea, and nasal congestion. Pruritus and sneezing are each induced by sensory nerve stimulation, whereas congestion results from vasodilation with resultant engorgement of cavernous sinusoids. Rhinorrhea can be induced by increased vascular permeability as well as direct glandular secretion. During the first 30 minutes after allergen challenge, concomitant with an increase in mediators, an enormous increase occurs in the plasma proteins albumin and IgG and a smaller increase in the glandular proteins lysozyme, lactoferrin, and secretory IgA in nasal lavage fluids.[18]

In the nares contralateral to antigen challenge, rhinorrhea also occurs and is comprised entirely of glandular proteins. This contralateral rhinorrhea appears to be cholinergically mediated because it can be inhibited by pretreatment with atropine. Thus antigen-induced rhinorrhea is caused mostly by vascular permeability on the ipsilateral side only and by reflex-mediated glandular secretion on both the ipsilateral and contralateral sides.[19] This pattern is identical to that of histamine-induced rhinorrhea. In addition, antigen challenge leads to a late inflammatory response,

TABLE I. Symptoms and pathologic features of allergic rhinitis and proposed mediators

Symptom	Pathologic feature	Proposed mediator
Pruritus	Sensory nerve stimulation	Histamine (H_1) Prostaglandins
Nasal obstruction	Mucosal edema due to vascular permeability and vasodilation	Histamine (H_1) Kinins LTC_4, LTD_4, LTE_4 TNF-α CGRP SP
Sneezing	Sensory nerve stimulation	Histamine (H_1) LTC_4, LTD_4, LTE_4
Rhinorrhea	Increased secretion of mucus	Histamine (via muscarinic reflex) LTC_4, LTD_4, LTE_4 SP VIP
Hyperirritability and prolonged congestion	Late-phase reaction	Inflammatory factors Eicosanoids Chemotactic factors IL-1, IL-5, IL-6, IL-8, and TNF-α PAF

which is associated with prolonged congestion,[20] and to an increased responsiveness to both antigen and histamine challenge.[21]

Each of the symptoms of acute allergic rhinitis, as well as the secretion of plasma and glandular proteins, can be inhibited largely by pretreatment with an H_1 antagonist. Sneezing and pruritus are caused exclusively by stimulation of histamine H_1 receptors on sensory nerve endings. Histamine-induced vasodilation and increased vascular permeability are also directly mediated by H_1 receptors on blood vessels. In contrast, histamine-induced glandular secretion is not mediated directly but rather by stimulation of a cholinergic reflex. Thus histamine is capable of inducing all of the features of acute allergic rhinitis except for the late-phase reaction (Table I).

Although it is clear that histamine is a major mediator of acute allergic rhinitis, other mediators are also important in causing congestion (through vasodilation) and rhinorrhea (through vascular permeability and glandular secretion). In addition to histamine, newly generated leukotrienes and bradykinin can induce both vasodilation and increased vascular permeability, whereas leukotrienes can also induce glandular secretion. Both parasympathetic and sensory neurons are stimulated during allergic reactions, and several of the neuropeptides localized to these neurons increase in nasal secretions after antigen challenge. The neuropeptides SP and VIP are capable of inducing glandular secretion, whereas CGRP, which is colocalized with SP to sensory fibers, is capable of inducing vasodilation and contributing to congestion. Mast cell–derived chemotactic factors as well as PAF, IL-5, and IL-8 are probably instrumental in attracting inflammatory cells into the late-phase reaction. IL-1, IL-6, and TNF-α also probably play a role in inducing inflammation through upregulation of adhesion molecule expression.[22] IL-2 may be important in activating lymphocytes after allergen challenge, providing the message for additional cytokine production. Finally, IL-3, -4, -6 and possibly -10 play a role in promoting mast cell growth and differentiation and in enhancing IgE synthesis.

Histamine is the major mediator of the immediate allergic reaction, although other inflammatory mediators and neuropeptides may also play roles in producing rhinorrhea and congestion. Thus antihistamines alone are insufficient to prevent all of the symptoms of allergic rhinitis. The late-phase reaction is triggered by the release of chemotactic factors from mast cells as well as by the generation and release of inflammatory and chemotactic cytokines. A combination of antihistamines and topical corticosteroids is capable of inhibiting the generation, release, and activity of most if not all of the mediators potentially involved in the allergic response.

