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PULMONARY AND RESPIRATORY TRACT RECEPTORS

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SUMMARY

Nervous receptors in the lungs and respiratory tract can be grouped into four general categories.

1. Deep, slowly adapting end-organs, which respond to stretch of the airway wall and have large-diameter myelinated fibres; those in the lungs are responsible for the Breuer–Hering reflex.

2. Endings in and under the epithelium which respond to a variety of chemical and mechanical stimuli (i.e. are polymodal), usually with a rapidly adapting discharge, and with small-diameter myelinated fibres; they are responsible for defensive reflexes such as cough and sneeze, and for the reflex actions to inhaled irritants and to some respiratory disease processes.

3. Receptors with nonmyelinated nerve fibres which, being polymodal, are stimulated by tissue damage and oedema and by the mediators released in these conditions; these receptors may be similar in function to 'nociceptors' in other viscera, and set up appropriate reflexes as a reaction to respiratory damage.

4. Specialized receptors such as those for taste and swallowing, and those around joints and in skeletal muscle.

Stimulation of any group of receptors may cause reflex changes in breathing (including defensive reflexes), bronchomotor tone, airway mucus secretion, the cardiovascular system (including the vascular bed of the airways), laryngeal calibre, spinal reflexes and sensation. The total pattern of motor responses is unique for each group of receptors, although it is probably unusual for one type of receptor to be stimulated in isolation. The variety of patterns of motor responses must reflect the complexity of brainstem organization of these systems.

INTRODUCTION

Pulmonary and respiratory tract receptors and the reflexes they produce have been extensively studied for well over 100 years. Their main interest is related to the defensive reflexes such as sneeze and cough, to the physiological role of the receptors in modifying the respiratory and cardiovascular systems, and to their potential importance in respiratory diseases. We know more detail about the mechanisms of receptors in the larynx, lower respiratory tract and lungs than for the upper respiratory tract; this is probably because in experimental animals the surgical approach to the nerves of the lungs – the vagus and sympathetic nerves – is easier than is that to the upper respiratory tract. In addition the importance of lung reflexes in relation to breathing has been of especial interest to physiologists from even before the classical description

Table 1. *Motor responses to airway receptors*

Stimulus or receptor	Motor responses				
	Respiration	Larynx	Bronchi	Mucus	c.v.s.
Nose	Apnoea or sneeze	Constriction	Constriction or dilatation	Secretion	BP ↑ HR ↓
Epipharynx	'Aspiration'	Constriction?	Dilatation	Secretion	BP ↑
Larynx	Cough, apnoea or expiration	Constriction	Constriction	Secretion	BP ↑ HR ↓
Tracheobronchial stretch	Apnoea	Dilation	Dilatation	? nil	HR ↑
Airway irritant	Cough or hyperpnoea	Constriction	Constriction	Secretion	BP ↑
C-Fibre	Apnoea or rapid rapid shallow	Constriction	Constriction	Secretion	BP ↓ HR ↓

of the Breuer–Hering reflex in 1868 (Breuer, 1868). Stimulation of different receptor groups in the respiratory tract and lungs causes a variety of reflexes including respiratory ones (Table 1).

RECEPTORS IN THE NOSE

Reflexes from the nose have been frequently studied, but little is known about the structure of the nervous receptors responsible. Nerve fibres, presumably afferent or sensory, have been identified in the nasal mucosa (Cauna, Hinderer & Wentges, 1969; Graziadei, 1971) but their involvement in reflexes is a matter of conjecture. On the other hand the importance of nasal reflexes is undoubted; most seem to be mediated via the trigeminal nerves (Kratschmer, 1870) but the olfactory and Vidian nerves may also carry some sensory fibres. The recent studies on substance P-containing nerves in the nasal epithelium, presumably afferent, is of considerable interest (Anggard, 1979).

Nasal reflexes include sneezing; this is easily blocked by anaesthesia and has not often been studied in experimental animals, although the work by Price & Batsel (1970) on central pathways for the sneeze reflex is noteworthy. Mechanical or chemical irritation of the nasal mucosa can also produce apnoea, and this may be a component of the 'diving reflex' (Angell James & Daly, 1972). Other nasal reflexes include laryngeal constriction, either bronchodilatation or bronchoconstriction, hypertension and marked changes in heart rate (Widdicombe, 1977). Irritation of the nose can also give rise to strong sensations of itching or even pain, and the nose is a powerful site for the arousal response. Histological and physiological studies of the nervous receptors responsible and their afferent pathways are urgently needed.

