

Sensory neurophysiology of the cough reflex

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The epithelium of the larynx, trachea, and larger bronchi contains sensory nerves that are responsible for cough. Their two main categories are rapidly adapting receptors (RARs) and C fiber receptors. Both types respond to a wide variety of mechanical and chemical irritants. The RARs are the main sensory complex responsible for cough. C fiber receptors cause neurogenic inflammation by the release of tachykinins such as substance P. The reflex action of C fiber receptors seems to be inhibition of cough. However, the released tachykinins can stimulate RARs and promote or enhance the cough response. The strength and pattern of cough depends on the sites of the airway that are stimulated and the local and central reflex interactions of the RARs and C fiber receptors. Tachykinins seem to be involved in cough, but their role needs further study. (J Allergy Clin Immunol 1996;98:S84-90.)

Key words: Capsaicin, C fiber receptors, cough, cough receptors, neuropeptides, rapidly adapting receptors, tachykinins

The origin of cough is restricted to structures innervated by the vagus nerves.¹⁻³ In addition to the airways, these structures include the external ear, the esophagus, and abdominal organs. The points of airway branching, including the tracheal carina, where inhaled irritant material may strike, seem especially sensitive to cough.

The pattern of cough depends on the part of the respiratory tract stimulated. Mechanical stimulation of the larynx causes immediate expiratory efforts, often referred to as the expiration reflex.¹ Although the larynx is sometimes said to be the most sensitive site for cough, block of the superior laryngeal nerves makes little difference to the cough threshold for inhaled irritants in human beings and enhances the cough reflex in guinea pigs, suggesting that some laryngeal afferent pathways may be inhibitory to cough.^{4,5} Lower down the respiratory tract, the inspiratory phase of coughing becomes more prominent, and the deep augmented breaths that can be produced from the bronchial tree may be a fragment of the cough reflex. Both in experimental animals and in human beings, it is difficult or impossible to induce cough from the small airways and alveoli.³

Abbreviations used

CGRP: Calcitonin gene-related peptide
RAR: Rapidly adapting receptor
SP: Substance P

Cough receptors are polymodal and respond to a large variety of mechanical and chemical irritants^{3,6} (Table I). In the cat, the receptors in the larynx and trachea are especially sensitive to mechanical stimuli, whereas those in the bronchi respond relatively more to chemical irritants.⁷ Thus the pattern of cough depends not only on the nature of the stimulus but also on the site or sites where it acts. The same consideration applies to coughing in disease, which is especially prominent with inflammation of the larynx, trachea, and larger bronchi. Diseases at the small airway and alveolar levels are not usually characterized by cough.

HISTOLOGY OF "COUGH RECEPTORS"

Sensory nerve fibers can be identified in the airway epithelium with the electron microscope⁸ (Fig. 1) or immunofluorescence^{9,10} and are presumed to cause coughing. The tracheal epithelium of the rat, for example, has an extensive plexus of nerves that contain both substance P (SP)⁹ and calcitonin gene-related peptide (CGRP)¹⁰ (Fig. 2). These nerves lie deep to the tight junctions between epithelial cells and also in the basal region of the epithelium. Activation of the nerves releases

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TABLE I. Stimuli to C fiber receptors and RARs

	C fiber receptors		RARs
	Pulmonary	Bronchial	
Mechanical	Inflation	Inflation Foreign bodies	Inflation Deflation Dust Mucus Foreign bodies
Chemical	Irritant gases Cigarette smoke Capsaicin Volatile anesthetics	Irritant gases Capsaicin	Irritant gases Cigarette smoke Capsaicin Volatile anesthetics
Mediator	Acetylcholine Histamine Serotonin Prostaglandins Bradykinin SP	Histamine Serotonin Prostaglandins Bradykinin	Acetylcholine Histamine Serotonin Prostaglandins Bradykinin SP
Disease	Microembolism Pulmonary edema Pulmonary congestion Pneumonia	Bronchial congestion	Anaphylaxis Microembolism Atelectasis Bronchoconstriction Pulmonary edema

In general these three types of receptor respond to same stimuli, but sensitivities vary greatly. Main differences in response relate to mechanical stimuli. These lists of chemical and mediator stimuli are incomplete, and not all agents have been tested on all groups of receptors.

