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How and why the nose runs

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Rhinitis may be defined as the occurrence of nasal congestion, itching, sneezing, and/or watery or mucoid rhinorrhea. Inflammation is a common, although it is not invariable, feature of some forms of rhinitis and is probably responsible for producing much of the misery and prolonged symptoms and signs associated with this disorder.

Many different stimuli are capable of producing inflammation of the nasal mucosa. These stimuli include allergic responses to inhaled aeroallergens, viral, bacterial, and fungal infections of the nose and nasopharynx, and exposure to noxious chemicals, medications, or irritants. During inflammatory responses, preformed and/or newly generated inflammatory mediators may be released from resident cells in the nasal mucosa (mast cells, basophils, glandular serous and mucous cells, epithelial cells, goblet cells, lymphocytes, macrophages, etc.), producing local tissue effects and attracting additional inflammatory cells, thereby setting up a vicious cycle of inflammation. Certain inflammatory mediators (H, leukotrienes, prostaglandins, and platelet-activating factor) may be derived from a variety of different cell sources and yet are capable of producing similar effects on

Abbreviations used

Alb%:	Albumin percent
CGRP:	Calcitonin gene-related peptide
GRP:	Gastrin-releasing peptide
H:	Histamine
Lf:	Lactoferrin
Lf%:	Lactoferrin percent
Ly:	Lysozyme
Ly%:	Lysozyme percent
MC:	Methacholine
NKA:	Neurokinin A
NPY:	Neuropeptide Y
nsIgA:	Nonsecretory IgA
nsIgA%:	Nonsecretory IgA percent
sIgA:	Secretory IgA
sIgA%:	Secretory IgA percent
SP:	Substance P
VIP:	Vasoactive intestinal peptide
SC:	Secretory component

the nasal mucosa. These effects include vascular dilatation (congestion), increased vascular permeability with local tissue edema (congestion), increased secretion of mucus and glandular proteins (rhinorrhea), and stimulation of sensory nerve endings (nasal pruritus and sneezing).

In addition to inflammation, other noninflammatory stimuli may produce the symptoms and signs of rhinitis. Examples of such stimuli include prolonged exposure to cold air,^{1,2} consuming spicy foods or drinks,³ or inhaling certain odors (e.g., perfume or ammonia). These stimuli may trigger reflex-induced sneezing and

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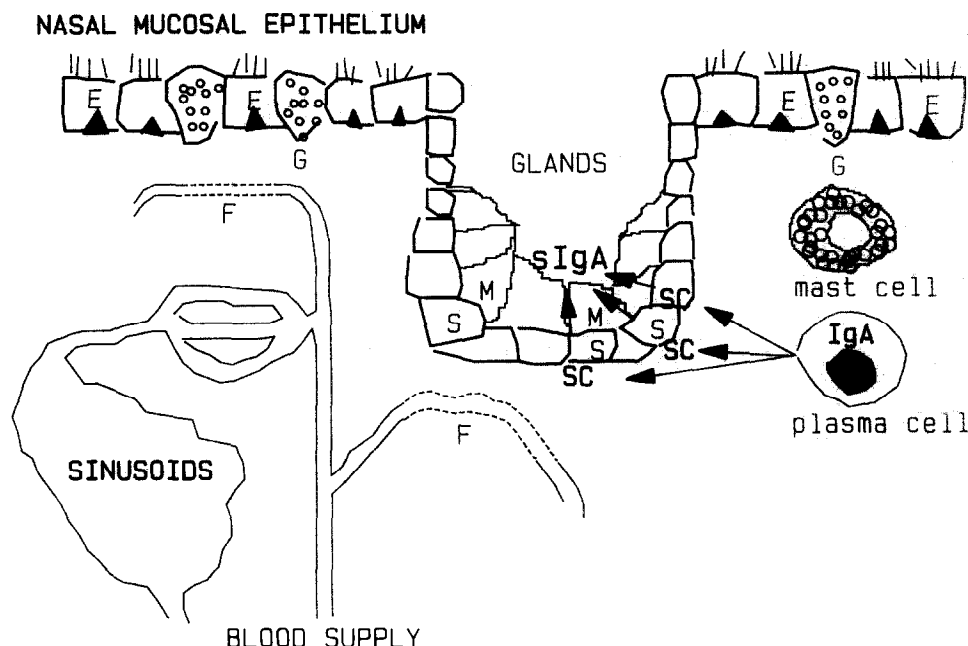


FIG. 1. Nasal protein secretion from the nasal mucosa is derived from three main sources: plasma proteins from the blood supply, glandular proteins from submucosal serous (S) and mucous (M) cells, and from other cellular sources, including epithelial cells (E), goblet cells (G), mast cells, and other cells within the mucosa. sIgA is formed when dimeric IgA binds to SC on serous cells and then is expelled into the lumen of the glands.