RECEPTORS IN THE NASOPHARYNX AND PHARYNX

A powerful sniff-like or 'aspiration' reflex can be elicited by mechanical stimulation of the nasopharynx of most mammalian species (Korpas & Tomori, 1979; Tomori & Widdicombe, 1969). Nerve fibres, which may mediate this reflex, have been identified

in the squamous-cell epithelium of this region (Fillenz & Widdicombe, 1971), and studies of their action potential traffic in the glossopharyngeal nerve have been made (Nail, Sterling & Widdicombe, 1969). As well as causing powerful but brief inspiratory efforts, other reflex actions include bronchodilatation, hypertension, an increase in vasomotor tone and mucus secretion from the lower airways (Richardson & Phipps, 1978; Widdicombe, 1977). Other nervous receptors, such as those which may mediate pain, have not been analysed for the nasopharynx.

The pharynx has been even less studied than the nasopharynx, at least with regard to receptors and reflexes. Sumi (1964) has recorded nerve impulses from pharyngeal mechanoreceptors, and presumably these mediate the swallowing and accompanying laryngeal closure and inspiratory inhibition observed when this area is stimulated mechanically.

RECEPTORS IN THE LARYNX

The laryngeal mucosa contains many afferent end-organs and several reflexes from this site have been described.

Receptor structure

In and under the laryngeal mucosa are several types of receptor. There are many free nerve endings, but in addition taste buds can be seen, especially in the epiglottis, and also encapsulated receptors and hederiform endings (Plaschko, 1897; van Michel, 1963; Koizumi, 1953; Feindel, 1956). The vocal folds contain no fibres actually in the epithelium (Jeffery, Korpas & Widdicombe 1978) in spite of its great mechanical sensitivity. The caudal laryngeal mucosa has been emphasized as an important site of receptors (Wyke & Kirchner, 1976).

Deep to the mucosa, many receptors have been identified in and around the laryngeal joints and intrinsic muscles (Wyke & Kirchner, 1976). Muscle spindles seem to be rare, however. Encapsulated endings are present around joints, and free nerve endings are seen both in muscles and joints (Gracheva, 1963).

Receptor properties

There have been many studies of action potentials in afferent fibres from the larynx, usually in the superior laryngeal nerve, but also occasionally in the recurrent laryngeal nerve. In general five groups of receptor have been identified (e.g. Storey, 1968; Suzuki & Kirchner, 1960; Boushey *et al.* 1974).

(1) Rapidly adapting endings with little spontaneous discharge, sometimes called Type 1 laryngeal receptors. When activated, the receptors have an irregular discharge which can be provoked both by mechanical stimulation and by irritants such as ammonia, sulphur dioxide and cigarette smoke (Fig. 1). Their properties are similar to those of 'irritant' and cough receptors studied for the lower respiratory tract (see below).

(2) Slowly adapting, regularly firing superficial endings which are mechanosensitive but give little response to chemical irritants (Type 2 receptors).

(3) Receptors with non-myelinated fibres which may be nociceptive in function and could give rise to painful sensations.

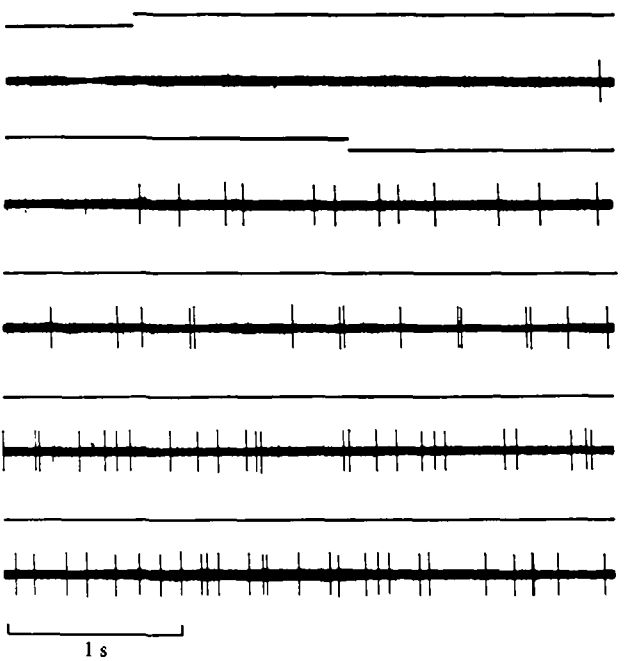

Fig. 1. Response of a laryngeal epithelial receptor (Type 1) to insufflation of cigarette smoke into the larynx of a cat. Single-fibre recording from the superior laryngeal nerve. Upper trace signal, smoke administered during upward deflection. Note irregular discharge of action potentials after a latency, and after discharge. (From Boushey *et al.* 1974).

(4) Deep receptors in muscles and joints, referred to above and probably concerned with control of laryngeal muscles in such activities as vocalization.

(5) Receptors which respond to changes in osmolality and chemical environment, in such a way as to suggest they may mediate swallowing.