neuropeptides such as SP and CGRP. These neuropeptides cause neurogenic inflammation, characterized by vasodilatation and exudation of plasma, epithelial damage, submucosal gland secretion, and possibly smooth-muscle contraction¹¹ (Fig. 3). In addition, some of the epithelial receptors produce cough and an array of reflex motor responses.⁶

The assumption that the nerves identified histologically cause cough when stimulated is based on several observations. They can be established as sensory by degeneration experiments.^{9, 12} They are absent in species such as mouse and ferret that lack a cough reflex from the lower airways.^{2, 3} Although they are present in the rat, which has no cough reflex from below the larynx, the rat responds instead with hyperpnea and deep breaths.¹ The nerves are scanty or absent in the smaller airways and alveoli, consistent with the weakness of the cough reflex from these sites. In the cat they are concentrated at the tracheal carina, the site most sensitive for eliciting cough.¹³

AFFERENT PATHWAYS FOR COUGH

Of the sensory nerves identified in the lower airways, two are candidates for cough receptors: the rapidly adapting pulmonary stretch receptors

(RARs) with small-diameter (A δ) myelinated fibers, and the pulmonary and bronchial C fiber receptors with nonmyelinated afferent fibers.^{2, 3, 6} The evidence that the RARs, but not the C fiber receptors, cause coughing in cats and dogs is as follows: (1) the sites in airways most sensitive for cough (the larynx and carina)¹³ correspond to concentrations of RARs assessed by single-fiber recordings from the vagus nerves⁷; (2) all of the mechanical and chemical stimuli that lead to cough also excite RARs^{2, 6} (Table I); (3) many of the nonmyelinated fibers in the epithelium are connected to myelinated fibers in the vagal trunks¹⁴; and (4) partial vagal block of conduction by cooling to 7° to 10° C inhibits the coughing that results from tracheobronchial mechanical and chemical stimuli (sulfur dioxide and citric acid)^{13, 15} and blocks conduction in fibers from RARs but not from C fiber receptors.^{7, 16}

Whether C fiber receptors also cause cough is controversial. In general they are activated by the same chemical and irritant stimuli that excite RARs and produce cough^{6, 16} (Table I). However, compared with RARs they are less sensitive to mechanical stimuli.^{6, 15} It is unlikely that C fiber receptors in the alveoli and bronchioles cause cough, because cough cannot be induced from

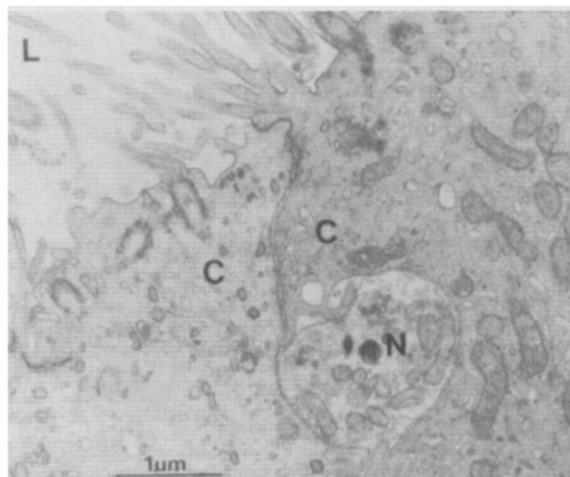


FIG. 1. Electron micrograph of axon (N) located closely to airway lumen (L) between two ciliated cells (C) in human tissue. Axon mitochondria and vesicles are visible ($\times 24,600$). (From Laitinen A. Adrenergic innervation of the human respiratory tract as revealed by histochemical and ultrastructural methods. *Eur J Respir Dis* 1985;140:1-42.)

these sites. Indeed, stimulation of pulmonary C fiber receptors in the cat inhibits the cough reflex,^{15, 17} and the same is probably true for bronchial C fiber receptors.^{15, 18, 19} In human beings, systemic 5-hydroxytryptamine, known to excite pulmonary C fibers in animals,¹⁶ can inhibit the cough that results from inhaled citric acid.²⁰ There is also extensive evidence that stimulation of C fiber receptors causes apnea followed by rapid shallow breathing, and not cough.^{2, 6} Indeed, in the extensive literature there is no example in which a chemical stimulus, given systemically and known to be selective for pulmonary or bronchial C fiber receptors, has caused cough.^{2, 6, 16} This finding applies to both anesthetized and nonanesthetized animals.