ANATOMY OF THE NASAL MUCOSA

The nasal mucosa is lined with a pseudostratified columnar epithelium resting on a basememt membrane that separates it from the deeper submucosal structures (Fig. 1). A bilayered epithelial lining fluid layer is on the epithelial surface. The outer layer consists of a sticky mucous blanket that traps foreign particles, including bacteria, viruses, and allergens. This layer also holds and concentrates certain glandular and vascular proteins. The outer mucous or gel layer is constantly being swallowed and replaced by glandular secretions.

The lower layer of the epithelial lining fluid is an aqueous periciliary layer. Cilia beating in this layer transport the mucous layer only by the tips of the cilia during the propulsive portion of the stroke. The periciliary layer is where the aqueous proteins secreted by the serous cells of the submucosal glands are concentrated. This layer provides most of the antimicrobial functions of secretions, whereas the outer gel layer traps and transports foreign particles through mucociliary clearance.[23]

Four types of cells contribute to the epithelium: ciliated columnar epithelial cells, nonciliated columnar epithelial cells, goblet cells, and basal cells. The goblet cells constitute the glandular portion of the epithelium. These cells, as well as the deeper submucosal glands, secrete mucous glycoproteins and other proteins onto the epithelial surface. All the columnar epithelial cells contain microvilli, nonmobile projections that increase cell surface area and contribute to hydration. In addition, most of the columnar cells contain cilia, which beat in a wavelike pattern through the sol layer of the mucous blanket to propel the sticky upper mucous layer. This process is the first line of defense against respiratory pathogens, and failure of this system leads to sinusitis, such as in Kartagener's syndrome.

Below the epithelial basement membrane is a submucosa rich in glands. Three types of glands can be found: mucous, seromucous, and serous glands. In seromucous glands, the mucous cells form the central portion of the gland, whereas serous cells form a crescent over the mucous cells. Mucous glycoproteins localize immunohistochemically to the mucous cells, whereas lysozyme, lactoferrin, neutral endopeptidase, secretory leukoprotease inhibitor, and secretory IgA localize to the serous cells.[23] The interstitial cells of the nasal mucosa are comprised primarily of lymphocytes with interspersed fibroblasts and mast cells.

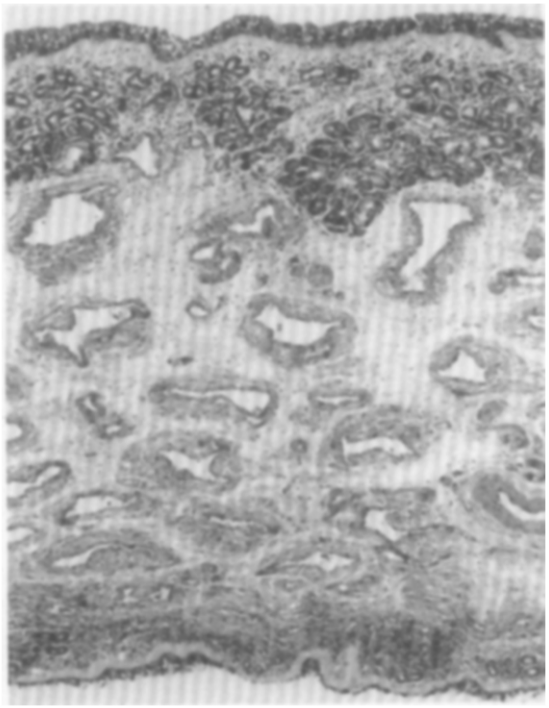

FIG. 1. This cross-section of nasal mucosa clearly shows the columnar epithelium *(top)* separated by the basement membrane from deeper mucosal structures *(bottom)*. Epithelial surface is coated with two layers of mucus. The top layer traps and removes foreign particles, and the bottom layer is responsible for antimicrobial functions. Beneath the basement membrane is the lamina propria, in which the lymphocyte population resides. Deeper still is the glandular area, composed of seromucous glands. Venous sinusoids comprise the core of the tissues.