TABLE I. Protein constituents in nasal secretions

Alb
Ly
Lf
Kallikrein
Antiproteases
β -Glucuronidase
α -Galactosidase
Succinic dehydrogenase
IgA, IgG, IgE, SC
Glutamate dehydrogenase
Leucine aminopeptidase

rhinorrhea without necessarily producing nasal inflammation.

A universal model of rhinitis has yet to be found, since the disorder is provoked by diverse stimuli and exhibits variable clinical features. However, many research models have been developed in attempts to simulate and study rhinitis. These models include exposing subjects to natural allergens during the appropriate allergy season⁴ and performing nasal provocation tests in the laboratory with allergens,⁵ mediators,^{6, 7} viruses,^{8, 10} and environmental stimuli.¹¹

Methods of assessing the rhinitis response have included recording symptoms scores,¹² counting

sneezes, or the number of tissues used,¹³ measuring nasal airway resistance,¹⁴ measuring the volume of nasal secretion,¹⁵ and analyzing nasal secretions for mediators,¹⁶ cellular constituents,¹⁷ and protein content.^{6, 17, 18} Each method of analysis focuses on a relatively limited component of rhinitis, and as a result, no method has been developed that accurately reflects the entire clinical spectrum of the disease. Yet, each model reveals important information about the pathophysiology of rhinitis.

THE NIH NASAL PROVOCATION MODEL

At the National Institutes of Health, an intensive effort has been made to better understand the physiology of the nasal mucosa. In particular, we are trying to determine the specific sources of secretions in rhinitis, regardless of the etiology. Nasal secretions contain an array of constituent proteins, including vascular proteins, immunoglobulins, antimicrobial proteins, and proteinases (Table I). The sources of several of these proteins have been well defined^{6, 7, 19, 20} and include the vascular system, submucosal glands, and cells and tissues within the interstitium of the nasal mucosa (Fig. 1). Measuring and analyzing these proteins in baseline and induced nasal secretions can determine the source and controls of these secretions.

A model involving nonirritating urethral catheters inserted into one or both nasal cavities and attached

to suction is used in nasal provocation and in the collection of nasal lavage fluid (Fig. 2). The nasal cavities are washed with normal saline delivered from a hand-held nebulizer bottle, and nasal lavages (secretions diluted with saline) are collected into collection traps. Nasal challenge solutions are sprayed into the nasal cavity, allowed to incubate, and then washed out with saline lavages. This technique allows for independent collections of secretions from both sides of the nose and is ideally suited to allow measurement of both ipsilateral and contralateral secretory responses to a single, unilateral stimulus.

Proteins in nasal secretions

To determine whether the proteins listed in Table I are found in significant concentrations in nasal secretions, polyacrylamide gel electrophoresis was performed on baseline and stimulated nasal secretions after reduction and alkylation (Fig. 3). As illustrated in the Fig. 3, *lane 5*, only a few protein bands were visualized in baseline lavages. MC, a pure glandular stimulant, accentuated several protein bands corresponding to molecular weights of around 88 kd (Lf), 67 kd (Alb), and 14 kd (Fig. 3, *lane 4*). Western blot analysis was also performed on these secretions to identify the protein bands immunologically. This technique easily demonstrated the presence of several of the proteins listed in Table I, including Alb, SC, IgA, IgG, Lf, and Ly.

Nasal challenges were then performed with MC and H, two secretagogues that have been well studied and whose actions have been previously defined. Nasal lavage samples were assayed for total protein, Alb, sIgA, nsIgA (most of which is serum IgA), Lf, and Ly. In addition, the proportion of each protein was calculated as a percentage of the total protein.