Why then is it claimed that activation of C fiber receptors can cause cough? The claim is based entirely on the use of aerosols of capsaicin to promote cough. Capsaicin is a selective C fiber receptor stimulant, but it can also stimulate RARs.^{21, 22} As with other C fiber receptor stimulants, given systemically it activates all of the reflex responses to C fiber activation, but it has never been shown to cause cough in anesthetized or nonanesthetized animals.^{2, 6} It did so in one study in conscious human subjects.²³ Given as an aerosol, it produces cough^{24, 25} and stimulates both C fiber receptors and RARs,²² and the most plausible hypothesis is that it causes cough by means of the RARs.

An additional argument that C fiber receptors may cause cough is that in guinea pigs, when

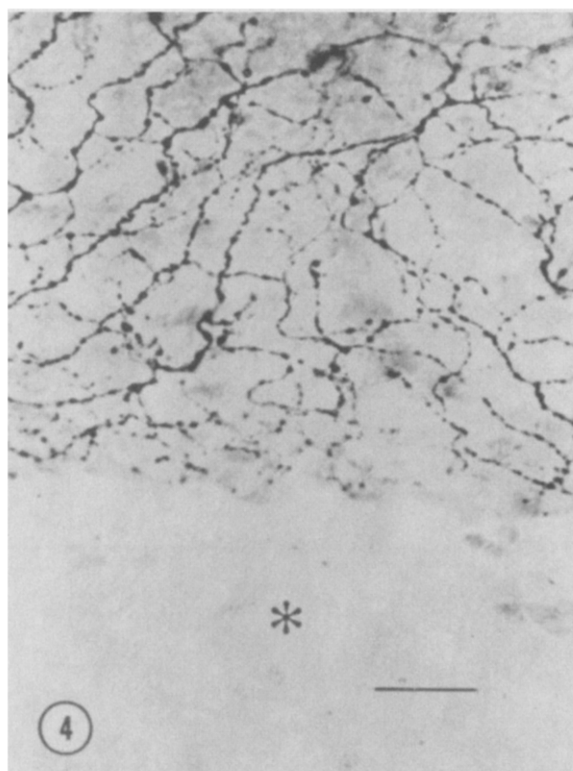


FIG. 2. Region of tracheal mucosa directly above cartilaginous ring of rat. Nerves are exhibited by immunofluorescence for SP. Density and orientation of intraepithelial plexus of SP-immunoreactive axons are similar to those found between cartilaginous rings. Intraepithelial nerve plexus is absent in region of epithelium (asterisk), which was accidentally removed during processing (bar, 25 μ m). (From Baluk P, Nadel JA, McDonald DM. Substance P-immunoreactive sensory axons in the rat respiratory tract: a quantitative study of their distribution and role in neurogenic inflammation. *J Comp Neurol* 1992;319:586-98. Copyright © 1992, John Wiley & Sons, Inc. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

sensory nerves are depleted of SP and CGRP by large doses of capsaicin, the cough reflex resulting from citric acid and capsaicin aerosols is blocked, but the reflex due to nicotine and mechanical stimulation remains intact.²⁴ It is suggested that the first two stimuli act by way of C fiber receptors and the later two by way of RARs. However, capsaicin can damage or destroy A δ myelinated fibers as well as C fibers,²⁶ and in the absence of physiologic evidence (e.g., fiber recordings) the results show only that different patterns of afferent activation can result in various types of cough. Furthermore, in dogs, the cough resulting from citric acid aerosol is prevented by vagal cooling that blocks myelinated fiber pathways from RARs but not C fiber pathways.¹⁵

