

Pathogenesis of allergic rhinitis

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Allergic rhinitis is an increasing problem for which new and exciting therapies are being developed. These can be understood through an appreciation of the newer concepts of pathogenesis of allergic rhinitis. Allergen induces Th2 lymphocyte proliferation in persons with allergies with the release of their characteristic combination of cytokines including IL-3, IL-4, IL-5, IL-9, IL-10, and IL-13. These substances promote IgE and mast cell production. Mucosal mast cells that produce IL-4, IL-5, IL-6, and tryptase proliferate in the allergic epithelium. Inflammatory mediators and cytokines upregulate endothelial cell adhesion markers, such as vascular cell adhesion molecule-1. Chemoattractants, including eotaxin, IL-5, and RANTES, lead to characteristic infiltration by eosinophils, basophils, Th2 lymphocytes, and mast cells in chronic allergic rhinitis. As our understanding of the basic pathophysiologic features of allergic rhinitis continues to increase, the development of new diagnostic and treatment strategies may allow more effective modulation of the immune system, the atopic disease process, and the associated morbidity. (J Allergy Clin Immunol 1997;99:S763-72.)

Key words: Allergic rhinitis, mast cell, inflammatory response, eosinophils, adhesion molecules

The discontented face of a person with allergic rhinitis is common to practicing allergists, and it is becoming better recognized by primary care providers. In recent years, great strides have been made in understanding the pathophysiologic process that leads to the development of the itch, sneeze, congestion, drip, fatigue, and dysfunction of allergic rhinitis. The features of allergen sensitization, mast cell events that follow allergen reexposure on a mucosal surface, and chemoattraction of the spectrum of inflammatory leukocytes that lead to the histologic features of allergic rhinitis are covered in this review.

SENSITIZATION

The respiratory mucosa of all human beings is exposed to picogram to nanogram quantities of pollen grain, dust mite fecal particles, animal dander, and other proteins. These mucosally deposited antigens are thought to be processed by Langerhans cells¹ and possibly other antigen-presenting cells (APCs) in the mucosal epithelium. The antigens are proteolytically cleaved into 7- to 14-amino acid long peptides that bind to the antigen recognition sites of some major histocompatibility complex (MHC) class II (HLA-DR, DP, DQ) molecules. The types of polymorphic MHC class II molecules expressed by each person and the affinity of the molecules for specific antigenic peptides contributes to the "decision" of the immune system to develop or not to develop an immune response to a specific protein.²

Abbreviations used

APCs:	Antigen-presenting cells
CKR:	Chemokine receptor
ECP:	Eosinophil cationic protein
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
HMT:	Histamine N-methyltransferase
ICAM-1:	Intercellular adhesion molecule 1
LT:	Leukotriene
MHC:	Major histocompatibility complex
NO:	Nitric oxide
PECAM-1:	Platelet endothelial cell adhesion molecule 1
PG:	Prostaglandin
TNF:	Tumor necrosis factor
VCAM-1:	Vascular cell adhesion molecule 1

These APCs may traffic to adenoids and tonsils in the ring of Waldeyer and local draining lymph nodes.

At some as yet unknown location, antigen is presented to naive Th0 lymphocytes that have been newly released from the thymus. It is presumed that these Th0 cells express cell-surface markers that allow them to home to airway mucosal vessels. In persons with an atopic diathesis, the antigen-specific T-cell receptors of Th0 cells recognize the antigenic peptides presented by MHC class II loci on APCs. Simultaneous contact is made between CD4 and MHC class II loci, CD28 and B7, and between other intercellular receptors and ligands on the T cell and APC, respectively. Cytokines may be exchanged. These composite factors trigger the peptide-specific Th0 cell to differentiate into a Th2 lymphocyte. Newly minted Th2 cells become committed to release their characteristic combination of cytokines (IL-3, IL-4, IL-5, IL-9, IL-10, IL-13, granulocyte-macrophage

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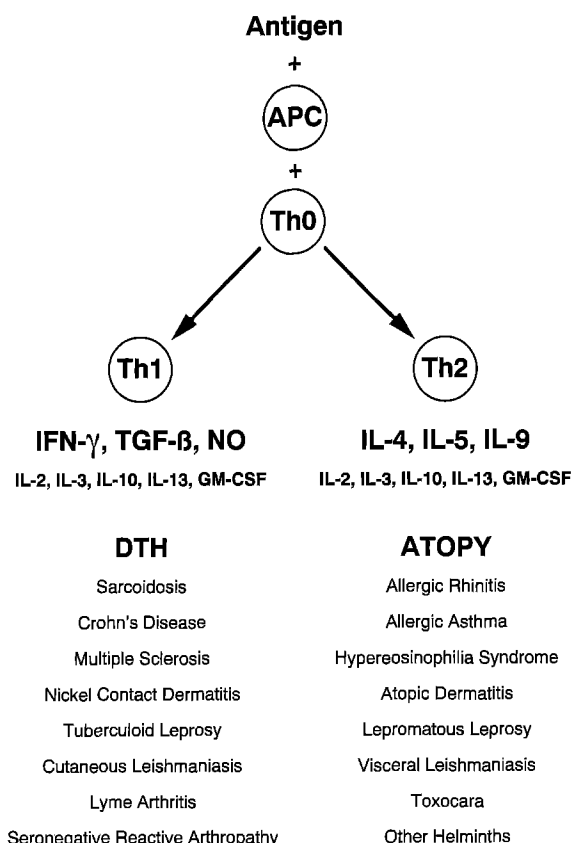