Control challenge with normal saline served as the baseline for both MC and H challenge. Although saline challenge produced neither symptoms nor signs, MC (25 mg) increased ipsilateral nasal secretion and produced mild nasal congestion and/or facial flush in an occasional subject. As compared to saline challenge, the concentration of all measured proteins, including the vascular proteins (Alb, IgG, and nsIgA), increased after MC challenge (Table II). The proportions of Alb, IgG, and nsIgA to total protein (the Alb%, IgG%, and nsIgA%) were unchanged by MC challenge (as compared to saline challenge). In contrast, the proportions of sIgA, Lf, and Ly, (the sIgA%, Lf%, and Ly%), all significantly increased after MC.

The effect of atropine, a cholinergic muscarinic antagonist, was examined next. After pretreating the nasal mucosa with topical atropine, an agent that does not measurably affect nasal secretion by itself, the ability of MC to stimulate nasal secretions was clin-

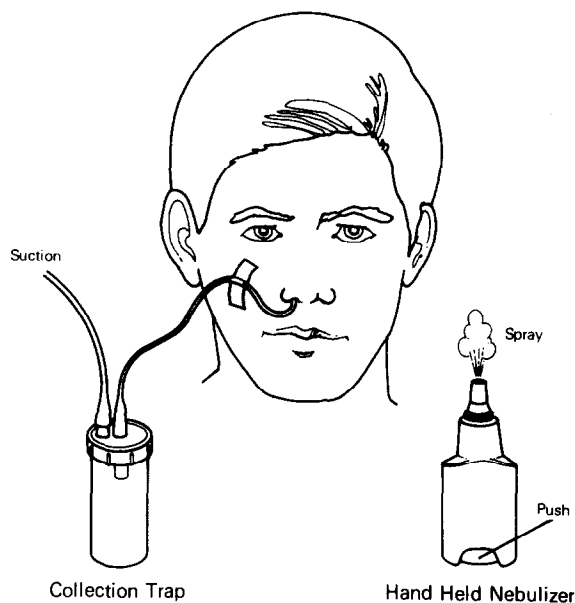


FIG. 2. The nasal provocation system. Nasal challenge solutions or lavage fluids are sprayed from a hand-held nebulizer bottle into one or both nasal cavities. Nasal lavage fluid is collected by suction through 8F rubber urinary catheters inserted along the floor of the nasal cavity.

ically blocked. In addition, atropine reduced the secretion of all proteins to control (saline challenge) levels (Table II). Thus, MC increases nasal protein secretion by stimulating muscarinic cholinergic receptors (on submucosal glands). Both vascular and nonvascular proteins are secreted after cholinergic stimulation. The vascular proteins increase in direct proportion to the total protein, whereas MC selectively augments the relative proportions of certain proteins (sIgA, Lf, and Ly).

H produced a dramatically different clinical response, as well as different proportions of protein secretion as compared to MC.^{7, 19, 20} When unilateral H (10 mg) was applied to the nose, sneezing, itching, and nasal congestion resulted, accompanied by bilateral nasal secretion. This finding is in contrast to the ipsilateral secretion stimulated by unilateral MC. As with MC, the concentration of all proteins increased after H stimulation (Table II). However, the proportions of secreted proteins differed significantly. The Alb%, IgG%, and nsIgA% increased ipsilaterally after H challenge, whereas the sIgA%, Lf%, and Ly% decreased. In contralateral secretions, the Alb%, IgG%, and nsIgA% were unchanged by ipsilateral H, whereas the sIgA%, Lf%, and Ly% all significantly increased on the contralateral side. Contralateral response to H is similar to direct response to MC described above.

Topical pretreatment of the ipsilateral nasal mucosa with the H₁ antihistamine, chlorpheniramine, inhibited both ipsilateral and contralateral secretory re-