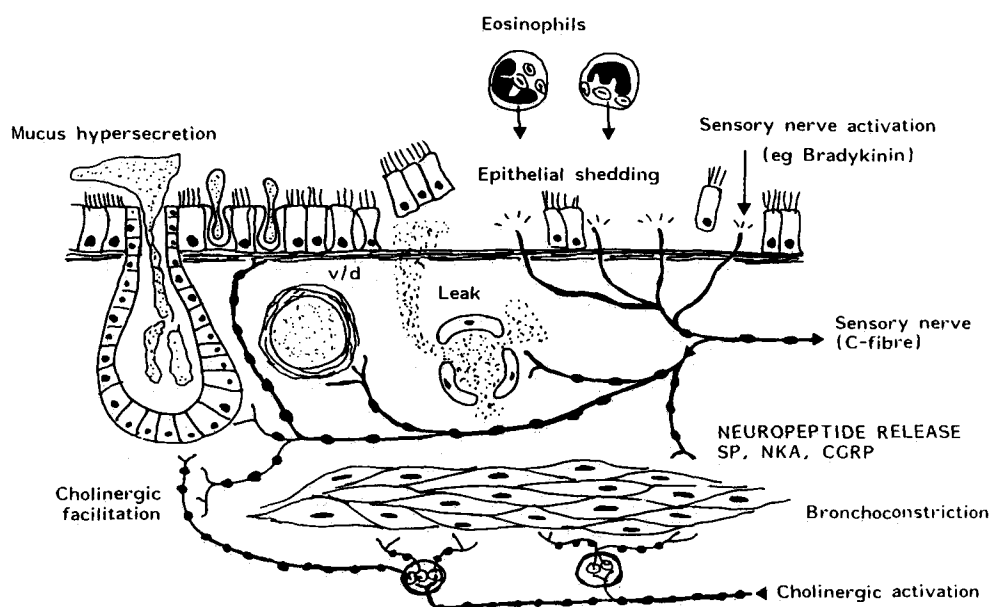


FIG. 3. Possible axon reflex mechanisms (neurogenic inflammation) in asthma. *NKA*, Neurokinin A; *v/d*, vasodilatation. (From Barnes PJ. Airway NANC nerves and neuropeptides. In: Barnes PJ, Rodger IW, Thomson NC, editors. *Asthma: basic mechanisms and clinical management*. London: Academic Press, 1992:359-89. Copyright 1992. Reprinted by permission of the publisher, Academic Press Limited London.)

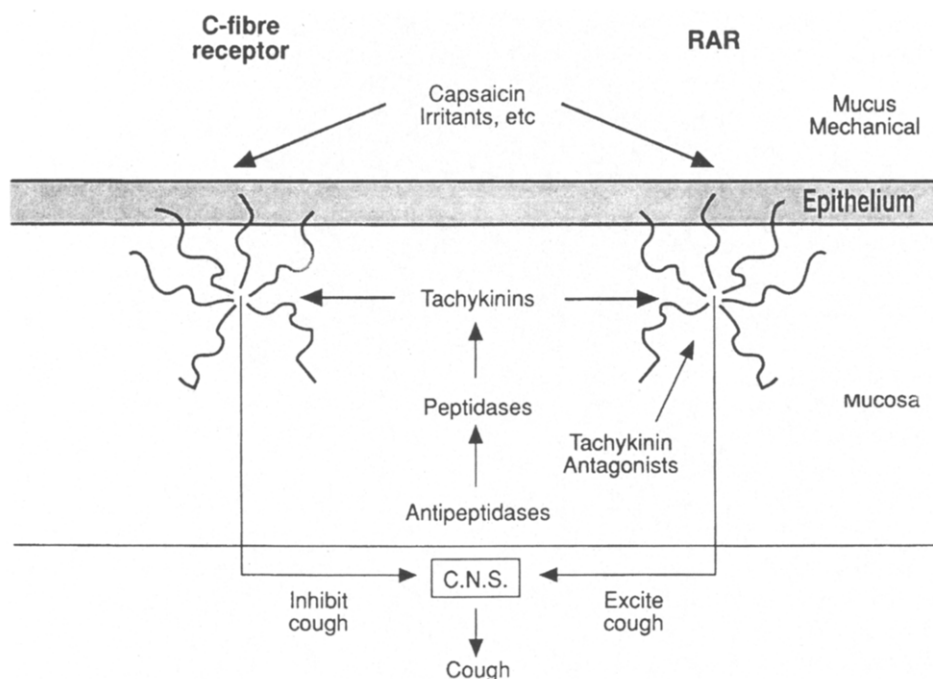


FIG. 4. Hypothetical role of tachykinins in cough. Tachykinins may be released from C fiber receptors and diffuse to RARs, which they stimulate to cause cough. They can be broken down by peptidases, which in turn can be inhibited by antipeptidases. Tachykinin antagonists can prevent action of tachykinins on RARs. If there is sufficient stimulation of C fiber receptors, they can cause central inhibition of cough. *CNS*, Central nervous system. (From Widdicombe JG. Neurophysiology of the cough reflex. *Eur Respir J* 1995;8:1193-202.)

