

the body and likely is the mechanism for this form of nasal congestion.

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# Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa

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*Neural mechanisms contribute to many nasal symptoms and syndromes. Sensory nerve stimulation by irritants, mast cell products, and inflammatory mediators leads to sneezing and other systemic reflexes. Parasympathetic reflexes and sensory axon responses combine to increase nasal blood flow, fill venous sinusoids (which thickens the mucosa and reduces nasal patency), induce plasma extravasation, and stimulate glandular secretion of mucous and serous cell products. These putative roles for nerves and neuropeptides in pathologic events open new therapeutic avenues. Anticholinergic agents, peptide neurotransmitter agonists and antagonists, drugs to reduce or modulate sensory or parasympathetic nerve function, potent topically applied glucocorticosteroids, and agents to inactivate inflammatory, secretory, or vascular cells may be of use. Ablation of sensory nerves by topical application of the chili pepper neurotoxin capsaicin has been successful in reducing the symptoms of refractory vasomotor rhinitis. (J ALLERGY CLIN IMMUNOL 1992;90:1045-50.)*

**Key words:** Vasoactive intestinal peptide, parasympathetic reflexes, rhinitis, neuropeptide

Sneezing, rhinorrhea, and cyclic changes in nasal patency and discharge rates are normal, healthy responses to the varied conditions of inhaled air and noxious stimuli. Nasal nerves play a central role in the regulation of nasal patency and secretion production.<sup>1</sup> Stimulation of sensory nerves leads to parasympathetic reflex-mediated glandular secretion, whereas sympathetic influences contract the mucosa.<sup>2</sup> Alter-

ations in the neural control of vascular and secretory processes may contribute to the symptoms of rhinitic syndromes.

## Abbreviation used

VIP: Vasoactive intestinal peptide

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## NOCICEPTIVE SENSORY NERVES

The discovery that many neurons use peptides as neurotransmitters has revolutionized our understanding of the nervous system in general and the innervation of human nasal mucosa in particular.<sup>3</sup> Trigeminal sensory neurons contain calcitonin gene-related

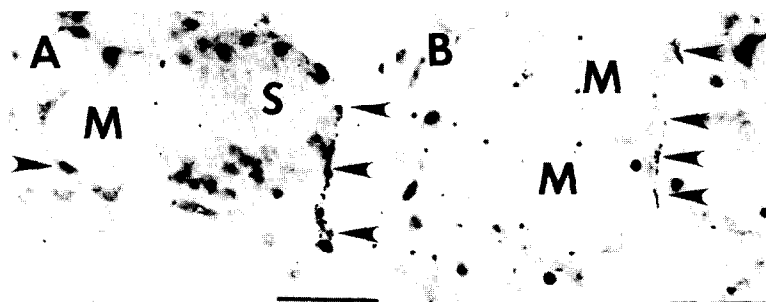


**FIG. 1.** VIP nerve fibers in human nasal mucosa. VIP-immunoreactive nerves (arrowheads) are seen in the walls of glandular acini near serous cells (A) and mucous cells (B). Immunogold method with nuclear fast red counterstain.

peptide, the tachykinins substance P and neurokinin A, gastrin-releasing peptide, and others.<sup>1, 4, 5</sup> The small-diameter C fibers that contain these peptides innervate arterial and venous vessels, submucosal glands, and the epithelium.<sup>6</sup> These neurons respond to noxious mechanothermal and chemical stimuli by conveying messages of injury (pain) to the central nervous system and by initiating local vascular inflammatory reactions (axon responses). Noxious stimuli produced by mast cells and during inflammation include  $H^+$ ,  $K^+$ , prostaglandin  $E_2$ , leukotriene  $C_4$ , platelet-activating factor, histamine, and bradykinin, whereas exogenous stimuli include  $SO_2$ , formaldehyde, capsaicin (essence of chili peppers), and other "irritants." Nerve depolarization leads to neuropeptide release from central and peripheral neurosecretory varicosities.<sup>5</sup> In the periphery axon responses and neuropeptide release lead to small increases in superficial blood flow. These nerves contain and release several peptides, but each of the peptides has unique actions that are determined by the distribution of cells bearing their specific receptor proteins.