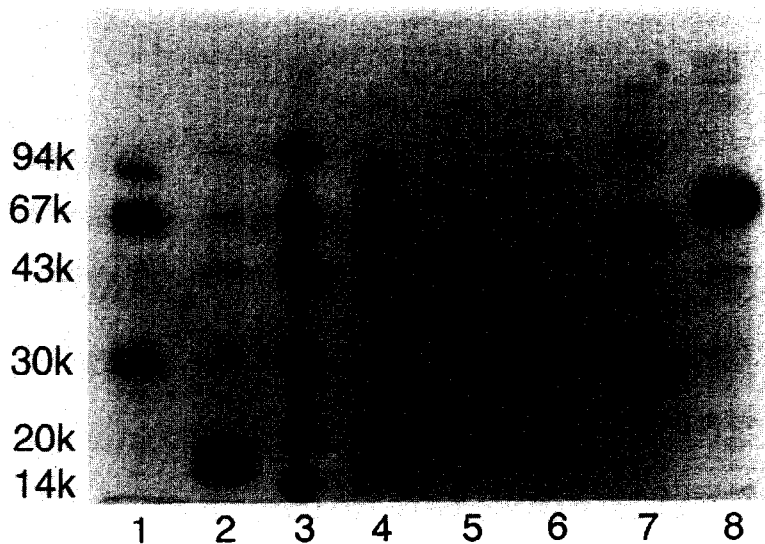


FIG. 3. Gel electrophoresis of nasal secretions and standards. Samples were electrophoreses on a 10% to 15% gradient gel after reduction and alkylation and stained with Coomassie brilliant blue stain. Baseline nasal secretions (*lane 5*) produced only a few discernable bands, several of which are accentuated in MC-induced secretions (*lane 4*). Standards of IgA (*lane 1*), Ly (*lane 2*), Lf (*lane 6*), IgG (*lane 7*), and Alb (*lane 8*) are presented for comparison. Low molecular weight standards in in *lane 3*. (Reproduced with permission: J Clin Invest 1989;84:1528-35.)

TABLE II. Changes in protein secretion in nasal lavages after challenge with MC (25 mg), hot foods, and MC or hot foods with and without atropine (0.1 mg), and H (10 mg)

	MC		Hot-food challenge		H	
	Atropine (-)	Atropine (+)	Atropine (-)	Atropine (+)	(I)	(C)
Total protein	▲	▶	▲	▶	▲▲▲	▲
Plasma proteins						
Alb	▲	▶	▲	▶	▲▲▲▲	▲
IgG	▲	▶	▲	▶	▲▲▲▲	▲
nsIgA	▲	▶	▲	▶	▲▲▲▲	▲
Glandular proteins						
Lf	▲▲	▶	▲▲	▶	▲	▲
Ly	▲▲▲	▶	▲▲▲	▶	▲▲	▲
sIgA	▲▲	▶	▲▲	▶	▲▲	▲
Percent of protein						
Alb %	▶	▶	▶	▶	▲▲	▶
IgG %	▶	▶	▶	▶	▲▲	▶
nsIgA %	▶	▶	▶	▶	▲▲	▶
Lf %	▲▲	▶	▲▲	▶	▼	▲
Ly %	▲▲	▶	▲▲	▶	▼	▲▲
sIgA %	▲▲	▶	▲▲	▶	▼	▲

(-), No atropine; (+), with atropine; (I), ipsilateral; (C), contralateral.

sponses to ipsilateral H, whereas topical atropine had no apparent effect.

These data suggest that H produces a local secretory response through H₁-receptor stimulation characterized by a disproportionate increase in vascular protein

secretion (Alb, IgG, and nsIgA). There is a smaller increase in ipsilateral sIgA, Lf, and Ly secretion, perhaps as the result of a direct or reflex glandular stimulation. However, because of the very large secretion of vascular proteins, the proportions of these latter