In normal subjects, there are approximately 150 lymphocytes per millimeter of basement membrane in the nasal mucosa.[24] Two thirds of these cells are $CD4^+$ and the remainder are $CD8^+$.[24] The population of $CD4^+$ and $CD8^+$ cells does not change during the allergy season.[25]

There are approximately 10 mast cells/mm of basement membrane, most of which are of the MC_{TC} subtype (mast cells that contain both tryptase and chymase).[25, 26] The mast cells are located in close proximity to the nerves and blood vessels and are occasionally seen between epithelial cells. Most nasal

mast cells are found in the superficial 200 μm of mucosa, generally clustered beneath the basement membrane and in the epithelium. The number of mast cells in normal subjects is approximately 7000/mm^3 in the tissue and only 50/mm^3 in the epithelium. Epithelial mast cells are of the MC_T subtype,[26] and the number of these epithelial mast cells increases during the allergy season.[27] The total number of mast cells and lymphocytes does not increase during the allergy season.[25] Interestingly, the only cells bearing IgE in the human nasal mucosa are mast cells.[26]

The nose is one of the most vascular organs of the body, with a total blood flow per cubic centimeter of tissue exceeding that in muscle, brain, and liver.[28] Blood flows in the superficial mucosa are at a rate of 42 ml/100 gm of tissue per minute, which is exceptionally high.[29] Blood vessels feeding the epithelium and glands contain fenestrations in their basement membranes, similar to those of the renal glomeruli. This anatomic arrangement facilitates rapid extravasation of fluid through the vascular walls, presumably to assist in the hydration of inspired air.

Although blood in the nose flows typically from arteries to capillaries and into veins, numerous arteriovenous anastomoses are also found in the nasal mucosa. In addition, cavernous sinusoids lie between the capillaries and venules. These vessels, which are most dense in the inferior and middle turbinates, contain smooth muscle cells that are under sympathetic control.[30] Normally, the cavernous sinuses are contracted; however, under conditions of reduced sympathetic tone or cholinergic stimulation, this erectile tissue becomes engorged and causes considerable nasal obstruction.

Nasal neuropeptides

Although the veins and venules in the nasal mucosa are predominately innervated by sympathetic nerves, the arterial vessels that supply the glands, as well as the glands themselves, are innervated by both cholinergic and sympathetic fibers.[31]

Cholinergic stimulation causes arteriolar dilation, theoretically enhancing passive diffusion of plasma protein into the glands. In addition, the same cholinergic stimulation simultaneously induces active secretion from serous and mucous cells.[19] Most of the cholinergic receptors on nasal glands and blood vessels are of the M3 type.[32, 33] In addition to containing the classic neurotransmitters, the three types of nerve fibers innervating the nose (the sensory, cholinergic, and sympathetic nerves) also contain neuropeptides. Sensory fibers from the trigeminal nerve are capable of responding to noxious stimuli such as mechanical or thermal injury, mediators such as bradykinin or histamine, and acute injury.[34] These nerves form the afferent limb of several central reflexes and also participate in local vascular responses that are similar to the cutaneous wheal-and-flare response.

Several neurotransmitters including CGRP, the tachykinins SP and NKA, and GRP have been found in sensory nerves.[34] Parasympathetic neurons contain acetylcholine as well as VIP and a neuropeptide called peptide histidine methionine. Sympathetic neurons contain norepinephrine and neuropeptide Y, a peptide that has many of the same effects as norepinephrine but produces very long-lasting vasoconstriction.

The exact role of these neuropeptides in allergic diseases is still being determined. Immunohistochemical studies have demonstrated weak staining for CGRP, SP, and NKA fibers in the nasal mucosal epithelium. The submucosal glands, arterioles, and venous sinusoids are innervated by fibers staining for GRP, CGRP, SP, NKA, and VIP. On the assumption that these neuropeptides can affect only structures that contain specific receptors, the distribution of neuropeptide binding sites has also been studied. The only neuropeptide for which both fibers and receptors have been localized to the epithelium is SP.[35]

Submucosal glands are rich in both receptors and fibers for (in descending order) GRP, VIP, and SP.[35-37] The venous sinusoids, however, contain only a few neuropeptide receptors for CGRP, SP, and VIP. In contrast, arterioles contain receptors for all of the neuropeptides studied except GRP; however, most of the receptors are for CGRP, which causes vasodilation,[38] or for neuropeptide Y, which induces vasoconstriction.[39]

To assess the effect of these neuropeptides on glandular secretion, nasal turbinate explants were incubated ex vivo with control fluids or with various neuropeptides, and the secretion of glycoconjugates from mucous cells and of lactoferrin from serous cells was measured.[19] Both GRP and VIP were potent secretagogues for serous cells and somewhat less so for mucous cells. SP and NKA were weak mucous cell secretagogues, whereas the latter was also a weak serous cell secretagogue.[19]

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