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LUNG C-FIBRE RECEPTOR ACTIVATION AND DEFENSIVE REFLEXES IN ANAESTHETIZED CATS

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SUMMARY

1. With pentobarbitone-anaesthetized cats we have elicited cough reflexes from the tracheobronchial tree and the larynx, and the aspiration and sneeze reflexes from the nasopharynx and the nose respectively. The reflexes were induced by mechanical stimulation of the mucosa, before and during activation of pulmonary C-fibre receptors by intravenous injections of capsaicin or phenylbiguanide.

2. During the 20–30 s apnoea due to C-fibre stimulation, the cough reflex from both sites and the sneeze reflex were completely abolished, whereas the aspiration reflex response was approximately halved. Reflex contractions of genioglossus muscle still occurred at this time, but were far weaker than in the control state.

3. During the rapid shallow breathing that immediately followed apnoea due to C-fibre receptor stimulation, the defensive reflexes recovered: the aspiration and sneeze reflexes fully and the cough reflexes to about half of the control response.

4. Acute hypotension due to haemorrhage, of a size considerably greater than that due to stimulation of the pulmonary C-fibre receptors, caused no significant inhibition of the cough reflex from the tracheobronchial tree.

5. We conclude that the pulmonary C-fibre reflex powerfully inhibits airway defensive reflexes, and that its activation is unlikely to contribute positively to coughing induced by aerosols of capsaicin and similar agents.

INTRODUCTION

Most laboratory studies of lung reflexes have been designed to isolate a particular afferent pathway, for example that from C-fibre receptors or from rapidly adapting irritant receptors. However, many physiological and pathological conditions activate both groups of receptors (Coleridge & Coleridge, 1986; Widdicombe, 1986; Sant'Ambrogio, 1982, 1987). We have therefore tried to see how reflexes from lung C-fibre receptors interact with those from rapidly adapting receptors.

A further reason for this study was to analyse the pathway for the cough reflex from the tracheobronchial tree. Many reviewers believe that cough is mediated by

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rapidly adapting (irritant) receptors in the airway walls (Sant'Ambrogio, 1982, 1987; Coleridge & Coleridge, 1986; Widdicombe, 1986), but recently a number of authors have suggested that cough can be induced by stimulation of C-fibre receptors in the lungs or larynx (Collier & Fuller, 1984; Midgren, Simonsson & Persson, 1986; Paintal, 1986; Forsberg & Karlsson, 1986, 1987; Karlsson, 1987; Fuller, Dixon, Cuss & Barnes, 1987). The evidence for this view will be considered in the Discussion. By stimulating C-fibre and rapidly adapting receptors selectively and simultaneously we hoped to resolve the difference of opinion. When preliminary results showed that pulmonary C-fibre stimulation had a powerful interaction with the cough reflex from the tracheobronchial tree, we extended the results to include the cough reflex from the larynx and the aspiration and sneeze reflexes from the nasopharynx and nose respectively.

METHODS

Eight cats of $3{\cdot}2 \pm 0{\cdot}21$ (mean $\pm$ S.E.M.) kg body weight were anaesthetized with 30 mg kg^{-1} sodium pentobarbitone (Sagatal, May & Baker). A cannula was inserted in the lower cervical trachea to allow breathing, and attached to a Fleisch pneumotachograph to record airflow. The recurrent laryngeal nerves were preserved. A femoral arterial catheter (4FG, Portex) was inserted for recording blood pressure (P23 ID, Gould), and a femoral venous catheter for injections of supplementary doses of anaesthetic and other drugs. The electromyogram of the genioglossus muscle (pharyngeal dilator) was recorded via two fine-wire hook electrodes, positioned with their tips about 5 mm apart.

Coughing was induced from the tracheobronchial tree by insertion of a 0·5 mm diameter Nylon fibre through the wall of the lower cervical trachea, until its tip was judged to be near the carina and main bronchi. Repeated caudal advancements of the fibre to touch the carina and nearby airway walls was carried out over periods of 5–7 s. To stimulate coughing from the larynx a similar procedure was carried out with the Nylon fibre inserted cranially into the cervical trachea until its tip could be pushed against the vocal folds. To stimulate the aspiration reflex from the nasopharynx the fibre was passed through one nostril until its tip was near the nasopharynx and then repeatedly pushed forward against the nasopharyngeal wall. (A few experiments where this intervention caused sneezing rather than the aspiration reflex were discarded.) To induce sneezing the fibre was inserted just into one nostril and then pushed forward 2–3 cm into the nose repeatedly. For each stimulus the Nylon fibre was first adjusted to ensure that the appropriate reflex could be induced repeatedly and consistently, and the periods of stimulation were always 5–7 s.