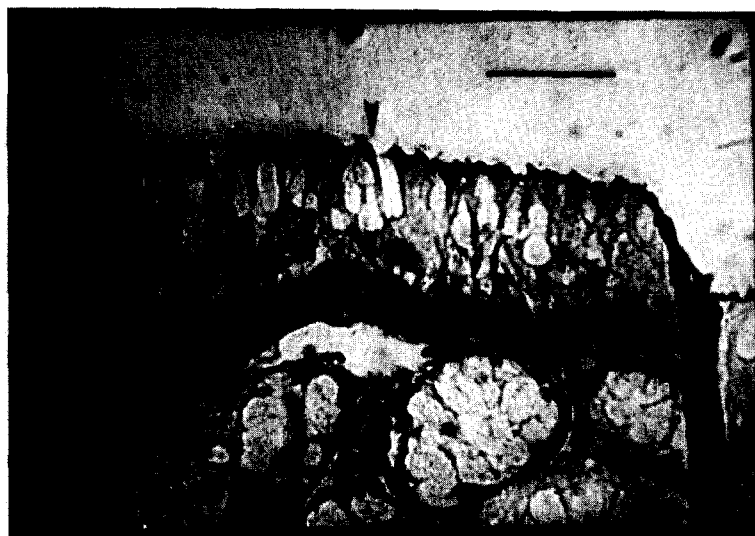


FIG. 4. IgG immunoreactivity (*dark stain*) in human nasal turbinate. IgG staining is located in the glycocalyx, epithelial basement membrane, interstitial spaces, and within blood vessel; immunoperoxidase technique without counterstain. The *bar* represents 50 μ m. (Reproduced with permission: J ALLERGY CLIN IMMUNOL 1989;84:920-30.)



FIG. 5. IgG in human nasal turbinate tissue. IgG immunoreactivity (*dark stain*) is located in the lumen (*arrows*) of these submucosal gland acini (*G*) and also in the surrounding interstitial spaces (*I*); immunoperoxidase technique without counterstain. The *bar* represents 50 μ m. (Reproduced with permission: J ALLERGY CLIN IMMUNOL 1989;84:920-30.)

three proteins decrease after H challenge. The contralateral secretion is similar to the MC-stimulated response and most likely represents a reflex-mediated stimulation of glandular secretion.

A third nasal provocation model uses an unusual form of stimulation, the consumption of hot and spicy foods. This phenomenon is referred to as gustatory rhinitis³ in which the consumption of certain foods produces a profound watery rhinorrhea. Subjects con-

sumed control (bland) foods and then positive (spicy or hot) foods, and nasal lavages were collected and analyzed as above. As presented in Table II, the positive foods produced similar protein secretion and proportions as observed with MC, with disproportionate increases in sIgA, Lf, and Ly, but proportional increases in Alb, IgG, and nsIgA. Nasal pretreatment with atropine inhibited the gustatory rhinitis response, reducing the proteins to control levels. Thus, gustatory

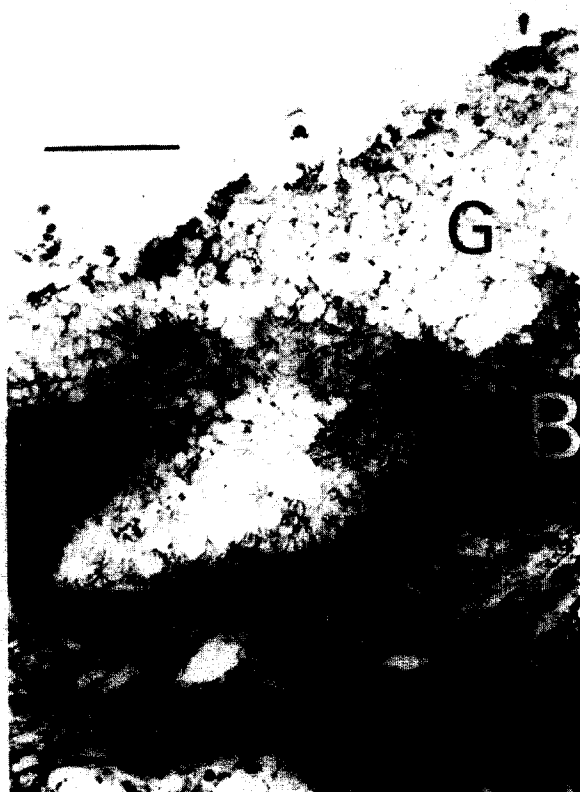


FIG. 6. Alb immunoreactivity in nasal turbinate tissue after topical treatment with H. Alb (*dark stain*) can be observed in the interstitium, in the basement membrane (*B*), and streaming between cells of the nasal mucosal epithelium. This oblique section permits visualization of individual epithelial cells and goblet cells (*G*) surrounded by Alb staining.

rhinitis stimulates a nasal reflex through afferent nerve receptors in the mouth, resulting in stimulation of glandular secretion in the nose.

Anatomy, histology, and physiology of the nasal mucosa

A clearer understanding of the anatomy and physiology of the nasal mucosa helps explain the observed pattern of protein secretion after nasal stimulation. The vasculature of the nasal mucosa is unusual in that capillaries that supply the basement membrane and the submucosal glands contain fenestrated endothelia,¹² much like the fenestrated vessels supplying the renal glomeruli. In theory, these vessels allow plasma products to passively diffuse into the basement membrane and into the body and lumen of the submucosal glands.