TACHYKININS AND COUGH

Capsaicin releases tachykinins from sensory nerves. In the rabbit it can stimulate both RARs and C fiber receptors.²⁷ In *in vitro* tracheal preparations of the guinea pig, capsaicin stimulates C fiber receptors but not RARs^{28, 29}; however, tracheal RARs are known to be insensitive to chemical stimuli,⁷ and the *in vitro* environment may affect the diffusion of chemicals. Tachykinins can cause cough when given by aerosol to guinea pigs³⁰⁻³² and human beings,^{33, 34} or they may have no action.³⁵ They may have difficulty penetrating the airway epithelium because it contains a barrier of peptidases that destroy tachykinins. In patients with airway infection, when the epithelium may be damaged, SP aerosols can cause cough.^{33, 34} The question is whether endogenous tachykinins released by the activation of C fiber receptors as a result of capsaicin application can stimulate RARs and produce cough.

The possibility that cough can occur by this mechanism is supported by the finding that tachykinin antagonists can block the cough in guinea pigs caused by citric acid, cigarette smoke, histamine, and acetylcholine^{32, 36, 37} and the cough caused by bradykinin in patients with asthma.³⁴ In these conditions C fiber receptors are stimulated and are thought to release tachykinins, which in turn would act on sensory receptors for cough. The use of peptidase inhibitors supports a role for endogenous tachykinins in cough. Angiotensin-converting enzyme inhibitors cause cough in human beings, presumably by preventing the breakdown of endogenous tachykinins or bradykinin.³⁸ The peptidase inhibitor phosphoramidon not only causes cough in guinea pigs³⁷ but also enhances the cough response to inhaled SP and histamine.^{30, 31, 37}

Therefore one hypothesis^{3, 32} (Fig. 4) is that both RARs and C fiber receptors are activated by stimuli that cause cough, such as capsaicin, other irritants, and inflammation. The RARs in the larynx and tracheobronchial tree are the primary sensory endings for cough, and C fiber receptors cause neurogenic inflammation and by their own reflex action inhibit cough by a central gating mechanism. The tachykinins released from the C fiber receptors activate the RARs and cause or enhance cough. The end result of this complex interaction depends on the following: the degree of activation of C fiber receptors and RARs by the tussive stimuli; the relative balance of stimulation of RARs directly by tussive stimuli and indirectly by tachykinins released from C fiber endings; and

the central inhibition of cough by C fiber reflex action.³ Apart from local and reflex sensory nerve interactions arising from a particular airway site, inhaled tussive agents act at different parts of the respiratory tract and give rise to different patterns of cough with central nervous interactions.

CONCLUSIONS

Sensory nerves in the airway epithelium are responsible for cough. In general, it is accepted that RARs cause cough, but it is disputed whether C fiber receptors also cause cough. However, there is good evidence that they do not. What seems certain is that the strength and pattern of cough depend on several factors: the distribution of airway sites activated by a tussive stimulus; the local action of mediators and neuropeptides released by irritation and inflammation; and the relative balance of action of RARs and C fiber receptors at the site of origin of cough. Tachykinins are involved in cough, but their role requires further analysis.

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DISCUSSION

P. J. Barnes. I disagree with John Widdicombe's theory, and there is evidence for the opposite view. Fox's data, for example, which precisely define the type of fiber in the airway by neurophysiologic techniques, show that capsaicin has highly specific effects for C fibers and has no effect on A δ fibers (Fox AJ et al. *J Physiol* 1993;46:21-35).

R. Pauwels. In what species?

P. J. Barnes. The guinea pig, which is a species that coughs in response to capsaicin. Furthermore, SP does not stimulate A δ fibers or C fibers, even at high concentrations. Thus, in guinea pigs at least, capsaicin activates C fibers and causes cough and does not appear to act through tachykinin mechanisms.

J. G. Widdicombe. I disagree. If I take your last point first, the work from Japan that I quoted showed that SP does stimulate cough (Kohrogi H et al. *J Clin Invest* 1988;82:2063-8; Sekizawa K et al. *Am J Respir Crit Care Med* 1995;151:815-21; Ujiie Y et al. *Am Rev Respir Dis* 1993;148:1628-32). How do you explain the publications showing that SP aerosol in guinea pigs causes cough?

P. J. Barnes. Other studies show that SP does not

cause cough in guinea pigs, and nebulized SP does not cause coughing in humans.