FIG. 1. When antigen is presented by antigen-presenting cells (APCs) to Th0 lymphocytes, the Th0 cells may differentiate into either Th1 or Th2 subtypes. In human beings,³ Th1 cells are characterized by the presence of interferon- γ (IFN- γ) and tumor growth factor β (TGF- β), whereas Th2 cells express IL-4, IL-5, and IL-9. Both sets of human lymphocytes express IL-2, IL-3, IL-10, IL-13, and GM-CSF. Th1 cells induce macrophage activation and granuloma formation.⁴ Th2 cells induce atopy and promote IgE, mast cell, and eosinophil production. This fundamental division in T cells appears to correlate with the phenotypic expression of various human diseases.⁴ NO, Nitric oxide; DTH, delayed-type hypersensitivity.

colony-stimulating factor [GM-CSF], and possibly others), which may maintain the local pro-atopy environment, stimulate induction of B-cell IgE production (IL-3, IL-4), and inhibit competing immune responses such as the development of Th1 delayed-type hypersensitivity responses (IL-13, IL-4) (Fig. 1).

Newly generated IgM-bearing B cells that recognize sensitized allergen and receive appropriate CD40-CD40 ligand signals plus cytokines, such as IL-4, IL-6, IL-10, and IL-13, undergo heavy-chain switching to produce IgE. In the setting of continued antigen presentation, these committed B-cell clones may continue to evolve by means of somatic mutation to produce higher avidity IgE molecules. The site of IgE heavy chain switching and IgE production in allergic rhinitis is yet to be defined.

B-cell IgE production may be enhanced by exposure to aromatic hydrocarbons from diesel exhaust.⁵ Diesel exhaust particles also increase production of IL-2, IL-4,

IL-5, IL-6, IL-10, and IL-13 mRNA and IL-4 protein from cells recovered in nasal lavage fluid.⁶ These pollutant effects may contribute to the increase in allergic rhinitis that has occurred in western industrialized societies in the past few decades.

MAST CELLS

Circulating IgE binds to high-affinity Fc ϵ receptors (Fc ϵ -RI) on the surfaces of mast cells and basophils. It is unclear if mast cells circulate through regions of IgE production to pick up their IgE or if they passively adsorb the IgE from plasma or interstitial fluid. Mast cells exit in postcapillary venules in the mucosa and reside in the submucosal regions. These mast cells are thought to express chymase, tryptase, and tumor necrosis factor α (TNF- α) and are called *connective tissue mast cells* (MC_{TC}).^{7,8} This cell population represents 85% of the IL-4-positive mast cells in the nasal lamina propria. Mast cells in the lamina propria also express IL-13, although it is unclear which subset or another is involved.⁹

During allergen assault, there is an increase in the proportion of epithelial mast cells.¹⁰ These cells produce predominantly tryptase without chymase and are called *mucosal cells* (MC_T). Mucosal cells are thought to express IL-5 and IL-6 and represent 15% of all of the IL-4-positive mast cells in the mucosa.^{7,8} These cells proliferate in allergic rhinitis, perhaps under the influence of Th2 cytokines.¹¹ Proliferation of mucosal cells appears to occur in the epithelium and most superficial layers of the lamina propria. Epithelial mast cells have a higher rate of cell division in allergic rhinitis compared with nasal mucosa not affected by allergy. Epithelial mast cell density is decreased by topical nasal application of glucocorticoids.¹⁰

Mast-cell degranulation is the critical initiating event of acute allergic symptoms.¹² The consequences of mast-cell degranulation are illustrated with an examination of results with nasal allergen provocation models (Fig. 2).

Application of allergen to the nasal mucosa of a person leads to a rapid, statistically significant increase in sneezing, nasal discharge, and resistance of nasal airways.¹⁴ Histamine, tryptase, prostaglandin (PG)_{D2}, PGF₂, and bradykinin are released rapidly during this immediate allergic response.¹⁵ Mast cell kininogenase releases bradykinin from plasma kininogens. Tryptase and chymase are believed to have proinflammatory proteolytic effects, and chymase may contribute to glandular hypersecretion.¹⁶ Cytokines, including TNF- α , IL-4, IL-5, IL-6, transforming growth factor β (TGF β), and IL-13, also may be released. Mast cells can degranulate in response to many histamine-releasing factors; their roles in allergic inflammation are under investigation.

Cross-linking of IgE on the surface of the mast cell activates tyrosine kinases. The activation leads to activation of phospholipase A₂, which releases arachidonic acid from the A₂ position of membrane phospholipids. Arachidonic acid can be metabolized by cyclooxygenase,

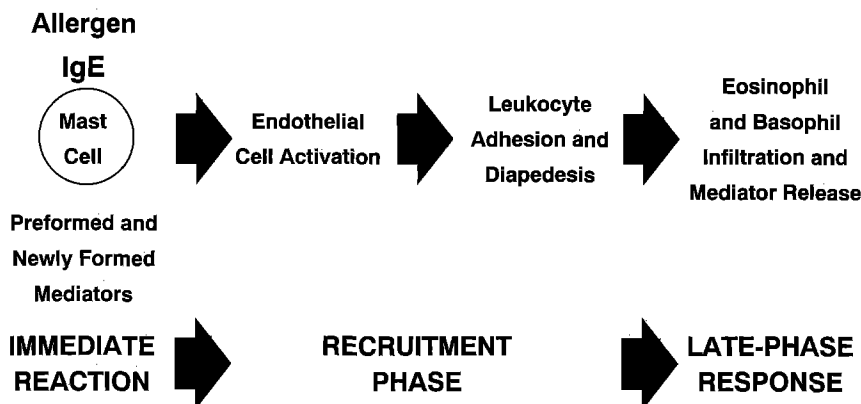


FIG. 2. The nasal allergen challenge model provides evidence for a step-like progression of allergic inflammation that begins when allergen binds to IgE on mast cells and the binding leads to release of mast-cell mediators. These mediators activate endothelial cells to express adhesion markers that bind circulating leukocytes. Eosinophils, basophils, and other leukocytes respond to chemoattractants¹³ and activators, enter the tissue, and release their own mediators during the late-phase response. The repetition of this process likely leads to the histologic appearance of chronic allergic rhinitis.