The binding sites for peptides released from sensory nerves have been mapped in human nasal mucosa. Calcitonin gene-related peptide receptors are present on arterial vessels and to a minor extent on other vessels.<sup>7</sup> Substance P receptors are present on epithelium, arterial, venous, and sinusoidal vessels and glands, whereas neurokinin A binds only to arterial vessels.<sup>8</sup> Gastrin-releasing peptide is present on the epithelium and submucosal glands.<sup>9</sup> These distributions of calcitonin gene-related peptide, substance P, neurokinin A, and gastrin-releasing peptide binding sites are consistent with their presumed effects *in vivo*. Calcitonin gene-related peptide, substance P, and neurokinin A cause vasodilation and lead to plasma extravasation, whereas substance P and gastrin-releasing peptide stimulate exocytosis from epithelial and glandular cells. These actions could be generated by axon responses *in vivo*.

In the central nervous system substance P and perhaps other transmitters convey pain messages to sensory systems. Additional central interneurons may be stimulated to release opioid peptides, which act on  $\mu$ -receptors to dampen the pain messages. More obvious consequences of sensory nerve stimulation are systemic reflexes, such as the sneeze,<sup>10</sup> and parasympathetic reflexes.

The actions of these peptides are limited by enzymatic degradation. Neutral endopeptidase 24.11<sup>11</sup> on the surfaces of epithelial cells, glands, and the endothelium plays an important role in limiting the extent and duration of neurogenic inflammation because it breaks down many neuropeptides and bradykinin. Destruction of neutral endopeptidase during viral infection or by inhaled agents such as cigarette smoke may potentiate the effects of the proinflammatory neuropeptides.<sup>12, 13</sup> Angiotensin-converting enzyme may also play a role in limiting the actions of peptides.<sup>14</sup>

## PARASYMPATHETIC REFLEXES

Parasympathetic nerves originate in the superior salivatory nucleus and pass by means of the seventh nerve through the vidian canal to the sphenopalatine ganglion. The postganglionic fibers contain acetylcholine, VIP, and probably other similar peptides. Nerve fibers that contain choline acetyltransferase (marker of cholinergic nerves) and VIP have been mapped in the nasal mucosa. Fibers that contain either of these two molecules densely innervate submucosal glands (Fig. 1). They also innervate arterial vessels and sinusoids.<sup>15</sup>

Acetylcholine acts on peripheral muscarinic receptors. Five muscarinic receptor genes are now known.<sup>16</sup> However, there are pharmacologic agonists and antagonists to only the M1, M2, and M3 subtypes. These antagonists have been used to identify the locations of acetylcholine-binding sites in human nasal mucosa by use of radiolabeled ligand binding, autoradiogra-

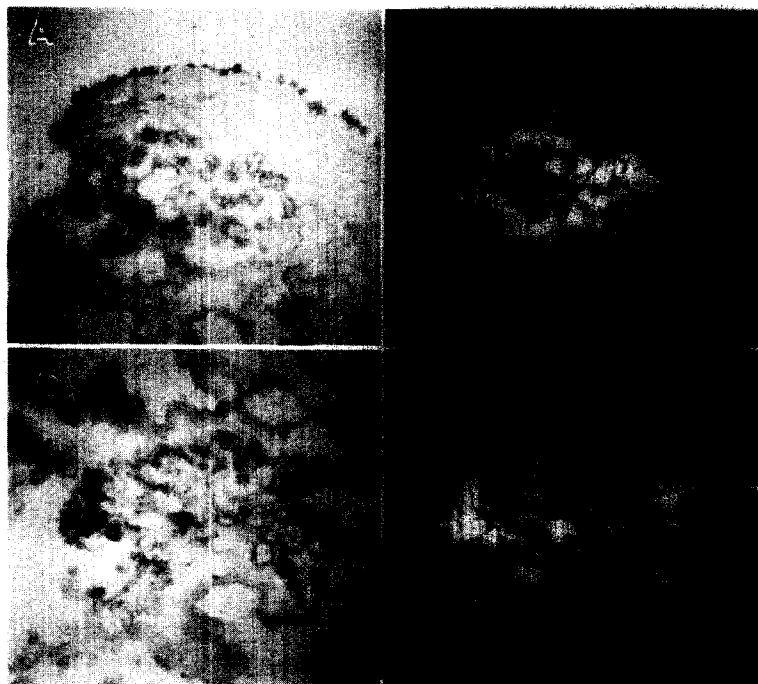


**FIG. 2.** VIP binding sites in human nasal mucosa. Brightfield images (A and C) show submucosal glands and the vascular plexus. The corresponding darkfield views (B and D) show white silver grains, which indicate iodine 125-VIP binding to submucosal glands, epithelial cells, and with low density to some endothelial cells.

