

Effects of nedocromil sodium on airway neurogenic mechanisms

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Evidence shows that nedocromil sodium has a major inhibitory effect on sensory nerve activation. Animal models in which inhibitory effects have been demonstrated include bradykinin- or ovalbumin-induced plasma extravasation; cigarette smoke- or sulfur dioxide-induced bronchial hyperresponsiveness and increase in inflammatory cells in the airway; and bradykinin-induced airway vasodilatation and nasal mucosal edema. Nedocromil sodium has prevented the edema in human skin induced by substance P and neurokinin A, and, in the isolated rabbit trachea, has prevented substance P-induced potentiation of cholinergic neural responses at preganglionic (but not postganglionic) sites. In vitro, the drug also has inhibited nonadrenergic noncholinergic bronchoconstriction in guinea pig bronchi. Although a protective effect against citric acid-induced cough in the dog has been reported, no data are available from models of enhanced cough reflex, such as that in asthma. Inhibition of sensory nerve activation and prevention of tachykinin release by nedocromil sodium probably contribute to its beneficial effects in the treatment of asthma. (J Allergy Clin Immunol 1996;98:S112-7.)

Key words: Nedocromil sodium, sensory nerve activation, tachykinins

Neural regulation of the airways is a complex process, but there is evidence of activated neural mechanisms in the airways that may lead to bronchoconstriction, airway microvascular leakage, and mucus secretion in some disease states.¹ These characteristic features of asthma underlie the airflow limitation and bronchial hyperresponsiveness in this disease. The frequent occurrence of a dry cough in asthma also supports a potential role for neurogenic mechanisms in asthma. How these neural mechanisms may become activated in asthmatic airways remains unclear. It has been proposed that the shedding of the epithelium that occurs in asthma² can expose sensory nerve endings, which may then be sensitized by inflammatory mediators such as prostaglandins and some cytokines. Once sensitized, these nerve endings may be activated by inflammatory peptides such as bradykinin formed from high-molecular-weight kininogens.

The selective activation of sensitized C fibers by bradykinin³ may result in a local axon reflex to release the sensory neuropeptides contained in

Abbreviations used

MBS:	Sodium metabisulfite
NK:	Neurokinin
SO ₂ :	Sulfur dioxide
SP:	Substance P
NEP:	Neutral endopeptidase

these nerves.⁴ In animal models such as the guinea pig, the effects of bradykinin are mediated largely through the release of these neuropeptides.^{5,6} Depletion of sensory neuropeptides by previous treatment with capsaicin markedly reduces the bronchoconstriction that is observed when bradykinin is instilled into the airways of guinea pigs.⁷ More recently, a neurokinin (NK)-receptor antagonist has been shown to inhibit bradykinin-induced bronchoconstriction in patients with asthma.⁸

Substance P (SP), NK_A, and calcitonin gene-related peptide are sensory neuropeptides with potent inflammatory effects on the airways. Axon reflexes that trigger the release of these agents may propagate bronchoconstriction, mucus secretion, and airway microvascular leakage along the asthmatic airway and amplify these effects. Release of sensory neuropeptides may be increased in the asthmatic airway and may mediate noncholinergic neural bronchoconstriction. SP-containing nerve profiles have

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been reported to be increased in airways obtained from patients with asthma.⁹

EFFECTS OF NEDOCROMIL SODIUM ON AIRWAY NERVES

Drugs that inhibit neuropeptide release from sensory nerves or that prevent activation of sensory nerves may be beneficial in the treatment of asthma. Evidence shows that nedocromil sodium may have a major inhibitory action on sensory nerve activation. Nedocromil sodium has been shown to inhibit citric acid-induced cough in the dog.¹⁰ Direct recordings of bronchial C fibers indicate that they are activated by nedocromil sodium administered by aerosol or into the aorta in the dog,¹¹ and it has been suggested that the mechanism of suppression of cough responses is inhibition of cough receptors by activation of C fibers.¹² However, sodium cromoglycate, which has been shown to inhibit dry cough in patients taking angiotensin-converting enzyme inhibitors,¹³ inhibits the C fiber excitation produced by capsaicin in dogs.¹⁴ In an *in vitro* model in the guinea pig, nedocromil sodium inhibited the release of neuropeptides from airway sensory nerves at lower doses than did sodium cromoglycate.