Reflexes from laryngeal receptors

Many reflexes have been elicited from the larynx, including cough, the 'expiration reflex' and apnoea, bronchoconstriction and mucus secretion in the lower respiratory tract (Richardson & Phipps, 1978) and various cardiovascular changes such as hypertension and bradycardia (Tomori & Widdicombe, 1969). In spite of these extensive studies, it has not proved possible convincingly to correlate individual reflexes with either receptor histology or patterns of afferent discharge in nerve fibres. Much further work needs to be done.

RECEPTORS IN THE TRACHEOBRONCHIAL TREE

Receptors in the lower airways and alveoli have two main functions; to regulate the pattern of breathing and other motor systems (such as bronchomuscular tone) in healthy conditions and in response to physiological changes; and to evoke appropriate changes in breathing and related functions as a protective mechanism, reacting to

harmful invasion of the lungs and during diseases of the airways and lungs. These reflexes are primarily vagal, as shown by their abolition by bilateral vagotomy in experimental animals, but in some species there may be a small sympathetic afferent component. It is convenient to divide receptors of the tracheobronchial tree and lung into those primarily involved in physiological control of pattern of breathing (slowly adapting pulmonary stretch receptors) and those primarily concerned with changes in pathological conditions (rapidly adapting-irritant and C-fibre receptors), but this distinction is not absolute (Sant'Ambrogio, 1982). As with other tissues, receptors chiefly involved in abnormal conditions may play a part in physiological control, and those with normal regulatory function may contribute to pathological mechanisms.

One of the major barriers to our understanding of respiratory afferent systems is that the histology of the receptors has been incompletely analysed. Although there are many papers on the structure of lung receptors, those with light microscopy are not definitive and those with electron microscopy usually illustrate only part of a receptor complex. By far the greatest efforts to study receptor physiology have been by recording single-fibre activity in nerves from the receptors, without identification of the receptors themselves.

Slowly adapting pulmonary stretch receptors

The initial studies by Einthoven (1908) and Adrian (1933) showed that the main pulmonary afferent component from the lungs consisted of fibres from receptors that responded to lung inflation with a low-threshold and slowly adapting discharge, and had all the characteristics appropriate to the Breuer–Hering inflation reflex. Subsequent studies, especially by Sant'Ambrogio and his colleagues (see below), showed that the receptors were localized in the smooth muscle of the airways and were concentrated in the trachea and larger airways of dogs, cats and rabbits.

Structure and localization

Light microscopy shows that there are nerve endings with myelinated afferent fibres in the airway smooth muscle, and these endings can be shown by degeneration experiments (Honjin, 1956; Pack, Al-Ugaily & Widdicombe, 1982) to be afferent rather than motor. A three-dimensional reconstruction of such an airway receptor is shown in Fig. 2 (von During, Andres & Iravani, 1974), although it must be stressed that there is no direct evidence that this is pulmonary stretch receptor. The receptor complex is as large as 100 μm in diameter, and its terminal branches are surrounded by many collagen fibres which may link them to smooth muscle fibres.

The localization of stretch receptors in smooth muscle is supported by physiological experiments (Bartlett *et al.* 1976*a*; Miserocchi & Sant'Ambrogio, 1974*a*). Endings in the posterior or musculo-membranous wall of the trachea retain their activity and response to stretch when the overlying mucosa is removed (Mortola & Sant'Ambrogio, 1979). Their properties are consistent with their being connected in series with airway smooth muscle, the contraction of which would be expected to sensitize or stimulate them.