To stimulate lung C-fibre receptors either capsaicin (5–15 $\mu g\ kg^{-1}$) or phenylbiguanide (25–50 $\mu g\ kg^{-1}$) was injected intravenously.

The experimental protocol consisted firstly of ensuring that one particular defensive reflex could be produced and repeated at intervals similar to those to be used subsequently with C-fibre stimulation. After recording the defensive reflex response, either capsaicin or phenylbiguanide was injected intravenously in a dose which had been shown in the same experiment to cause apnoea for 20–30 s followed by rapid shallow breathing. As soon as the apnoea occurred, i.e. when the expiratory pause after injection of drug was longer than the immediately preceding control, the mechanical stimulus to the airway was repeated. As soon as the animal showed rapid shallow breathing the stimulus was repeated for a third time.

With two of the cats we tested the effect of acute hypotension on the cough reflex. The cats were heparinized (5000 U, I.V.) and a carotid arterial catheter was inserted. 45–65 ml of blood was withdrawn through the catheter into a syringe as quickly as possible, while monitoring blood pressure until it had fallen to less than half of the control value. After testing the cough reflex during hypotension, the blood was reinfused.

The qualitative presence or absence of the reflexes was always clear (see Figs 1–3). To quantitate coughs, sneezes and the aspiration reflex response we measured the number of strong respiratory efforts induced by each stimulus, giving flow rates at least four times greater than those of eupnoeic controls. Student's t test for paired values was used for comparisons of numbers of respiratory efforts in the different conditions.

RESULTS

Cough reflex from the lower airways

As shown in Fig. 1 and Table 1 mechanical stimulation of the lower airway caused repeated coughs which continued after the stimulus had stopped. During the apnoea induced either by phenylbiguanide or by capsaicin the same stimulus caused no coughs. This effect was not due to accommodation or refractoriness of the reflex,

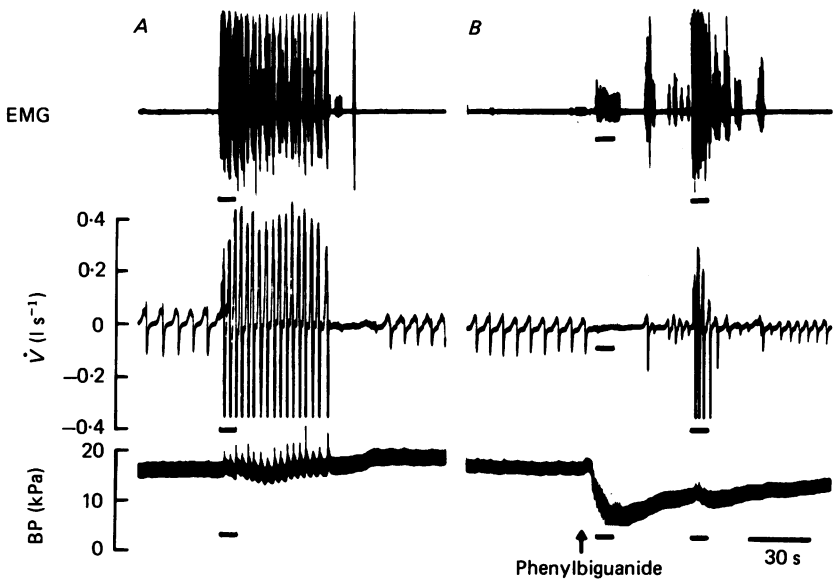

Fig. 1. Effect of pulmonary C-fibre reflex on coughing induced from the tracheobronchial tree. Traces from above down: EMG of genioglossus muscle, airflow ($\dot{V}$) from tracheal cannula, and systemic arterial blood pressure (BP). In *A*, the tracheobronchial mucosa was stimulated mechanically during the signal marks, causing increased EMG activity and airflow, corresponding to cough efforts. The cough efforts continued long after the stimulus had stopped. In *B*, phenylbiguanide (25 μg kg^{-1}) was injected intravenously at the arrow, causing hypotension, bradycardia and apnoea. During the apnoea at the signal marks the tracheobronchial stimulus was repeated, causing no change in airflow but some increase in EMG activity. Later, during the phase of rapid shallow breathing, the tracheobronchial stimulus was repeated and caused four cough efforts, with no coughing after the end of the stimulus.