There is indirect evidence to suggest that on the isolated rabbit vagus nerve the depolarization induced by nedocromil sodium involves the opening of a chloride channel, because lowering of the chloride concentration and application of a channel blocking agent (4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid) inhibited the depolarization.¹⁵

EFFECTS ON ALLERGEN RESPONSES

In an ovalbumin-sensitized guinea pig model, local instillation of ovalbumin on the nasal mucosa induced plasma extravasation that was inhibited by an NK₁ antagonist, suggesting that tachykinins stimulating NK₁ receptors play a role in this model.¹⁶ Nedocromil sodium, topically applied to the nasal mucosa, inhibited plasma extravasation induced by local application of ovalbumin and bradykinin.¹⁷ Nedocromil sodium did not inhibit SP-induced plasma extravasation. Sodium cromoglycate was inactive against both allergen-induced and bradykinin-induced plasma extravasation. These studies suggest that the effect of nedocromil sodium occurs by inhibition of tachykinin release from sensory nerve endings.

EFFECTS ON CIGARETTE SMOKE-INDUCED EFFECTS

Cigarette smoke is a potent airway irritant and induces several acute protective responses, includ-

ing coughing, bronchoconstriction, airway microvascular leakage, and mucus secretion. Cigarette smoke is a stimulant of airway sensory nerves, and there is experimental evidence from rodents to suggest that cigarette smoke provokes neurogenic inflammation in the airway through the release of endogenous tachykinins.¹⁸⁻²⁰ In the guinea pig, exposure to cigarette smoke also induces airway hyperresponsiveness to SP, and this effect is associated with inactivation of neutral endopeptidase (NEP).²¹ In this model, airway hyperresponsiveness to histamine but not to acetylcholine has been reported,²² an effect mediated by the release of sensory neuropeptides.²³ Cigarette smoke-induced airway plasma exudation in the guinea pig is inhibited by capsaicin and an SP antagonist and is potentiated by an NEP inhibitor, phosphoramidon, but not by captopril.²⁴ It has been hypothesized that free-radical release from inflammatory cells may degrade NEP activity.²¹

In the guinea pig, nedocromil sodium demonstrates inhibitory effects against cigarette smoke-induced airway microvascular leakage and hyperresponsiveness to SP and histamine.²⁴⁻²⁶ In a study by Daffonchio *et al.*,²⁶ cigarette smoke-induced airway inflammation (as assessed by the total number of cells recovered in bronchoalveolar lavage fluid) was reduced by nedocromil sodium, a finding that suggests that nedocromil sodium also inhibits inflammatory mechanisms. The inhibitory effect of nedocromil sodium does not appear to result from prevention of NEP inactivation by cigarette smoke.²⁵

EFFECTS ON BRADYKININ

Bradykinin is a potent bronchoconstrictor when administered by inhalation to patients with asthma and can also induce cough.²⁷ It has little direct constrictor effect on human bronchial smooth muscle *in vitro*, indicating that the *in vivo* effects are indirect. A cholinergic reflex contributes partly to the bronchoconstrictor effect of bradykinin, because anticholinergic drugs have inhibitory effects. In the guinea pig, additional bronchoconstriction has been shown to result from the release of sensory neuropeptides, because capsaicin and an NK₁-receptor antagonist reduce the degree of bronchoconstriction and airway microvascular leakage induced by bradykinin.^{7, 28} In patients with asthma, a combined NK₁- and NK₂-receptor antagonist has been shown to be effective in blocking bradykinin-induced bronchoconstriction.⁸

Nedocromil sodium is very effective in blocking in a dose-dependent manner the bronchoconstrict-

tor response to inhaled bradykinin in patients with asthma and exerts an inhibitory effect at a lower dose than does sodium cromoglycate.²⁹ Nedocromil sodium inhibits bradykinin-induced airway vasodilation in the pig and nasal mucosal edema in the guinea pig.^{17,30} These findings suggest that nedocromil sodium may prevent bradykinin from activating sensitized C fiber endings in the airway.