which is present as a constitutive enzyme or an inducible form that can be upregulated in some forms of inflammation. In mast cells, PGD₂ is the predominant product. Epithelial cells generate predominantly PGE₂, endothelial cells PGI₂, and platelets thromboxane A₂. The phospholipid backbone may become a substrate for the formation of platelet activating factor.

Myeloid series cells also possess 5-lipoxygenase, which combines with 5-lipoxygenase activating protein to generate leukotriene LTA₄.¹⁷ In neutrophils, LTA₄ is metabolized to LTB₄, a potent neutrophil chemoattractant. Other cells, including mast cells and eosinophils, preferentially generate the peptidyl leukotrienes LTC₄, LTD₄, and LTE₄ (slow-reacting substance of anaphylaxis). These interact with LTD₄ receptors to induce glandular exocytosis and vascular permeability and may contribute to tissue eosinophilia and airway mucosal hyperresponsiveness. The leukotriene system moved from the arena of academic arcana to center stage of clinical research with the introduction of 5-lipoxygenase inhibitors (e.g., zileuton), 5-lipoxygenase activating protein inhibitors (e.g., MK-886), LTB₄ antagonists (e.g., U-75,302), and cysteinyl leukotriene antagonists (e.g., zafirlukast, pranlukast, and verlukast).¹⁷ Initial studies indicate beneficial responses in asthma, and it is anticipated that these drugs will have benefits in allergic rhinitis.

The explosive degranulation of mast cells induced by allergen leads to release of a complex cascade of mediators, which may have synergistic effects on resident cells in tissues (Fig. 3). Leukotrienes and chymase stimulate glandular exocytosis and mucous secretion.^{16, 17} Histamine, bradykinin, leukotrienes, and platelet-activating factor activate the endothelial cells of postcapillary venules to induce vasodilatation, vascular permeability, and cellular adhesion. Contraction of postcapillary venule endothelial cells opens gaps, which allows hydrostatic intravascular pressure to force plasma into the interstitial space. A pressure of 5 mm H₂O can drive

fluid from the vessels through the interstitium, across the epithelial basement membrane, and between epithelial cells and their tight junctions into the nasal lumen.¹⁸ This is a nondamaging reversible event that is driven by hydrostatic pressure. Plasma exudation may occur without marked tissue edema.

Histamine is an important mediator of mast-cell degranulation. It accounts for approximately half the symptoms of allergic rhinitis (Fig. 4).¹⁹ Histamine is released in the immediate phase by mast cells and by basophils in the late-phase response. Histamine H₁-receptor mRNA is upregulated in allergic rhinitis.²⁰ H₁ receptors are present on endothelial cells, where they induce vascular permeability and the watery rhinorrhea of allergic rhinitis.²¹ Histamine is metabolized by epithelial and endothelial histamine N-methyltransferase (HMT).²² Submucosal glands do not express HMT mRNA. The lack of H₁-receptors and HMT on nasal submucosal glands is consistent with the lack of histamine-induced exocytosis observed *in vitro*.²³ Antihistamines are clearly effective for relieving symptoms common in allergic rhinoconjunctivitis.

NEUROGENIC INFLAMMATION

In addition to inducing vascular permeability, histamine binds to H₁ receptors on nociceptive type-C nerves. These nociceptive neurons are extensively branched in the epithelium and submucosal regions.²⁴ These neurons originate from the first and second divisions of the trigeminal nerve. In the mucosa, depolarization of the neuron may lead to the release of neurotransmitters such as substance P, calcitonin gene-related peptide, neurokinin A, gastrin-releasing peptide, and possibly others by the axon response mechanism. The axon response has been extensively studied in rodents and is believed to induce vascular permeability and leukocyte infiltration.²⁵ However, in human beings and pigs, the axon response appears to have little if any