since stimulations repeated with the same time intervals but without phenylbiguanide or capsaicin were effective. During the apnoea in six of the ten tests, the stimulus caused small expiratory efforts with peak airflows about 10–60% of those during tidal breathing without cough. During the apnoea the tracheobronchial stimulation also caused contractions of genioglossus (Fig. 1), but far smaller than those seen in coughing. During the rapid shallow breathing after the apnoea, stimulation of the lower airway again caused coughing but the numbers of cough efforts were 45% of those in controls (Table 1).

TABLE 1. Changes in defensive reflexes during C-fibre receptor stimulation

Reflex	Site	C-fibre stimulus	n	Strong respiratory efforts during: Control breathing	Apnoea	Rapid shallow breathing
Cough	TB tree	PBG	5	9·8 ± 2·85	0*	5·0 ± 0·95*
Cough	TB tree	Capsaicin	5	14·4 ± 1·54	0**	5·8 ± 1·24**
Cough	Larynx	Capsaicin	4	5·0 ± 2·04	0*	3·3 ± 1·60
Aspiration	Nasopharynx	PBG	5	21·8 ± 3·07	12·5 ± 2·90**	20·4 ± 3·63
Aspiration	Nasopharynx	Capsaicin	2	21, 18	0, 4	18, 20
Sneeze	Nose	PBG	3	2·7 ± 0·88	0*	3·5 ± 1·5

Values are total numbers of strong respiratory efforts caused by each stimulus. PBG, phenylbiguanide; TB tree, trachea and main bronchi. *$P < 0·05$, **$P < 0·01$ for response during apnoea or rapid shallow breathing compared to that during control breathing.

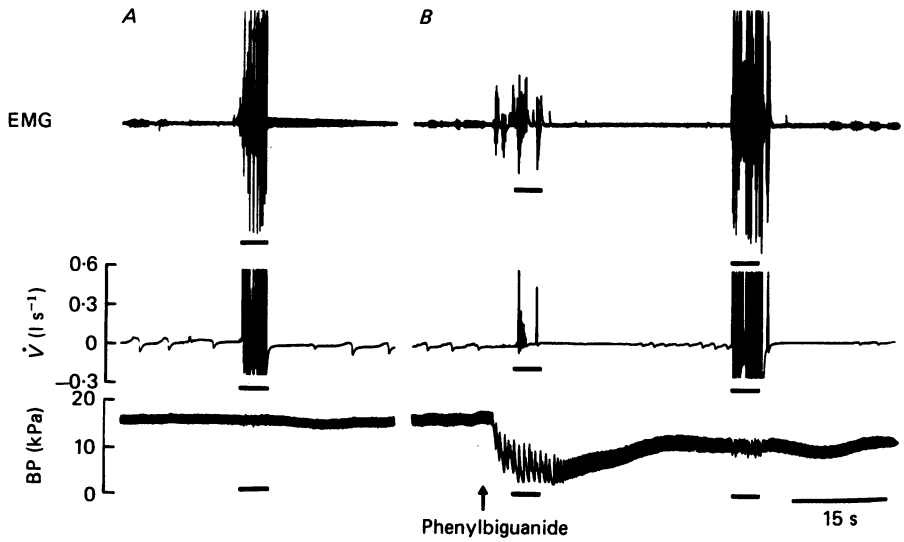

Fig. 2. The effect of pulmonary C-fibre stimulation on the aspiration reflex. Traces as in Fig. 1. In *A*, the nasopharynx was stimulated mechanically during the signal bars, and caused increased EMG activity and a rapid series of vigorous respiratory efforts. In *B*, phenylbiguanide (50 μg kg^{-1}) was injected at the arrow. During the subsequent apnoea the nasopharynx was stimulated again at the signal marks and caused a few inspiratory efforts and increased EMG activity. During the rapid shallow breathing phase the nasopharyngeal stimulus was repeated again at the signal marks, and caused respiratory efforts and increases in airflow similar in number to those of the control.