EFFECTS ON SULFUR DIOXIDE AND SODIUM METABISULFITE

Inhaled sulfur dioxide (SO₂) gas and sodium metabisulfite (MBS) aerosols cause bronchoconstriction in patients with asthma, an effect that is only weakly modulated by anticholinergic agents.³¹⁻³³ It is possible that in patients with asthma this bronchoconstrictor response is mediated by a noncholinergic neural mechanism involving neuropeptide release. In the guinea pig, MBS has also been shown to be potent in causing bronchoconstriction and airway microvascular leakage, effects that are inhibited by NK₁- and NK₂-receptor antagonists.³⁴ MBS also induces an increase in bronchial blood flow in conscious sheep.³⁵ Pulmonary administration of SO₂ evokes reflex airway constriction through the stimulation of afferent C fibers.³⁶

Nedocromil sodium is effective in inhibiting the bronchoconstrictor response to inhaled SO₂ and MBS in patients with asthma.³⁷⁻⁴⁰ In addition, in anesthetized dogs exposed to SO₂, nedocromil sodium prevents the increase in bronchial responsiveness to histamine challenge and suppresses the cellular changes in the lungs induced by SO₂.⁴¹ In sheep, nedocromil sodium has no effect on the MBS-induced increase in bronchial blood flow, and in guinea pigs it has no effect on MBS-induced bronchoconstriction and airway microvascular leakage.⁴²

EFFECTS ON TACHYKININS (NK_A AND SP)

In patients with asthma, NK_A and SP have been shown to induce bronchoconstriction, effects that are inhibited by nedocromil sodium.^{43,44} However, nedocromil sodium does not affect SP-induced smooth-muscle contraction in the guinea pig airway *in vitro*.⁴⁵ In human skin, sodium cromoglycate has been shown to cause dose-dependent inhibition of SP and NK_A-induced edema.⁴⁶ This finding has led to the suggestion that nedocromil sodium acts as a receptor antagonist at NK receptors, but there is no direct evidence to support this possibility. Rather, it has been suggested that the effects of

NK_A, for example, are mediated by an effect on the mast cell, which would be the site of inhibition by nedocromil sodium. Nedocromil sodium has been shown to inhibit IgE-mediated release of histamine from human lung mast cells.⁴⁷ In the isolated innervated rabbit trachea, nedocromil sodium inhibits SP-induced potentiation of cholinergic neural responses selectively at preganglionic sites but not postganglionic sites.⁴⁸

EFFECTS ON COUGH

In the conscious dog that has undergone tracheostomy, nedocromil sodium significantly increases the time to the first cough after challenge with citric acid aerosol and decreases the number of coughs.^{10,41} In human beings, nedocromil sodium has been observed to inhibit cough induced by capsaicin or nebulized distilled water,⁴⁹ but in another study the inhibition of capsaicin-induced cough was not confirmed.⁵⁰ It would be more relevant to test nedocromil sodium in models of an enhanced cough reflex rather than the basal protective reflex, but currently there are no data available in this regard. Patients with asthma may have a persistent dry cough despite adequate control of asthma attacks with inhaled or oral corticosteroids.⁵¹ However, clinical studies in patients with asthma show that nedocromil sodium reduces the severity of cough after long-term treatment. This finding suggests that nedocromil sodium has an inhibitory effect on airway sensory nerves in asthma.

EFFECT ON NONADRENERGIC NONCHOLINERGIC NERVES IN VITRO

Nedocromil sodium has been found to inhibit nonadrenergic noncholinergic bronchoconstriction in guinea pig bronchi *in vitro* in a concentration-dependent manner, with a maximum inhibition of 40% at 100 µmol/L. Nedocromil sodium does not affect the contractile response to SP and also does not modulate cholinergic bronchoconstrictor responses to electrical field stimulation in tracheal smooth muscle.⁴⁵ These results indicate that nedocromil sodium may modulate the release of tachykinins from airway sensory nerves. In contrast, nedocromil sodium does not modulate nonadrenergic relaxation in guinea pig trachea *in vitro*.⁵²

CONCLUSIONS

The published data available on nedocromil sodium with regard to its effects *in vivo* suggest that one of its actions is inhibition of airway

sensory nerve activation and thus prevention of tachykinin release. There is little evidence of an effect on cholinergic nerves. The mechanism by which activation of C-fibers by nedocromil sodium leads to an inhibition of tachykinin release deserves clarification. Further work is also needed to define the chloride channel through which nedocromil sodium works. The beneficial effects of nedocromil sodium in the treatment of asthma⁵³ may relate to its actions on sensory nerves—including inhibition of cough, airway microvascular leakage, sensation of chest tightness, and wheeze—which may result from sensory nerve activation through local axon reflexes.