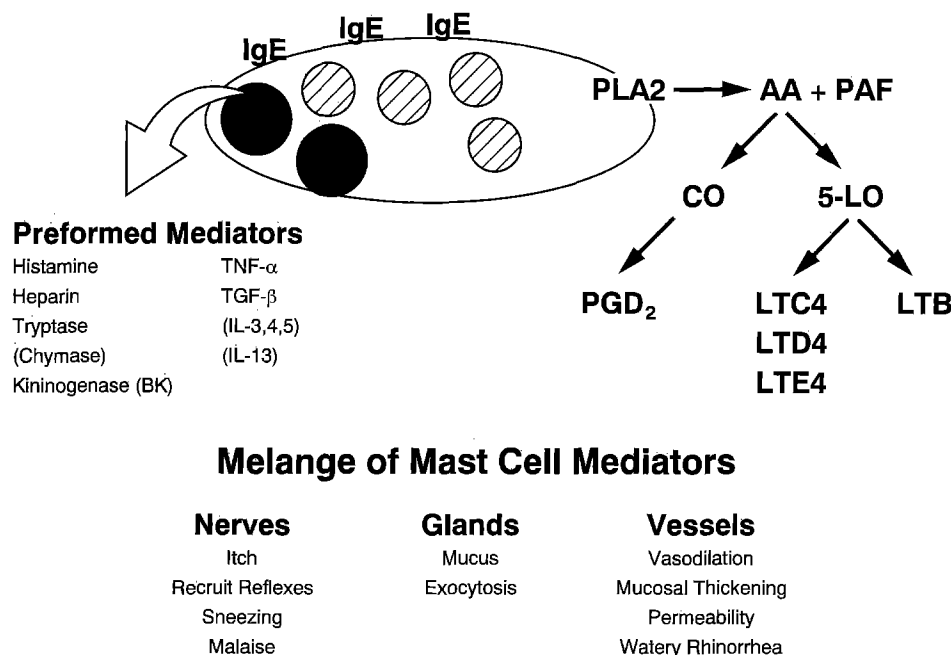


FIG. 3. Both preformed mediators released from mast cell granules and newly synthesized leukotrienes and PGD₂ may have direct effects on vessels, glands, and other inflammatory cells during the immediate-phase reaction. *Mediators in parentheses* may be released by different subsets of mast cells. PLA, Phospholipase; PAF, platelet-activating factor; CO, cyclooxygenase; 5-LO, lipoxygenase; TGF, transforming growth factor.

effect on vascular leak.^{26, 27} As a result, the role of the nociceptive nerve axon response in the nasal mucosa has been called into question.²⁸ Other actions of the axon response such as glandular secretion and endothelial adhesion marker expression are conceivable because substance P and calcitonin gene-related peptide are released within 3 minutes after allergen challenge.²⁹ This controversy will likely rage until tachykinin antagonists that block the actions of substance P are investigated in human allergic rhinitis.

Substance P does have potent effects in the mucosa of patients with allergic rhinitis. Repeated application of substance P leads to vascular permeability with an increase in albumin-rich plasma exudation.³⁰ In one study the percentage of eosinophils in nasal secretions increased after substance P treatment, from approximately 18% to 42%, a statistically significant difference. In vitro, treatment of human nasal mucosal explants with substance P leads to statistically significant increases in IL-3, IL-4, IL-5, IL-6, IL-1 β , IL-2, TNF- α , and interferon- γ mRNA production from nasal mucosa affected by allergic rhinitis.³¹ In tissue from persons without allergies, substance P increased only IL-6 and IL-1 β in a statistically significant way. This suggests that during acute inflammation substance P may have a greater effect than in nonallergic rhinitis and on normal mucosa. The sites of substance P-induced cytokine production may include epithelial, endothelial, and inflammatory cells in these explants.

In the central nervous system, trigeminal nociceptive neurons enter the pons through the sensory root and

turn caudally in the trigeminal spinal tract to terminate in the pars caudalis of the nucleus of the spinal tract in the lower medulla and upper three cervical segments of the spinal cord.²⁴ Pars caudalis interneurons cross the midline to enter the trigeminothalamic tract and terminate in the medial part of the ventral posterior thalamic nucleus. Painful and strong thermal stimuli are appreciated at the thalamic level. Tertiary neural relays to the lower third of the parietal cortical somesthetic areas provide localization of nasal stimuli. Glossopharyngeal afferents innervate the posterior third of the tongue, upper pharynx, tonsils, eustachian tube, and middle ear and are relevant to allergic rhinitis. These thermosensitive and nociceptive neurons terminate in the dorsal portion of the trigeminal spinal tract. Activation of these central registries is responsible for the sensations of itch and congestion that are the hallmarks of allergic rhinitis.

Connections between afferent interneurons, the tractus solitarius, nucleus ambiguus, and salivatory nucleus of the seventh nerve recruit parasympathetic reflexes. Seventh nerve motor fibers synapse in the sphenopalatine ganglia and pass with sympathetic fibers through the Vidian canal to enter the nasal mucosa. These postganglionic neurons contain acetylcholine, vasoactive intestinal peptide, vasoactive intestinal peptide-like peptides (e.g., PHM), and nitric oxide (NO) synthetase, which generates NO. It is possible that these are packaged in different sets of neurons. Parasympathetic reflexes are rapidly recruited after allergen challenge because vasoactive intestinal peptide is released within 3 minutes after nasal allergen provocation.²⁹

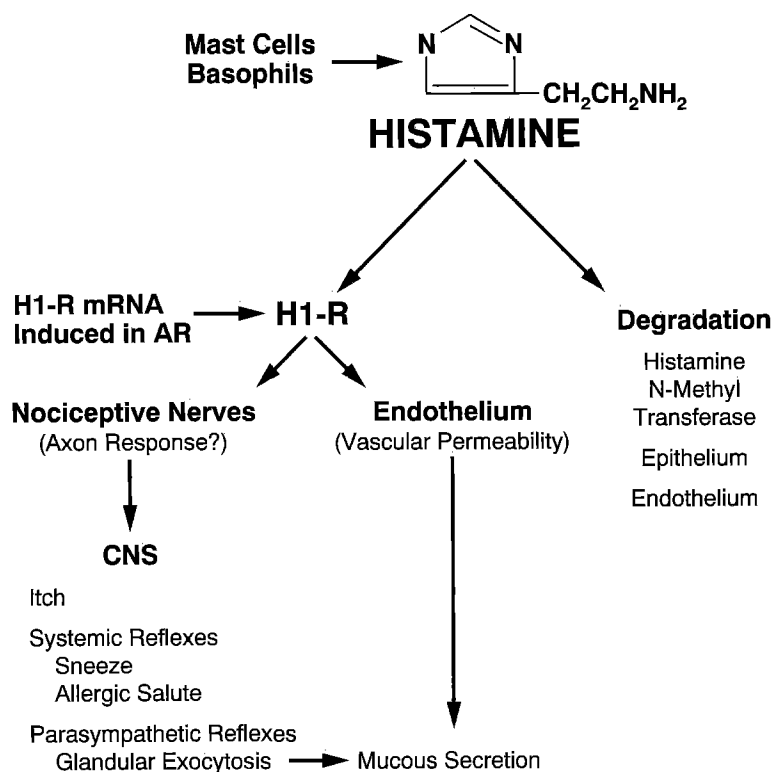


FIG. 4. Histamine acts on H₁ receptors to induce vascular permeability and activate nociceptive nerves that recruit parasympathetic reflexes.