Cough reflex from the larynx

Coughing induced by mechanical stimulation of the larynx was absent during the apnoea due to C-fibre receptor stimulation with capsaicin (Table 1). In three of the four tests there were very weak expiratory efforts similar to those described with tracheobronchial stimulation. During the rapid shallow breathing after the apnoea, laryngeal stimulation caused coughing which was less intense than that seen in the controls (Table 1).

Aspiration reflex from the nasopharynx

In control conditions stimulation of the nasopharynx caused the rapid and vigorous inspiratory efforts that define the aspiration reflex (Tomori & Widdicombe, 1969; Korpas & Tomori, 1979). During the apnoea induced by either phenylbiguanide or capsaicin the same stimulus still caused the aspiration reflex, although the number of inspiratory efforts was far smaller (Fig. 2, Table 1). Genioglossus EMG also

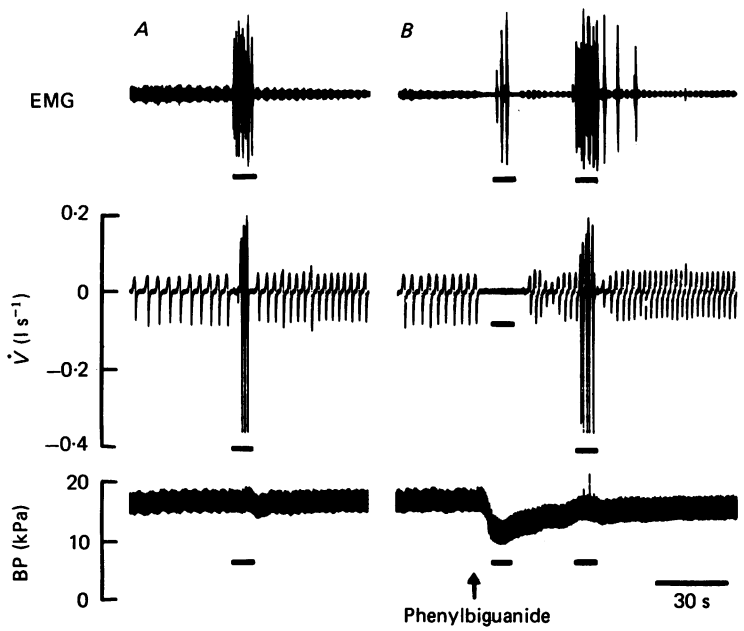

Fig. 3. The effect of pulmonary C-fibre stimulation on the sneeze reflex from the nose. Traces as in Figs 1 and 2. In *A*, the nasal mucosa was stimulated mechanically during the signal bars, and caused three sneezes and an increase in EMG activity. In *B*, phenylbiguanide (25 μg kg^{-1}) was injected at the arrow and, during the subsequent apnoea, repeated stimulation of the nose no longer caused sneezing but did cause some increase in EMG activity. During the rapid shallow breathing that followed, the stimulus was repeated again and now caused five sneezes and an increase in EMG activity as strong as or larger than during the control.

increased, but far less than without C-fibre stimulation (Fig. 2). During the rapid shallow breathing after the apnoea, the same stimulus caused responses very similar in size and number to those in the control period (Fig. 2, Table 1).

Sneeze reflex from the nose

In three experiments mechanical stimulation of the nose caused sneezing during and sometimes after the stimulus. During the apnoea induced by phenylbiguanide the same stimulus caused no sneezing and no detectable changes in airflow, although genioglossus EMG increased (Fig. 3, Table 1). During the rapid shallow breathing after the apnoea the responses were restored to their control strengths.

Hypotension and the cough reflex

To test whether the hypotension induced by capsaicin or phenylbiguanide might influence the cough reflex, in two tests in each of two cats we investigated the cough reflex from the tracheobronchial tree before, during and after acute hypotension due to haemorrhage. The number of control cough efforts was $9{\cdot}5 \pm 1{\cdot}35$ ($n = 6$) before and after hypotension. During hypotension there were $6{\cdot}5 \pm 1{\cdot}2$ ($n = 4$) coughs. The difference was not significant. Control mean blood pressure was $136 \pm 7{\cdot}4$ mmHg ($18{\cdot}1 \pm 0{\cdot}98$ kPa) and that during hypotension was $49 \pm 5{\cdot}9$ mmHg ($6{\cdot}5 \pm 0{\cdot}78$ kPa), a decrease of $64 \pm 9{\cdot}7$ %. By comparison, the mean blood pressures with capsaicin and phenylbiguanide were a control of $125 \pm 2{\cdot}1$ mmHg ($16{\cdot}6 \pm 0{\cdot}28$ kPa) and a hypotensive level of $74 \pm 9{\cdot}9$ mmHg ($9{\cdot}8 \pm 1{\cdot}32$ kPa), a decrease of $40 \pm 10{\cdot}0$ %.