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DISCUSSION

L. A. Laitinen. How would the concentrations of nedocromil sodium that you were using compare with the real-life situation?

A. C. Myers. What would be normal, 4 mg inhaled? You saw the concentration response; 50 μ mol/L had no effects, so we just increased the concentration from there.

A. A. Norris. It is always difficult to equate in vitro concentrations because you never know the local concentration in the airway mucosa in vivo.

J. G. Widdicombe. If you give nedocromil sodium as an aerosol, do you think it would penetrate to the ganglia in sufficient concentration to have this effect?

A. C. Myers. I do not know. With long-term use, perhaps nedocromil sodium could gain access to the parasympathetic ganglion. Certainly it could affect the fibers innervating smooth muscle that are closer to the lumen.

A. Laitinen. It is said that the majority of the afferent fibers travel in the parasympathetic system in the vagus nerve. How many afferent nerves, if any, travel in the sympathetic nervous system?

A. C. Myers. More come from the dorsal root ganglia, the sensory ganglia near the spine. There are not many sensory fibers from the sympathetic nerve. Retrograde tracing from the guinea pig airway shows that there are some fibers that project to the sympathetic ganglia because there is innervation from the superior cervical ganglion. They are not tachykinin positive, however, so they

are not the sensory-type fibers. There are through fibers going through the sympathetic ganglia, but I do not think they innervate the airways.

J. G. Widdicombe. In relation also to Fox's work, have you looked at afferents in the smaller airways, the bronchi? Certainly in the cat trachea, rapidly adapting receptors are largely mechanosensitive and not chemosensitive. Only in the bronchi does one find chemosensitivity.

A. C. Myers. We have recorded from some receptor fields that are located in the bronchus, but the majority are from the trachea.

J. P. Seale. Could an effect on chloride currents in endothelial cells be responsible for the effect of nedocromil sodium on plasma extravasation?

P. J. Barnes. That possibility is unlikely because nedocromil sodium does not block SP-induced extravasation.

K. F. Chung. The effect of nedocromil sodium on nerves is probably an effect on chloride channels in nerves, or it may be an indirect effect on the epithelium because I presume that changing the volume of the epithelium might affect the sensory nerve endings by deforming them.

A. A. Norris. The exquisite sensitivity of some of the neuronal responses to nedocromil sodium and cromolyn sodium in people with asthma is not always mirrored by the effects in animal studies. The drug is much more active in the inflammatory, asthmatic state. I wonder if that idea answers the question posed earlier about the possible lack of sensitivity of some of the *in vitro* ion-channel studies to the effects of the drug. That the drug works with much greater sensitivity in the asthmatic state than in the neuronal animal models suggests that the drug is down-regulating two

processes: the underlying inflammatory process itself and the neuronal mechanism in the asthmatic state.

K. F. Chung. I suppose I was trying to say that, in relation to the cough response. We may see much better effects if we look at an enhanced response, particularly one that results from an inflammatory process, because then the inflammatory cells, in addition to the nerves, would be inhibited. I think this work is quite possible. Now, one would probably like to relate that idea to the more basic possibility that nedocromil sodium acts through chloride channels. I do not know if these chloride channels are up-regulated in inflammation; it may be that in the presence of inflammation one may observe an inhibitory effect of nedocromil on up-regulated chloride channels, while not having an effect on the physiological chloride-channel activity of the resting cell.

A. A. Norris. One could almost make that criticism of our studies carried out in resting coils or resting channels. The next set of experiments may be to look at those channels or coils under states of activation induced by cytokines or inflammatory mediators.

E. W. F. W. Alton. To emphasize what we were trying to say earlier: it was an episodic chloride-channel increase from the constitutive level. We do need to stress the system and look at effects then rather than at something that is "house-keeping."

P. J. Barnes. The concept that nedocromil sodium does not have effects in healthy people but works only in people with allergic inflammation, is very important and should be remembered when we discuss the mechanism of action of this drug.