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CORRESPONDENCE

Neurophysiology of the cough reflex

To the Editor:

We read with much interest the recent review "Neurophysiology of the cough reflex" by WIDDICOMBE [1], which appeared in the July issue of the Journal. The review gave a detailed account of afferent nerves in the airways, with particular reference to those that may directly or indirectly be involved in the cough reflex. Based primarily on data with select irritants which trigger electrical activity in sensory nerves and cough in cats and dogs, the author concludes that thin, myelinated, rapidly adapting stretch receptors (RARs), "irritant receptors", uniquely mediate the cough reflex and that lung C-fibres suppress coughing.

In our opinion, published experimental data in guinea-pig and man indicate instead that both RARs and bronchial C-fibres are important in mediating the cough reflex. The following observations support a direct role for bronchial C-fibres in cough.

Firstly, capsaicin is a relatively selective stimulus of C-fibres compared with RARs and slowly adapting stretch receptors (SARs). Low doses of capsaicin trigger cough when inhaled by conscious guinea-pigs and human subjects. Electrophysiological recordings of afferent neural activity from a guinea-pig tracheobronchial preparation demonstrate that capsaicin stimulates C-fibres but not A-δ fibres (RARs) [2]. Capsaicin is also a more potent stimulant of C-fibres than RARs in the cat [3] and dog [4]. Importantly, capsaicin causes a burst of activity in C-fibres, which are normally silent, whereas it merely potentiates a pre-existing spontaneous discharge in myelinated fibres [3, 4].

Secondly, capsaicin-pretreatment of guinea-pigs (causing degeneration of a population of chemosensitive C-fibre afferents) inhibits coughing due to capsaicin and citric acid, but not that due to cigarette smoke, histamine and mechanical stimulation, indicating that different types of afferent nerves can directly mediate this reflex [5]. Interestingly, nicotine and histamine have been shown to stimulate RARs in guinea-pigs [6].

Thirdly, chronic exposure of guinea-pigs to cigarette smoke selectively enhances the sensitivity of capsaicin-sensitive C-fibres mediating cough, and increases the neuropeptide content of airway nerves, whilst leaving the bronchoconstrictor response unaffected [7]. At the same time, the cough response to cigarette smoke is unchanged, suggesting a selective upregulation of capsaicin-sensitive C-fibres.

Fourthly, although capsaicin releases tachykinins and calcitonin gene-related peptide (CGRP) from C-fibres *via* an axon-reflex, it is unlikely that they activate airway RARs and, thereby, indirectly trigger the cough reflex. Inhaled tachykinin peptides do not cause cough in healthy subjects [8], and when thiorphan (an inhibitor of neutral-endopeptidase metabolism of tachykinins) is inhaled by human subjects, reportedly only the bronchoconstrictor response to neurokinin A is enhanced [9]. Similarly, in guinea-pigs, we found that, thiorphan enhanced the citric acid-induced bronchospasm but not the cough response [10]. One study has reported that thiorphan potentiates the cough response to substance P (SP) but the significance of this finding is difficult to assess since very low concentrations of SP (10^{-19} to 10^{-16} M) were studied, coughing was measured up to 13 min after a 2 min aerosol exposure, and the ethanol vehicle also produced coughing [11]. It was recently shown that a neurokinin-1 (NK_1)-receptor antagonist does not inhibit hypertonic saline-induced cough in asthmatic subjects [12].

Finally, guinea-pig and human [13] bronchi are more sensitive to the tussive effect of inhaled C-fibre stimulants than the larynx and central airways, which is consistent with the distribution of unmyelinated bronchial C-fibres predominantly to intrapulmonary airways. The pulmonary chemoreflex, characterized by apnoea, bradycardia and hypotension, is mediated *via* pulmonary C-fibres. As described in the review, stimulation of these fibres inhibits cough, which is only to be expected when the respiratory rhythm generator in the central nervous system (CNS) is suppressed during the apnoea. Furthermore, the cough reflex would of course not be effective as a defense mechanism if evoked from the respiratory bronchioles and alveoli, which seems to be the site of these particular sensory nerve endings.

Cough is an important clinical problem, not only in subjects with chronic cough but also in asthma, since it can be an early, and sometimes the only, sign of disease. We agree with WIDDICOMBE [1] that RARs mediate the cough reflex and that pulmonary C-fibres may be inhibitory, but in our opinion a wealth of experimental data support a direct role for bronchial C-fibres in cough. Sensory hyperresponsiveness in capsaicin-sensitive bronchial C-fibre afferents is a characteristic feature of chronic cough (see [14]) and, inferentially, identification of neural pathways in airway reflexes may lead to a better understanding of the pathophysiology of airway diseases, including asthma, as well as to the development of more efficacious therapeutic agents.