Although the veins and venules in the nasal mucosa are predominantly innervated by sympathetic nerves, the arterial vessels that supply the glands are inner-

TABLE III. Organization of neuropeptides in human nasal mucosa

Nervous system	Peptides
Sensory	CGRP Tachykinins SP NKA GRP
Parasympathetic	VIP PHM
Sympathetic	NPY

PHM, Peptide histidine methionine.

vated by both cholinergic and sympathetic nerves (as are the serous and mucous cells in the glands). Cholinergic nerve stimulation dilates these arterioles, increasing blood flow to the glands, thereby increasing passive diffusion of plasma proteins into the gland. In addition, the same cholinergic stimulation simultaneously produces active secretion from serous and mucous cells. The net effect is that the absolute secretion of plasma proteins increases after cholinergic stimulation, but the proportion of these proteins relative to the total protein secretion is relatively unchanged because of the active glandular secretion.

Histologic stains of the nasal mucosa support this concept. Human nasal turbinate tissue stained for IgG (and Alb) reveals diffuse staining throughout the interstitium, with intense staining along the basement membrane (Fig. 4). Although less frequently observed, when mucus is identified within the lumen of the submucosal glands, IgG (and Alb) immunoreactivity can be found associated with the mucus (Fig. 5). This observation confirms the penetration of plasma proteins into the body of the glands.

In contrast, both the absolute concentration and relative proportions of plasma proteins increase dramatically after H challenge, consistent with an increase in vascular permeability. Although plasma proteins are found diffusely throughout the interstitium, they normally do not penetrate across the nasal mucosal epithelial barrier. However, after H stimulation of human nasal mucosa, Alb immunoreactivity increases diffusely within the interstitium (presumably caused by generalized increased vascular permeability), and albumin can be observed streaming between respiratory epithelial cells (Fig. 6), suggesting that the epithelial barrier becomes permeable.

Histologic examinations of the nasal mucosa for sIgA, Lf, and Ly also help explain the observed protein changes after nasal provocation. SC, Lf, and Ly are histologically localized to the serous cell of the



FIG. 7. Distribution of SC in human nasal mucosa. SC (*dark stain*) is observed only in serous cells of submucosal glands. Mucous cells and the epithelium are not stained; immunogold technique without counterstain. The *bar* represents 50 μ m. (Reproduced with permission. J ALLERGY CLIN IMMUNOL 1989;84:920-30.)

submucosal glands (Figs. 7 and 8). Periglandular plasma cells produce dimeric IgA, which forms sIgA after binding to SC (a membrane receptor) uniquely situated on glandular serous cells.^{6, 7, 22} The sIgA molecule is then transported into the glandular lumen, and when the nasal mucosa is stimulated by cholinergic stimuli, it is secreted along with mucus into nasal secretions.⁶

Similarly, Lf and Ly are produced and stored within grandules of the serous cell.^{20, 23-25} In several *in vivo* and *in vitro* studies of respiratory mucosa in both human and nonhuman primates, cholinergic stimulation actively stimulates the secretion of Lf and Ly from the serous cells.²⁵⁻²⁷ Thus, it appears that direct cholinergic stimulation, or indirect stimulation via activation of nasal reflexes, results in an augmented secretion of sIgA, Lf, and Ly from the glands into nasal secretions.

Nasal neuropeptides

The regulatory role of the neural supply to the nasal mucosa is currently being unraveled, but it has become clear that neuropeptides play a major role in the physiology of nasal secretions.

In addition to classic neurotransmitters, neuropeptides are found in three types of nerves in the nasal mucosa: type C sensory nerves, parasympathetic nerves, and sympathetic nerves.²⁸⁻³⁷ Each neuron contains and releases specific combinations of neurotransmitters (Table III). This concept is revolutionary and demands a reexamination of the physiology of nerves and their interaction with tissue that they innervate.^{38, 39}

TABLE IV. Concentrations of neuropeptides in human nasal mucosa

Peptide	N	pmole/gm wet weight (mean $\pm$ SEM)
GRP	9	0.60 $\pm$ 0.25
CGRP	7	0.54 $\pm$ 0.08
SP	26	1.03 $\pm$ 0.12
NKA	7	0.76 $\pm$ 0.23
VIP	18	3.31 $\pm$ 0.59
NPY	6	3.13 $\pm$ 0.79