One of the most important functions of nociceptive nerves appears to be activation of the central itch registries with recruitment of systemic reflexes, such as sneezing, and organ-specific parasympathetic reflexes that lead to cholinergic glandular secretion (Fig. 5). Reflex vasodilatation appears to occur, but may be of lesser functional significance. Suggestions of parasympathetic nerve-related cellular or chemoattraction remain controversial.^{15, 32}

Cholinergically mediated glandular secretion is probably the most important single influence inducing glandular exocytosis in the respiratory tract. Histamine induces glandular secretion by activating these nociceptive-parasympathetic reflexes, which provide the rationale for the use of ipratropium bromide and other anticholinergic antagonists in allergic rhinitis.³³ The m3-muscarinic receptor is likely the most important of the five cloned muscarinic receptors in human nasal mucosa, according to the results of functional and in situ hybridization studies.^{34, 35}

CELLULAR RECRUITMENT PHASE

The mediators of the immediate-phase response generate the acute symptoms of itch, rhinorrhea, congestion, and sneezing of allergic rhinitis. As the mediators are metabolized and cleared from the mucosa, the symptoms wane. However, the release of cytokines and activation of endothelial cells leads to a latent recruitment phase that ushers in the inflammatory late-phase response.

LATE-PHASE RESPONSE

The late-phase response occurs 4 to 6 hours after the immediate phase. It is noted clinically by an increase in nasal mucosal thickness that can be detected as increased nasal air flow resistance with little change in other nasal symptoms.^{14, 36, 37} During the recruitment phase, inflammatory granulocytes, including eosinophils, basophils, and, less dramatically, neutrophils, infiltrate the mucosa. Numbers of mononuclear cells and metachromatic cells (mast cells or basophils) also increase. The increase in eosinophils is reflected by large increases in eosinophil cationic protein (ECP) and other eosinophil products in nasal secretions. Mediators of the late-phase response include leukotrienes (LT), histamine, and IL-5.^{14, 15, 36, 37} Histamine increases without a change in tryptase, suggesting an influx of basophils rather than a secondary degranulation of mast cells. In addition, IL-5, IL-6, and IL-1 α also are markedly increased. It is believed that these cytokines are released from the newly infiltrating granulocytes. GM-CSF and IL-8 may be released from leukocytes and the epithelium.

The mechanisms underlying the infiltration of inflammatory cells are an exciting new chapter in the annals of allergic rhinitis. Circulating leukocytes bind to endothelial cells of postcapillary venules. The shear forces of blood flow force these leukocytes to roll along the surface of the endothelium. Their adhesiveness is due to interactions between endothelial cell glycoprotein lectins called *selectins* (E-selectin for eosinophils, P-selectin

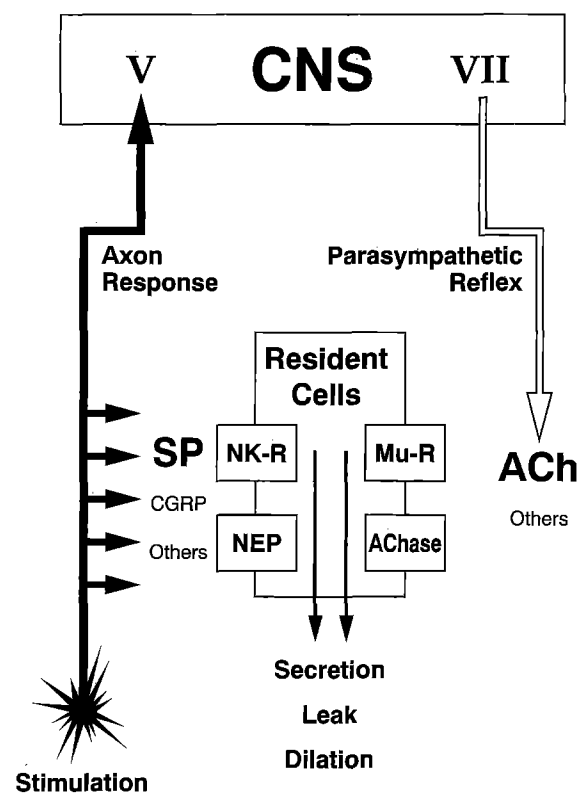


FIG. 5. Activation of nociceptive nerves may lead to axon-response mediated release of neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP), but the most potent effects are to activate pain centers in the brain and recruit systemic reflexes such as sneezing and parasympathetic cholinergic reflexes that mediate glandular secretion in allergic rhinitis. *NK-R*, Neurokinin receptor; *Mu-R*, muscarinic receptor; *ACh*, acetylcholine.

for polymorphonuclear cells) and leukocyte glycoproteins bearing the Lewis^x blood group marker.^{38, 39} Specific adhesion markers may contribute to tissue-specific homing of T-cell subsets. In response to the myriad of mediators released in the immediate response, endothelial cells become activated and rapidly relocate cytoplasmic selectin-containing Weibel-Palade bodies to the endothelial surface, where they bind sialylated Lewis^x antigens on leukocytes.³⁸

The complex of mediators also induces and upregulates expression of other adhesion molecules. Those of the immunoglobulin gene superfamily include intercellular adhesion molecule 1 (ICAM-1), ICAM-2, platelet endothelial cell adhesion molecule 1 (PECAM-1), and vascular cell adhesion molecule 1 (VCAM-1).^{14, 38} A third set of adhesion molecules are the integrins, which consist of more than a dozen heterodimers with distinct α chains and a common β chain.