phy, and competitive binding analysis.<sup>17</sup> Muscarinic receptors are present on the epithelium, submucosal glands, arterial vessels, and capacitance vessels. M1 binding sites are present on the epithelium and glands, whereas M3 sites are present on the epithelium, glands, and vessels. M2 sites have not been found. Some muscarinic binding sites on vessels have been identified that did not appear to be M1, M2, or M3. It is not possible to quantify these because M4 and M5 receptor ligands are not available. Approximately 40% of the identifiable muscarinic binding sites are M1.

This distribution<sup>17</sup> of muscarinic receptors on glands and the epithelium is consistent with the well-recognized potency of muscarinic agonists and parasympathetic reflexes as secretagogues.<sup>10</sup> The presence of receptors on arterial and capacitance vessels suggests that parasympathetic cholinergic reflexes could also increase nasal blood flow, which would lead to filling of sinusoids, thickening of the mucosa, and decreasing airway patency. The use of anticholinergic agents to "dry" the nasal mucosa, reduce secretion volume, and increase nasal patency is consistent with this distribution of muscarinic receptors. At present, nonselective muscarinic antagonists are in use that act on all pharmacologically defined receptor subtypes. In the future, subtype-specific muscarinic antagonists such

as M1 and M3 antagonists may have greater selectivity.

VIP and its relatives are derived from one region of DNA. Alternate transcription of the same gene region leads to the production of the peptide histidine methionine (peptide histidine isoleucine in some species) and the peptide histidine valine.<sup>3, 18</sup> They share related sequences, and their functional effects as secretagogues and dilators are similar.<sup>18-20</sup> VIP is the most potent vasodilator of the group; however, peptide histidine methionine may cause slightly more secretion in some systems. VIP is also a bronchodilator in vitro,<sup>16</sup> but its potential as an antiasthma drug is limited because intravenous infusion causes profound hypotension. Small improvements in airflow noted in subjects who had asthma after the administration of VIP may be caused by adenosympathetic reflexes. In human explant culture in vitro, VIP stimulated serous cell secretion, whereas mucous cell secretion was only marginally enhanced.<sup>15</sup> In contrast, VIP is reported to inhibit secretion from human tracheal explants.<sup>21</sup> Unlike its activity in the feline trachea,<sup>22</sup> VIP did not augment the secretion induced by suboptimal methacholine administration in human tissue. These highly variable effects in various animals and anatomic sites make it difficult to extrapolate from one system to another. In addition, extrapolations to pathologic sit-

uations must be done with care because increases in VIP-immunoreactive material have been detected by immunohistochemical tests in nasal mucosa from subjects who have vasomotor rhinitis.<sup>23</sup>

VIP-binding sites have been identified by autoradiography in human nasal mucosa (Fig. 2) and the lower respiratory tract.<sup>15, 24</sup> The suggested putative vasodilator and secretagogue roles are consistent with the autoradiographic localization of VIP-binding sites on the epithelium, glands, and vessels in human nasal mucosa.<sup>15</sup> At these sites VIP may dilate vessels, increase plasma flux across the membrane, and enhance serous cell glandular secretion. This secretory effect may be of clinical relevance because serous cells contain lactoferrin, lysozyme, secretory component, and many other enzymes and antibacterial proteins.<sup>25</sup> Specific enhancement of secretion of these components without concomitant secretion of mucins from mucous cells may be useful in the prevention of mucosal infection.