DISCUSSION

During the apnoea caused by stimulation of pulmonary C fibres the cough reflex, induced from the tracheobronchial tree or the larynx, and the sneeze were completely inhibited. This effect was not due to spontaneous refractoriness, since the cough and sneeze could be repeatedly produced at time intervals similar to those used before and during C-fibre stimulation. Nor was the inhibition due to hypotension, since considerably larger hypotensions due to acute haemorrhage caused only a small insignificant decrease in the number of cough efforts; Tatar, Oblyvach & Korpas (1987) reported that only during irreversible shock due to severe chronic haemorrhage was the cough reflex abolished. Since defensive reflex stimuli were usually applied immediately at the start of apnoea due to capsaicin or phenylbiguanide, asphyxial blood gas changes are unlikely to be involved. Although capsaicin and phenylbiguanide in the intravenous doses used selectively stimulate pulmonary C-fibre receptors (Coleridge & Coleridge, 1986), we cannot rule out the possibility that the drugs may have also stimulated cardiac and/or bronchial C-fibre receptors, the afferent input from which might depress defensive reflexes. However the fact that the defensive reflexes could be inhibited immediately at the start of the apnoea (e.g. Fig. 1), together with the relative selectivity of intravenous injections of the drugs on pulmonary C-fibre receptors, suggest that the major inhibition of the defensive reflexes was from activation of the latter receptors. The small expiratory efforts sometimes seen with respiratory tract stimulation during the apnoeas were small in size, and in no way resembled cough. In spite of the absence of cough and sneeze reflexes, genioglossus EMG increased, although much less than in controls. This last result supports the evidence that there is quantitative independence between the reflex control of the muscles of breathing and of those that dilate the pharynx (van Lunteren & Strohl, 1986). The results add inhibition of cough and sneeze to the other inhibitory effects known to result from C-fibre stimulation: apnoea, hypotension, bradycardia and spinal reflex depression (Coleridge & Coleridge, 1986). They also add to the known interactions between lung and defensive reflexes, since several studies have shown that stimulation of slowly adapting pulmonary stretch receptors enhances the cough reflexes from the tracheobronchial tree and the larynx (Hanacek, Davies & Widdicombe, 1984; Sant'Ambrogio, Sant'Ambrogio & Davies, 1984); C-fibre receptor stimulation has the opposite effect.

Pathological conditions when pulmonary C-fibre receptors are stimulated, such as pulmonary oedema and microembolism (Coleridge & Coleridge, 1986; Sant'Ambrogio, 1987), should depress the cough reflex. This depression occurs in experimental studies in rabbits and cats (Polacek, Plank, Korpas, Tatar & Turcan, 1983; Polacek, Korpas, Tatar, Plank & Pullman, 1986) and it is a clinical impression that moderately severe pulmonary oedema and microembolism can occur without induction of coughing (Henderson & Haggard, 1943; West, 1978; Tisi, 1980).

During the rapid shallow breathing that occurred after apnoea due to C-fibre receptor stimulation, the cough reflexes returned but remained depressed. Quantitative comparison is difficult since the patterns of breathing compared with controls were so different, but in particular the cough efforts that occurred after the end of the mechanical stimulus were far fewer during the rapid shallow breathing. Certainly there was no enhancement of the cough reflex during this phase. We only assessed the strength of the cough and sneeze reflexes from the number of powerful expiratory efforts, partly because the pneumotachograph manometer was set to register quiet breathing and either saturated (Figs 1–3) or would become very alinear at the very fast flows during defensive reflexes.

The aspiration reflex elicited from the nasopharynx was also depressed during the apnoea due to C-fibre receptor stimulation, but was not completely suppressed. This observation is consistent with the evidence that the aspiration reflex is resistant to many other interventions that can depress the cough reflex, for example deep anaesthesia, severe hypoxia and hypercapnia, and hypothermia (Korpas & Tomori, 1979).