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REPLY

From the authors:

I am glad that my review on cough aroused controversy, as intended, and the comments by Fuller *et al*. are important and stimulating. We agree that rapidly adapting stretch receptors (RARs) can cause cough, and that pulmonary C-fibre receptors can inhibit it. However, they believe that bronchial C-fibre receptors can induce cough. There is much contrary evidence.

When stimuli, such as capsaicin or bradykinin, selective to bronchial C-fibre receptors, are restricted to the bronchial circulation they cause apnoea and rapid shallow breathing; cough has never been described [1]. When the same agents, or water or citric acid, which are non-selective are applied generally to the tracheobronchial tree as a liquid or an aerosol, they stimulate RARs as well as bronchial C-fibres [2]. The reflex response is cough or apnoea in dog [3, 4], rat [4], and man [5]. We agree that the RARs mediate the cough, and it seems logical that the bronchial C-fibre receptors cause the apnoea. Otherwise, one would have to postulate a third type of bronchial receptor and such has not been described or claimed. Slowly adapting receptors (SARs) in the smooth muscle of the airways can be excluded, since they are not sensitive to the agents used.

The cough induced by citric acid aerosol or sulphur dioxide, presumed to act on C-fibre receptors, is prevented in dogs [3] and cats [6] by cooling the vagus nerves to 5–8°C, which blocks conduction in δ-fibres but leaves that in C-fibres intact. Thus, in these species, citric acid and sulphur dioxide cause cough *via* RAR's.

Fuller *et al*. imply that because capsaicin is a more potent stimulus of C-fibres than of RARs, the former must mediate cough. However, one should not equate nerve impulse frequency with size of response. A biscuit crumb in the larynx stimulates a few RARs with a few dozen nerve impulses and causes vigorous coughing, whereas a large lung inflation stimulates thousands of SARs each relaying hundreds of impulses but with a far weaker effect on breathing. The most talkative politicians are not usually the most influential, thank goodness.

Fox *et al*. [7] showed that capsaicin stimulates C-fibres but not δ-fibres in the guinea-pig trachea *in vitro*; this work is important, but tells us little about cough. The results are largely restricted to the trachea, which we know to have mechanosensitive RARs with little chemosensitivity [8]; whereas, as agreed, capsaicin is most effective in the intrapulmonary bronchi. Capsaicin, serotonin (5HT), histamine and bradykinin have no effect on tracheal RARs in the guinea-pig [7], but the agents are all stimulants to bronchial RARs in various other species [2]. The results of Fox *et al*. [7] are consistent with the view that tracheal RARs are predominantly mechanosensitive; since RARs deeper in the airways are more chemosensitive, selected populations of RARs have been studied.

Fuller *et al*. emphasize that capsaicin activates silent C-fibres but merely potentiates pre-existing spontaneous discharge in δ-fibre receptors. This is correct, but the implication that cough must be caused by activation of a silent group of receptors and is not due to increased activity in a group that is tonically-active is not valid. The crucial condition is when afferent activity, previously

either silent or tonically-active, reaches a central nervous threshold and triggers a response. There are abundant examples of tonically-active receptors which do not exert a central reflex effect until their discharge reaches a central threshold value, for example Golgi tendon organs and lung SARs.

An important experiment by FORSBERG *et al*. [9] demonstrated that large doses of capsaicin inhibit cough due to capsaicin and citric acid, but not to cigarette smoke, histamine and mechanical stimuli. This result shows that different types of afferent nerves are involved in coughing. However, it does not follow that C-fibre afferents are responsible for cough due to capsaicin and citric acid. Capsaicin pretreatment can act both on C-fibre and δ-fibre afferents [10]. There are several different types of RARs in the airways, from the larynx through the trachea to the bronchi, causing different patterns of cough and changes in breathing, and the interaction of these groups of receptors (plus C-fibre receptors) will determine the final pattern of cough; their relative destruction by capsaicin will block some types of cough but not others, without giving any indication of whether the reflexes are mediated by C-fibres or δ-fibres. Incidentally RARs almost certainly have nonmyelinated terminals on which capsaicin can presumably act [11].

The involvement of tachykinins in cough is rather speculative, as I made clear. However, although Fuller *et al*. describe some negative or debatable results, they do not mention the many positive ones: that inhaled tachykinins can cause cough in guinea-pigs [12–14] and man [15–16]; that cough can be enhanced in guinea-pigs by phosphoramidon [14] and inhibited by tachykinin antagonists [16–18]; and that tachykinins can stimulate RARs in rats [19] and rabbits [20].

In summary, I know of no evidence that bronchial C-fibre receptors cause cough, and quite a lot of evidence that they do not. It is an important question and may need further testing.

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