Both acetylcholine and the VIP-like peptides are released during parasympathetic reflexes. These reflexes can be induced by nasal provocation with histamine, capsaicin, nicotine, and oral provocation with chili peppers ("gustatory rhinitis," "salsa sniffles," "curry nose").<sup>25-28</sup> It is tempting to speculate that parasympathetic reflexes play a role in allergic rhinitis and vasomotor rhinitis. The cholinergic component appears to be predominant because atropine blocks reflex-induced glandular secretion.<sup>25, 26</sup> The noncholinergic component (caused by the effects of VIP, peptide histidine methionine, and the other peptides) has not been clearly demonstrated *in vivo* in human nasal mucosa, but experimental conditions and the strength of the inciting stimulus may determine the neural nature of the parasympathetic reflex. Acetylcholine may be released at low nerve-impulse frequencies, whereas the peptides may be released at higher frequencies. The impulse frequency may be a measure of the magnitude of the sensory stimulation and other afferent reflex inputs that are part of nasal secretory reflex arcs.

### SENSORY-PARASYMPATHETIC REFLEX ARC

Sensory nerve stimulation and the subsequent parasympathetic reflexes lead to coordinated vascular congestion with mucosal thickening and obstruction to airflow, glandular secretion, and expulsion of offending noxious stimuli by sneezing. These rapid events that protect the airway from further injury constitute the cardinal features of inflammation: pain, redness, heat, swelling, and loss of function. Pain is caused by sensory nerve depolarization and transmission of the neural impulses to the central nervous system. Vascular events may be mediated by both

sensory nerve axon responses and parasympathetic reflexes. It can be difficult to discriminate between these two mechanisms *in vivo*. Arterial dilation, which produces the heat and redness, may be caused by calcitonin gene-related peptide, substance P, neurokinin A, VIP, or muscarinic receptors. The swelling is caused by sinusoidal filling, which follows the opening of arteriosinusoidal/arteriovenous anastomoses, and edema, which is produced by plasma extravasation through fenestrated capillaries and postcapillary venules. The increases in blood flow and transmitted blood pressure result from the arterial dilation and the direct effects of substance P and VIP on endothelial cells. Contraction of endothelial cells lays bare the underlying basement membrane and permits the passage of fluid and the adherence of leukocytes. In the presence of chemotactic stimuli these leukocytes may be enticed into the interstitium. In this scenario sensory nerve stimulation with axon response activation and parasympathetic reflexes can combine to produce many of the cardinal features of acute inflammation and nasal secretion, which is a hallmark of rhinitis.

### SYMPATHETIC INFLUENCES

Sympathetic nerves contain norepinephrine and neuropeptide Y.<sup>29</sup> These transmitters act on arterial and arteriovenous anastomotic vessels<sup>6</sup> to produce vasoconstriction, which reduces nasal blood flow and allows distended venous sinusoids to collapse.<sup>1</sup> This collapse leads to a thinning of the nasal mucosa and an increase in nasal patency. Norepinephrine also stimulates modest serous and mucous cell secretion. The actions of the sympathetic and parasympathetic nervous systems are probably integrated at the brain stem level. The coordinated actions of the autonomic systems probably produce the nasal cycle. Sympathectomy, Horner's syndrome, and Vidian neurectomy disrupt the nasal cycle.

### NERVES AND RHINITIS

As outlined, neural mechanisms contribute to many nasal symptoms and syndromes. Sensory nerve stimulation by irritants, mast cell products, and inflammatory mediators leads to sneezing and other systemic reflexes. Parasympathetic reflexes and sensory axon responses combine to increase nasal blood flow, fill venous sinusoids (which thickens the mucosa and reduces nasal patency), induce plasma extravasation, and stimulate glandular secretion of mucous and serous cell products. These putative roles for nerves and neuropeptides in pathologic events open new therapeutic avenues. Anticholinergic agents, peptide neurotransmitter agonists and antagonists, drugs to reduce or modulate sensory or parasympathetic nerve func-

TABLE I. Neural events, rhinitic syndromes, and potential treatments

| Event                     | Effect                                                                                                  | Potential treatments                                                                                                                                                                                              |
|---------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sensory nerve stimulation | Superficial vasodilation, parasympathetic reflexes, systemic reflexes (sneeze), leukocyte infiltration? | Capsaicin ablation of sensory nerves<br>Neuropeptide antagonists (SP, NKA, CGRP, GRP, others?)<br>Modulate nerves with steroids, cromolyn, ion channel blockers, $\mu$ -opioid agonists<br>Bradykinin antagonists |
| Parasympathetic reflexes  | Serous cell secretion, mucous cell secretion, epithelial secretion, vasodilation                        | Anticholinergics, M3 antagonists, M1 antagonists, VIP antagonists                                                                                                                                                 |
| Sympathetic responses     | Vasoconstriction, shrink mucosa                                                                         | $\alpha$ -Agonists, NPY agonists                                                                                                                                                                                  |

CGRP, Calcitonin gene-related peptide; GRP, gastrin-releasing peptide; NKA, neurokinin A; NPY, neuropeptide Y; SP, substance P.