Endothelial cells constitutively express ICAM-1, ICAM-2, and PECAM (Table I).³⁸ ICAM-1 and VCAM-1 are induced by cytokines such as IL-1, TNF- α , interferon- γ , and IL-4. These interact with eosinophil and basophil integrins, including LFA-1 (α L β 2), Mac-1

(α M β 2), VLA-4 (α 4 β 1), and Act-1 (α 4 β 7). These interactions cause leukocytes to flatten and bind tightly to the endothelial surface.

Expression of VCAM-1 is increased in allergic inflammation.^{38, 40} The importance of VCAM-1 in the inflammatory cascade has been demonstrated with use of antibodies to VLA-4, the ligand for VCAM-1. In guinea pig nasal mucosa, this antibody markedly reduced the allergen-induced influx of eosinophils.¹⁴ This is an exciting development because it suggests that new drugs that interfere with VLA-4-VCAM-1 interactions may be useful at decreasing eosinophilic infiltration. VCAM-1 also is increased by IL-4.

Tissue infiltration requires the presence of cell-specific chemoattractants.³⁸ For eosinophils, exposure to IL-3, IL-5, or GM-CSF promotes adhesion to endothelium, whereas eotaxin, IL-5, and RANTES promote eosinophil chemoattraction. Basophil chemoattraction is promoted by IL-3, IL-5, IL-8, MCP-1, macrophage inflammatory protein (MIP-1 α), and RANTES. In contrast, neutrophils respond to IL-8 and GRO, whereas RANTES, MIP-1 α , and eotaxin have no effect. In allergic inflammation, it appears that the factors released from mast cells, eosinophils, and Th2 cells may promote the expression of a combination of adhesion markers and the production of a combination of chemoattractants that further promote eosinophilic and basophilic infiltration while reducing the likelihood of Th1 and neutrophilic infiltration.

EOSINOPHILS

The influx of eosinophils produces profound changes in the airway mucosa. Eosinophils are activated by interactions of CD40 with CD40 ligand on other inflammatory cells, mediators such as platelet-activating factor (PAF), C5a, IL-16, and MCP-3, and allergen-antibody complexes involving IgA, IgG, and possibly IgE (low affinity Fc ϵ -RII).⁴¹ The presence of IL-3, IL-5, and GM-CSF promotes eosinophil survival in tissue. Because these cytokines can be produced by eosinophils, autocrine positive feedback loops may lead to autonomous eosinophilic inflammation (Fig. 6).

Eosinophil granules release very basic, highly charged polypeptides that include major basic protein (MBP), ECP, eosinophil-derived neurotoxin, and eosinophil peroxidase. These highly charged cations may bind to basement membrane proteoglycans and hyaluran to cause cellular disaggregation and epithelial desquamation. These proteins can also act on cell membranes, which lead to cell death. Eosinophil-derived neurotoxin may inactivate mucosal nerves. Eosinophil peroxidase may play a role in the generation of HClO₄ which can lead to free radical damage of cells.

Eosinophils express 5-lipoxygenase and are an important source of LTC₄. LTC₄ and ECP are potent glandular secretagogues.

Eosinophils also appear to be an important source of cytokines.⁴² In addition to IL-3, IL-5, and GM-CSF, which promote eosinophil survival, eosinophil chemoat-