J. G. Widdicombe. I know the elegant work by Fox very well, but it is an *in vitro* model of the trachea. We have shown that if capsaicin aerosols are given to guinea pigs RARs are stimulated, as in other species in which the response to capsaicin aerosol has been studied. I think that results *in vivo*, including in the guinea pig, are more representative of what is going to happen in the airways in humans than is the *in vitro* model of the guinea pig trachea. In the Fox work, for example, histamine does not stimulate C fiber receptors, but we know in other animals that it does.

R. Pauwels. Several groups have shown that tachykinins cause cough in guinea pigs.

P. J. Barnes. But other groups have shown that it does not, and we have to find out why there are differences among studies.

K. F. Chung. I tend to agree with Peter Barnes; we also have not been able to show that guinea pigs cough in response to SP, although Kohrogi H et al. (*J Clin Invest* 1988;82:2063-8) have shown that their guinea pigs do cough at very low concentrations of SP.

J. G. Widdicombe. Their study was unusual in that minute concentrations of SP produced coughing, whereas the investigators in Japan (Kohrogi H et al., Sekizawa K et al., Ujiie Y et al.) observed greater responses with far higher concentrations. One can explain away negative results in terms of methods, but positive results cannot be dismissed without giving an adequate explanation.

K. F. Chung. The problem with this area is that there is a lot of "guilt by association" rather than by direct evidence, and there is a lot of species variation. For example, bradykinin specifically activates C fibers in the guinea pig, in Fox's work, whereas in the rabbit it has a large effect on the irritant receptors.

J. G. Widdicombe. I think in all species where it has been looked at, *in vivo*—bradykinin aerosols have stimulated RARs.

K. F. Chung. But we have no idea which receptors are predominantly activated by these substances in the human; our knowledge is assumed from work in other species.

J. G. Widdicombe. I was careful not to make any assumptions about humans.

S. T. Holgate. Is cough homogeneous in the human, or could asthmatic cough be something different?

J. G. Widdicombe. People do have a "cough print," and a person can be identified by the sound of the cough. But certainly in animals, if you stimulate cough in different ways with different aerosols—for example, in different parts of the respiratory tract—different patterns of cough are produced. I suspect the same is true

for humans, although I do not know of any work in humans in which cough has been stimulated from different parts of the respiratory tract. In somebody with a bronchoconstriction, the air in the constricted airways would probably change the pattern of sound, and of course the presence of mucus changes the cough sound dramatically.

T. W. Higenbottam. I am rather suspicious about distinguishing different types of cough, and Widdicombe's explanation of the different sounds in asthma would be a good one, in that, for instance, peripheral airflow obstruction would modify the sound that is generated. I suspect that the perturbation of the breathing pattern that is excited by these afferent nerves, whether C fibers or RARs, is fairly constant.

A. A. Norris. I never felt particularly comfortable about the idea that nedocromil sodium was inhibiting cough by activating C fibers. The work by Jackson DM et al. (*Pulm Pharmacol* 1989;2:179-84) showed C fiber activation during a period of about 30 seconds. We know from other experiments that after an initial activation of the nerve, there seems to be an inhibition or refractory period. If that is superimposed on the *in vivo* studies that you showed, which were performed over a much longer time, up to 80 minutes, what you might be seeing is an initial activation and then a longer-lasting block of the action potential, which might explain a longer-term effect in the *in vivo* cough model.

J. G. Widdicombe. What you say is entirely consistent with what we know about the way in which C fiber reflexes work. They can be activated for a short time, perhaps a minute, but some of the central nervous reflex changes continue for half an hour or more, as shown by Paintal and Kalia (*Physiol Rev* 1973;53:159-227) in their observations of spinal reflexes. These long-lasting effects are triggered by a short burst of impulses, so even if the fiber is then inhibited, the effect continues for a long time. This does not apply to all of the reflex effects (for example, blood pressure and heart rate changes), but it does apply to the spinal reflex effects and may apply to the cough reflex.

P. J. Barnes. Another mechanism may be that nedocromil sodium is stimulating other types of afferent nerve. A characteristic symptom that people have described with the drug is a feeling of flushing, which suggests that it may activate thermoreceptors. Jackson (Loughborough) found some neurophysiologic evidence for that possibility. It may be that activation of other afferent nerves then inhibits C fibers, and not that C fibers inhibit other nerves.

J. G. Widdicombe. Cold receptors are in the larynx, not further down, so there cannot be a local interaction with C fibers at the lower level. There may be inhibition centrally.