TABLE II. Involvement of nerves in some rhinitic syndromes and potential treatments

| Condition                              | Effect                                                                                                         | Potential treatments                                                                                           |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Mast cell degranulation                | Direct effects on glands and vessels, sensory nerve stimulation, parasympathetic reflexes                      | Antihistamines, bradykinin antagonists, anticholinergics, vasoconstrictors, glucocorticosteroids               |
| Irritant rhinitis                      | Sensory nerve stimulation, parasympathetic reflexes                                                            | Capsaicin ablation of sensory nerves, anticholinergics                                                         |
| Vasomotor rhinitis<br>"Wet"<br>"Dry"   | Increased sensitivity to inhaled irritants, parasympathetic reflexes, altered vascular or glandular responses? | Capsaicin ablation of sensory nerves, anticholinergics, $\alpha$ -agonists, NPY agonists, glucocorticosteroids |
| Rhinitis medicamentosa                 | Refractory vasodilation, $\alpha_2$ -receptor desensitization                                                  | Glucocorticosteroids, NPY                                                                                      |
| "Hypertrophic rhinitis"                | Obstruction of airflow                                                                                         | Glucocorticosteroids?                                                                                          |
| Atrophic rhinitis                      | Loss of sensory nerve trophic influences? Sympathetic hyperactivity?                                           | Trophic factors                                                                                                |
| Nasal polyps, ASA sensitivity          | Atrophy, inflammation                                                                                          | Glucocorticosteroids, antimetabolites?                                                                         |
| Nonallergic rhinitis with eosinophilia | Lymphocyte eosinophilotactic factors?                                                                          | Glucocorticosteroids, cytokine antagonists                                                                     |
| Horner's syndrome                      | Absence of sympathetic vasoconstriction                                                                        | $\alpha$ -Agonists, NPY, anticholinergics                                                                      |
| Hormonal rhinitis                      | Vascular congestion                                                                                            | $\alpha$ -Agonists, glucocorticosteroids, anticholinergics                                                     |

NPY, Neuropeptide Y.

tion, potent topically applied glucocorticosteroids, and agents to inactivate inflammatory, secretory, or vascular cells may be of use in modification of the actions of nasal nerves.

Ablation of sensory nerves by topical application of the chili pepper neurotoxin capsaicin has been successful in reducing the symptoms of refractory va-

somotor rhinitis.<sup>28, 30</sup> It may appear odd that a pain-provoking agent can be used as an "analgesic," but capsaicin, like many local anesthetics, causes pain before inactivating nociceptive nerves. Capsaicin acts on a nonspecific cation channel and allows the influx of calcium into the cell.<sup>31</sup> The increase in internal calcium and a passive, reciprocal leakage of potassium

out of the cell leads to depolarization of the neuron and to pain, neuropeptide release, and the axon response. Prolonged administration of capsaicin produces continued calcium and sodium influx, inactivation of calcium-dependent enzymes, mitochondrial destruction, and eventually NaCl-mediated osmotic lysis. These steps lead to the loss of sensory neural function and the inability to detect peripheral injury (analgesia). Without nociceptive sensory input the parasympathetic reflex cannot be activated, and therefore this significant mechanism of nasal secretion production and vascular congestion is thwarted.

The potential roles of nasal nerves in pathologic syndromes are only just beginning to be explored. Pathologic syndromes could result from either the overactivity of sensory, parasympathetic, or sympathetic systems or their inactivity. Tables I and II speculate about the roles of nerves and potential future treatment options. The regulation of neuropeptide gene expression, neurotransmitter release, and depolarization are other potential points for therapeutic intervention. The functions of nerves and the regulation of neutral endopeptidase activity during infections will also require clarification.<sup>32</sup>

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