EOSINOPHILS

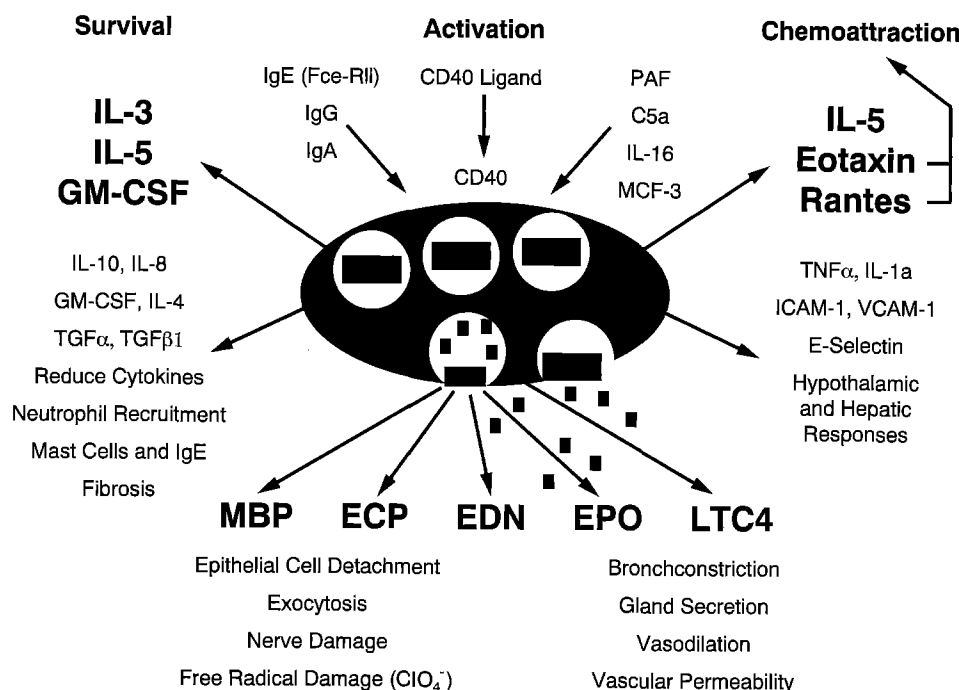


FIG. 6. A large number of inflammatory factors can activate eosinophils and attract them to sites of allergic inflammation. Autocrine release of cytokines may promote autonomous eosinophilic infiltrates. The cationic eosinophil granule proteins have potent destructive effects that lead to tissue necrosis. Leukotrienes have multiple important effects on glands, vessels, and other cells, whereas cytokines promote local and systemic effects of the atopic reaction. *MBP*, Major basic protein; *ECP*, eosinophil cationic protein; *EDN*, eosinophil-derived toxin; *EPO*, eosinophil peroxidase; *LTC $_4$* , leukotriene C $_4$.

TABLE I. Endothelial, eosinophil, and basophil adhesion molecules

Endothelial cell	CD Number	Induced by	Eosinophil and basophil ligand	CD number
ICAM-1	CD54	Constitutive IL-1, TNF, IFN- γ	LFA-1 (α L β 2)	CD11a/CD18
ICAM-2	CD102	Constitutive	Mac-1 (α M β 2)	CD11b/CD18
PECAM-1	CD31	Constitutive	LFA-1	CD11a/CD18
VCAM-1	CD106	IL-1, TNF, IL-4	VLA-4 (α 4 β 1)	CD49d/CD29
VCAM-1	CD106	IL-1, TNF, IL-4	Act-1 (α 4 β 7)	None
MAdCAM-1	—	—	Act-1 (α 4 β 7)	None
GlyCAM-1	CD34	—	L-Selectin	CD62L
E-selectin	CD62E	IL-1, TNF	L-Selectin	CD62L
P-selectin	CD62P	Histamine, thrombin	sLe ^{x}	CD15s
Fibronectin	—	—	sLe ^{x}	CD15s
Laminin	—	—	VLA-4 (α 4 β 1)	CD49d/CD29
Unknown	Unknown	Unknown	VLA-6 (α 6 β 7)	CD49f/CD29
			p150,95 (α X β 2)	CD11c/CD18

From Bochner BS, Schleimer RP. The role of adhesion molecules in human eosinophil and basophil recruitment. *J Allergy Clin Immunol* 1994;94:427-38.

tractant polypeptides, including eotaxin, IL-5, and RANTES, are released. These may act in an autocrine manner; IL-3, IL-4, IL-5, and IL-8 receptors have been identified on their surfaces.³⁹ Eosinophils also express the integrins (VLA-4, VLA-6, α 4 β 7, LFA-1, and Mac-

1), PECAM, ICAM-3, L-selectin, ligands for P-selectin and E-selectin, and CD44, the receptor for hyaluronan.⁴³

Eotaxin is a newly cloned C-C chemokine that is a potent, selective, and specific eosinophil chemoattractant.⁴⁴ Eotaxin shares a novel receptor with RANTES

and MCP-3 on eosinophils that is distinct from the two C-C chemokine receptors: CKR-1 for macrophage inflammatory protein and RANTES and CKR-2a,b for MCP-1. Eotaxin is also expressed by nasal polyp epithelial cells; its release might promote migration through the epithelium and into the airway lumen.

IL-3, IL-4, and GM-CSF promote mast cell and IgE production. IL-8 may promote neutrophil and basophil chemoattraction. IL-10 may reduce production of Th1 cytokines such as interferon- γ . TNF- α and IL-1 α up-regulate endothelial cell adhesion marker expression and may circulate systemically to promote proinflammatory responses in the hypothalamus and liver that generate low-grade fever, malaise, fatigue, and acute-phase protein responses. Transforming growth factor β and platelet-derived growth factor can induce fibroblast collagen production that may contribute to thickening of collagen deposits beneath the epithelial basement membrane and fibrosis with "stiffening" of nasal polyp, nasal mucosa, and bronchial airways.⁴⁵ Although eosinophils are an important component of the antiparasite function of the Th2-IgE-mast cell mucosal immune response, their misguided toxic assault on innocent allergens contributes to airway morbidity.

Topical glucocorticoid therapy reduces tissue eosinophilia and the number of eosinophils and cationic proteins in nasal secretions.^{1, 10, 36}

Lymphocytes are attracted to active allergic inflammatory sites. The percentage of lymphocyte subsets in the nasal mucosa of persons with allergic rhinitis has been compared with that of persons with chronic infectious rhinitis⁴⁶ both during and out of allergen season.⁴⁷⁻⁴⁹ CD4 cells are increased. There is an increase in CD4⁺CD45 Ro⁺ memory T cells, suggesting that these proliferate in the mucosa of patients with allergic rhinitis. The percentage of CD8-positive T-cytotoxic cells also appears to be increased. CD3⁺CD4⁻CD8⁻ cells with a predominant γ - δ T-cell receptor type also are increased in allergic rhinitis. Numbers of B lymphocytes (CD20⁺) are higher in allergic rhinitis than in chronic infectious rhinitis, whereas numbers of natural killer cells (NK, CD16⁺) are lower. Numbers of lymphocytes in normal nasal mucosa are too low to allow accurate comparison with a fluorescence-activated cell sorter for each of these lymphocyte subsets.