Our results do not support the view that pulmonary C-fibre receptor stimulation can cause coughing. The evidence for this view is threefold.

(1) Intravenous capsaicin can cause coughing in man (Winning, Hamilton, Shea & Guz, 1986). However, although minimal doses of capsaicin may selectively activate lung C-fibre receptors in experimental animals, slightly larger doses can stimulate rapidly adapting irritant receptors usually thought to be responsible for coughing (Armstrong & Luck, 1974; Kaufman, Coleridge, Coleridge & Baker, 1980; Coleridge, Coleridge & Roberts, 1983). There is no evidence on the lung receptors stimulated by I.V. capsaicin in man, and the most plausible hypothesis is that the drug stimulates the rapidly adapting irritant receptors to cause coughing.

(2) Administration of capsaicin aerosols to man and guinea-pig can cause coughing (Collier & Fuller, 1984; Forsberg, Karlsson & Persson, 1986; Forsberg & Karlsson, 1986, 1987; Midgren *et al.* 1986). There is no evidence that capsaicin aerosols are selective stimulants of lung C-fibre receptors. Even if this were established in experimental animals with threshold concentrations of capsaicin, it might have little relevance to the situation in man due to striking species differences in sensitivities of airway receptors to drugs (Dawes & Comroe, 1954; Coleridge & Coleridge, 1986).

(3) Destruction of lung C-fibre receptors by large doses of capsaicin in guinea-pigs blocks some forms of induced cough (Forsberg & Karlsson, 1986; Forsberg *et al.* 1986), and it is assumed that large doses of capsaicin selectively destroy C-fibre receptors. However, large doses of capsaicin can damage receptors with myelinated afferent fibres (e.g. Buck & Burks, 1986; Such & Jancso, 1986), so the results could be due to damage to rapidly adapting irritant receptors which have myelinated vagal

fibres with non-myelinated terminals in the airway epithelium (Das, Jeffery & Widdicombe, 1978; Sant'Ambrogio, 1987). This possibility is supported by the observation that large doses of capsaicin destroy these epithelial non-myelinated nerve terminals (Hoyes, Barber & Jagessar, 1981).

In experimental animals intravascular capsaicin and phenylbiguanide have never been shown to cause coughing (Coleridge & Coleridge, 1986; Widdicombe, 1986). Since three of the studies were with unanaesthetized animals (Ginzel & Eldred, 1969; Kalia, Koepschen & Paintal, 1973; Clifford, Litzow & Coon, 1987), the anaesthetic does not selectively block the cough reflex.

Lung C-fibre receptors are usually subdivided into 'pulmonary' and 'bronchial' types, and intravenous injections of capsaicin and phenylbiguanide stimulate the former more strongly (Sant'Ambrogio, 1982, 1987; Coleridge & Coleridge, 1986). It is possible that bronchial C-fibre receptors could cause coughing whereas the pulmonary ones may not. However, selective stimulation of bronchial C-fibre receptors with low intravascular doses of bradykinin does not cause coughing; increased doses stimulate rapidly adapting irritant receptors (Kaufman *et al.* 1980; Roberts, Kaufman, Baker, Brown, Coleridge & Coleridge, 1981; Coleridge & Coleridge, 1986). The fact that bradykinin aerosols in man can cause coughing (Simonsson, Skoogh, Berg, Andersson & Svedmyr, 1973; Fuller *et al.* 1987) could therefore be due to stimulation of rapidly adapting receptors.

With regard to inhalation of capsaicin aerosols, these could cause coughing primarily by an action on the larynx (Collier & Fuller, 1984). The receptors in the larynx that cause coughing are usually thought to have myelinated afferent fibres and to be rapidly adapting (Boushey, Richardson, Widdicombe & Wise, 1974; Widdicombe, Sant'Ambrogio & Mathew, 1988), but there is no evidence which receptor groups are stimulated by capsaicin.

We conclude that in experimental animals lung C-fibre activation does not cause coughing but rather inhibits coughing and sneezing. Cough due to capsaicin administration in man by aerosol or I.V. injection can be explained by activation of rapidly adapting irritant receptors in the larynx or lower airways. The distinction could be clinically important since appropriate antitussive therapy may depend on the afferent nervous receptors and pathways involved.

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