The sensation of pain is mediated by the trigeminal sensory nerves that respond to noxious stimuli, such as mechanical or thermal injury, acid, bradykinin, or H.⁴⁰ 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.^{41, 42} Several neurotransmitters have been identified in trigeminal sensory neurons,^{28, 30-32, 40} including CGRP, the tachykinins, SP and NKA, and GRP.^{43, 44}

Parasympathetic neurons contain acetylcholine, VIP, and a peptide with histidine at the *N* terminal and methionine at the *C* terminal called peptide histidine methionine.⁴⁵ Sympathetic neurons contain norepinephrine and NPY,^{46, 47} a peptide that has many of the same effects as norepinephrine but is slower in onset and longer in duration.

To understand the role of each neuropeptide, an analytical approach has been developed that involves (1) extracting neuropeptides from nasal mucosal tissue



FIG. 8. Lf immunoreactivity in submucosal glands. Lf (coarse black deposits) is found only in submucosal serous cells, whereas alcian blue (uniform gray stain) stains only submucosal mucous cells and goblet cells. The staining pattern is identical for Ly. (Reproduced with permission: J ALLERGY CLIN IMMUNOL 1989;84:914-9.)

(turbinate tissue) and measuring their concentrations by radioimmunoassay, (2) histologically locating the neuropeptides within the nasal mucosa, (3) identifying specific receptors for the neuropeptides by autoradiography, and (4) measuring secretory responses to neuropeptide stimulation of tissue explants in vitro. GRP will be used as a model to illustrate this analytical approach. GRP stimulates exocrine secretion, and preliminary evidence suggest that GRP is a transmitter of sensory nerves.⁴⁴

Turbinate tissue extracts were prepared, and radioimmunoassays were used to measure specific neuropeptides. The concentrations of GRP, CGRP, SP, and NKA were similar to each other, ranging from 0.54 to 1.03 pmol/gm (wet weight) of turbinate tissue (Table IV). The concentrations of VIP and NPY were significantly higher.

Immunohistochemistry was performed to identify structures innervated by each type of neuropeptide-containing neuron. Tissues were fixed by microwave, embedded in paraffin sections, immunologically stained, and visualized by the immunogold technique. GRP immunoreactivity was widely distributed within nerves in the walls of venous sinusoids and venules

and near submucosal glands (Fig. 9). Free fibers were also occasionally found in connective tissues, beneath the epithelial basement membrane, and between epithelial cells. The distributions of CGRP, SP, and NKA fibers were similar to GRP (Table V), and all four neuropeptides stained nerve bundles deep within the nasal mucosa, suggesting that these peptides are contained in the same nerves.

Binding sites for these neuropeptides were visualized by autoradiography and dark-field microscopy. This technique revealed GRP binding sites on human nasal mucosal epithelial cells and submucosal gland epithelia (Table VI), but the technique could not determine whether or not individual cells possessed specific binding sites for GRP or the other neuropeptides.

Even though these four neuropeptides colocalized within the same neuron, the binding site distributions within the nasal mucosa differed significantly. In particular, GRP bound to the epithelium and to submucosal glands. In contrast, CGRP bound to arterioles. SP bound to vessels, glands, and epithelium, whereas NKA bound only to arterioles.

The function of each peptide was then examined in terms of its ability to stimulate radiolabeled glycoconjugate (mucous cell marker) and/or Lf (a serous cell marker) release from nasal mucosal explant tissue in vitro (Table VII). GRP stimulated the release of both glycoconjugate and Lf, consistent with stimulation of both mucous and serous cells and also consistent with GRP binding sites on submucosal glands. The tachykinins SP and NKA also stimulated secretion, but to a lesser degree. NKA stimulated secretion despite the apparent absence of binding sites on the glands. NPY did not stimulate secretion of either glandular marker. VIP was found to stimulate the secretion of both glycoconjugate and Lf, consistent with the plentiful supply of VIP receptors on submucosal glands (Table VI).