It is unclear if B cells synthesize IgE in the nasal mucosa. IgA-producing B cells are clustered around submucosal glands.⁵⁰ Igarashi et al.⁵¹ found no changes in total T-cell, T-cell subset, B-cell, or macrophage numbers among persons with allergies compared with healthy persons. However, the number of cells bearing the activated IL-2 receptor (CD25) and the number of eosinophils were markedly increased.

EPITHELIAL CELL CHANGES IN ALLERGIC RHINITIS

The influx of inflammatory cells and upregulation of endothelial cell function are not the only changes in allergic rhinitis. Epithelial cells also appear to be acti-

vated, because they express increased amounts of GM-CSF, IL-1 α , IL-8, IL-1 receptors, TNF- α receptors, and class II HLA (HLA-DR).^{52, 53} Cytokines and ECP also upregulate ICAM-1 expression.⁵⁴

Endothelin-1, which is known to be expressed by epithelial and submucosal gland cells in human mucosa⁵⁵ and the enzyme that generates endothelin-1 (endothelin converting enzyme 1) are upregulated in chronic rhinitis.⁵⁶

NO is present in nasal air, and its levels in exhaled nasal air are increased during allergic rhinitis. Levels rise from 24.7 ± 2.2 ppb to 35.4 ± 2.0 ppb ($p < 0.001$).⁵⁷ The source of NO is under active investigation. It may include endothelial cells that express constitutive Type III NO synthetase, parasympathetic neurons that express Type I NO synthetase and colocalized vasoactive intestinal peptide, or macrophages, neutrophils, mast cells, arterial smooth muscle cells, and fibroblasts that may be induced to express Type II NO synthetase.⁵⁸ NO may promote vasodilatation, glandular secretion, and immunomodulation, and because it is a free radical, it may have an antibacterial function.

Submucosal gland area is increased in perennial allergic rhinitis compared with the normal state and hypertrophic rhinitis. Submucosal glands represent approximately 15% of the lamina propria in people without allergies. However, in perennial allergic rhinitis and chronic sinusitis, gland area increases to approximately 25%.⁵⁹ This is consistent with the mucus hypersecretion that has been suggested to be present in allergic airway disease.

MUCOSAL HYPERRESPONSIVENESS

Hyperresponsiveness is a characteristic of mucosal surfaces during inflammation. Hyperresponsiveness indicates an increased mucosal response to "nonspecific" irritants such as histamine, methacholine, bradykinin, hypertonic saline solution, and other provocative agents.⁶⁰⁻⁶² Persons with allergic rhinitis have increased glandular secretion in reaction to stimulation with endothelin-1, bradykinin, and histamine. Stimulation of nociceptive nerves with recruitment of parasympathetic reflexes is the postulated mechanism. Glandular responses to methacholine also are increased.⁶³ The mechanisms of neural sensitivity and mucosal responses are unclear. However, topical nasal steroids reduce allergen-induced nasal hyperresponsiveness, suggesting that the latter may contribute to the benefits of these drugs in allergic rhinitis.^{61, 64}

In contrast to glandular hypersecretion, which may involve neural reflexes, histamine-induced vascular permeability and "exudative hyperresponsiveness" do not appear to involve nociceptive axon responses or other neural effects.²⁶

Glucocorticoids

The beneficial effects of topical application of glucocorticoids were alluded to earlier. These effects include decreases in numbers of epithelial Langerhans cells, mast cells, IL-4 immunoreactive cells, and Th2 cells.^{1, 10, 38, 61, 64}

However, numbers of submucosal mast cells are unaffected. In one study topical application of fluticasone propionate reduced the number of IL-4-positive cells in the nasal mucosa in a statistically significant way, but had no significant effect on the numbers of IL-5 and IL-6 immunoreactive cells.⁶⁵ IL-4 and IL-6 were localized predominantly to mast cells, whereas IL-5 was present in mast cells and eosinophils. Topical glucocorticoids may reduce the numbers of epithelial and submucosal eosinophils by increasing eosinophil apoptosis. These beneficial changes appear to be reversible; discontinuation of topical nasal steroids allows the return of seasonal allergic inflammation. The molecular actions of glucocorticoids have been reviewed.⁶⁶

Immunotherapy

In contrast to the reversible effects of topical glucocorticoids, allergy shots provide a long-term reduction in allergic inflammation. Persons with allergic rhinitis who have had allergy shots have significantly less nasal blockage ($p < 0.05$) and lower influxes of CD4⁺, major basic protein⁺, and EG2⁺ cells into the mucosa after nasal allergen challenge. Allergy shots reduce immediate and late-phase responses to intradermal allergen skin tests. In one study histamine, bradykinin, and TAME-esterase concentrations were decreased in lavage fluids collected during both the immediate and early phase after nasal allergen challenge, but cellular infiltration was not affected.⁶⁷ Durham et al. showed that numbers of cells expressing interferon- γ mRNA were increased in the nasal mucosa after allergy shots ($p < 0.03$).^{68, 69} This may represent an increase in Th1 cells that downregulate mucosal Th2 responses.³

CONCLUSIONS

Dramatic progress is being made in understanding the basic pathophysiologic process of allergic rhinitis. New concepts in allergen sensitization, commitment and differentiation of Th2- and IgE-producing B cells, mast cell cytokine production, cellular adhesion and chemoattraction, and the complex but disease-specific combinations of mediators, adhesion markers, chemoattractants, and inflammatory cells that typify atopy will lead to the development of new diagnostic and treatment strategies. These allow more effective modulation of this Th2-IgE-mast cell-eosinophil axis of the immune system, the atopic disease process, and its attendant morbidity.⁴

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