CONCLUSION

The interrelationship between the nervous control of nasal secretions and secretions stimulated by allergens, irritants, or infections is currently being unraveled, but it is certain to be illuminating and will present us with new and useful ways to regulate secretions pharmacologically. The new body of information derived from these studies is applicable to other diseases that involve nasal pathology, such as sinusitis, allergic rhinitis, common variable immunodeficiency, IgA deficiency, Wegener's granulomatosis, and perhaps to other respiratory diseases, such as asthma. In addition, this information may help us understand the pathophysiology of mucous membrane disease elsewhere in the body. Indeed, the nasal mucous membrane is a readily available and accessible

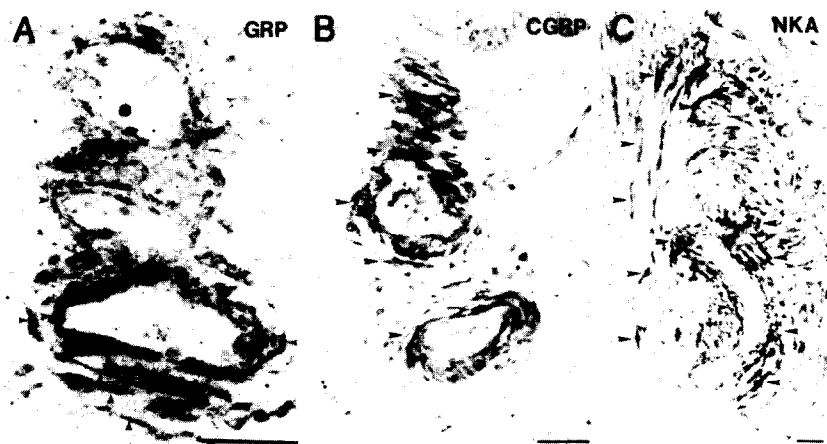


FIG. 9. Nerve fibers in arterioles in human nasal mucosa. **A**, GRP immunoreactivity (*dark stain, arrowheads*) is observed in the wall of a coiled arteriole. GRP is found at the adventitial, medial junction, between smooth muscle cells, and at the intima. **B**, In an adjacent section, CGRP is observed in essentially the same pattern as GRP. **C**, In a section of 20 to 24 μm deeper, NKA immunoreactive neurons are observed around the same arteriolar complex; nuclear red counterstain. The *bars* equal 25 μm .

TABLE V. Immunohistochemical distribution of neuropeptides containing neurons

Peptide	Immunohistochemical distribution			
	Epithelium	Submucosal glands	Arterioles	Vein sinusoids
GRP	0	++	+++	++
CGRP	+	++	+++	++
SP	+	+	++	+
NKA	+	+	+++	++
VIP	0	++	+	+
NPY	0	+	+++	++

0, Immunoreactive fibers not present; +, immunoreactive fibers occasionally observed; ++, individual immunoreactive fibers present in low density; +++, immunoreactive fibers present in high density.

TABLE VI. Autoradiographic distribution of neuropeptide binding sites in human nasal mucosa

Peptide	Autoradiographic binding sites			
	Epithelium	Submucosal glands	Arterioles	Vein sinusoids
GRP	++	+++	0	0
CGRP	0	0	+++	+
SP	+	+	+	+
NKA	0	0	+	0
VIP	+	++	+	+
NPY	0	0	+++	0

0, Not present; +, low density of binding sites; ++, moderate density of binding sites; +++, high density of binding sites.

model of mucous membrane physiology and host defense and should therefore be of interest to the other medical disciplines.

One note of caution needs to be mentioned, how-

ever. It appears that secretory products from serous cells provide the host with a primary defense against microbial infection. Indeed, up to 25% of the nasal secretory protein is Ly and another 4% is Lf. Both of

TABLE VII. Release of glycoconjugates and Lf from human nasal mucosal explants

Peptide	Glycoconjugate	Lf
GRP	++	+++
CGRP	0	0
SP	+	0
NKA	+	+
VIP	++	+++
NPY	0	0

0, No stimulation of secretion; +, secretion increased by 15% to 20%; ++, secretion increased by 20% to 40%; +++, secretion increased by >40%.

these proteins have important, nonspecific, antimicrobial properties. If serous cell secretion is actively suppressed, it is possible that the host may become predisposed to prolonged infection. This disquieting feature of regulating secretions suggests that we must always consider the potential adverse effects of pharmacologic manipulation of seemingly beneficial, yet annoying, body functions.

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