Recordings of action potentials from single myelinated vagal fibres attached to

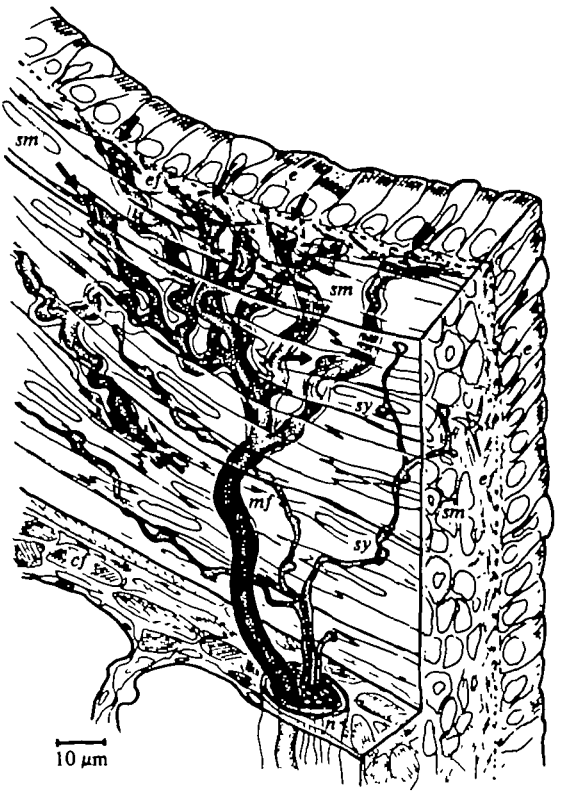

Fig. 2. Schematic representation of a segment of a rat bronchus wall with the nerve endings (arrows) of the supposed pulmonary stretch receptor. The lanceolate terminals are anchored within the reticular connective tissue below the respiratory epithelium (*e*). The smooth muscle cell layer (*sm*) is interrupted in the receptor field of the pulmonary stretch receptor. Efferent nerve terminals (*sy*) derive from non-myelinated nerve fibres. Afferent myelinated nerve fibres (*mf*) of the receptor, elastic network (*ef*), a small nerve (*n*), collagen fibre (*cf*). (From Von During *et al.* 1974.)

slowly adapting stretch receptors show that, for the dog, 17% are in the extrathoracic trachea (Miserocchi, Mortola & Sant'Ambrogio, 1973). For the extrapulmonary airways, the proportions are 56% for dog, 39% for cat and 87% for rabbits (Miserocchi & Sant'Ambrogio, 1974*b*; Sant'Ambrogio & Miserocchi, 1973; Roumy & Leitner, 1980). A further concentration seems to be at the hilum of the lung. Within the lung the localization is less precise, since physiological experiments with single-fibre recording do not allow exact localization, and histological studies do not allow identification of the function of any nervous structure visualized. However, since there are only about 1000 pulmonary stretch fibres in each vagus nerve of the cat, if the receptors are in the walls of small airways only a few of the latter can be represented, unless the fibres branch considerably and have many terminals.

Receptor properties

Although slowly adapting, most pulmonary stretch receptors have an appreciable dynamic component, i.e. respond to rate of change of stretch as well as to stretch itself. This property has been studied especially for the endings in tracheal muscle (Bartlett, Sant'Ambrogio & Wise, 1976*b*). The volume threshold of the receptors varies widely, some being tonically active at FRC (Functional Residual Capacity), others starting to discharge only at lung volumes greater than eupnoeic tidal volume; those in the lungs seem to have a higher threshold than those outside (Sant'Ambrogio, 1982). It follows that deflation of the lungs and airways will decrease stretch receptor reflex activity, and inflation will increase it by recruitment and by increasing the discharge of individual receptors; the total range of stretch receptor sensitivity therefore probably covers that of total lung volume changes from residual volume to vital capacity.

The primary stimulus to the stretch receptors is mechanical, and it had long been assumed that they are insensitive to physiological chemical changes. However a number of recent studies have shown that the pulmonary stretch receptor can be inhibited by increases in CO_2 tension in the airways (Bartlett & Sant'Ambrogio, 1976; Bradley, Noble & Trenchard, 1976; Coleridge, Coleridge & Banzett, 1978*a*), as had earlier been established for similar receptors in birds (Burger, Osborne & Banzett, 1974). The main range of sensitivity is at P_{CO_2}'s below 30 mmHg, and it might be more correct to say that severe hypocapnia stimulates the endings, rather than that hypercapnia inhibits them. It should also be remembered that the chemical environment of the receptors is influenced both by the composition of blood in the bronchial and pulmonary circulations, and by that in the airway lumen; the latter fluctuates between alveolar and atmospheric values. Finally it should be stressed that the physiological or pathological importance of the action of CO_2 on lung stretch receptors has not been established in spite of many attempts. Possibly the right experiments have yet to be performed.

Pulmonary stretch receptors are affected by a number of foreign chemicals, such as the veratrum alkaloids which are effective in intravenous doses too low to stimulate most other end-organs (Dawes & Comroe, 1954). This group of chemicals has been used as a 'specific' stimulus for slowly-adapting lung stretch receptors. Other chemicals change the activity of the endings, probably modifying smooth muscle tone around the receptor; histamine and acetylcholine are in this group (Koller & Kohl, 1975). The receptors are inhibited by volatile anaesthetics such as halothane and trichlorethylene (after initial sensitization) (Coleridge *et al.* 1968) and, in the rabbit, are completely inhibited to mechanical stimulation by 150–200 p.p.m. sulphur dioxide (Davies *et al.* 1978). This selective action of SO_2 has been used to test the reflex action of rapidly adapting lung receptors (see below).

Reflex actions on breathing

Breuer (1868) and Hering introduced the concept of the 'selbststeuerung' (self-regulation) of breathing through the vagus nerves. Inflation of the lungs reflexly inhibits inspiration, and deflation excites it. Adrian (1933) showed, by recording from

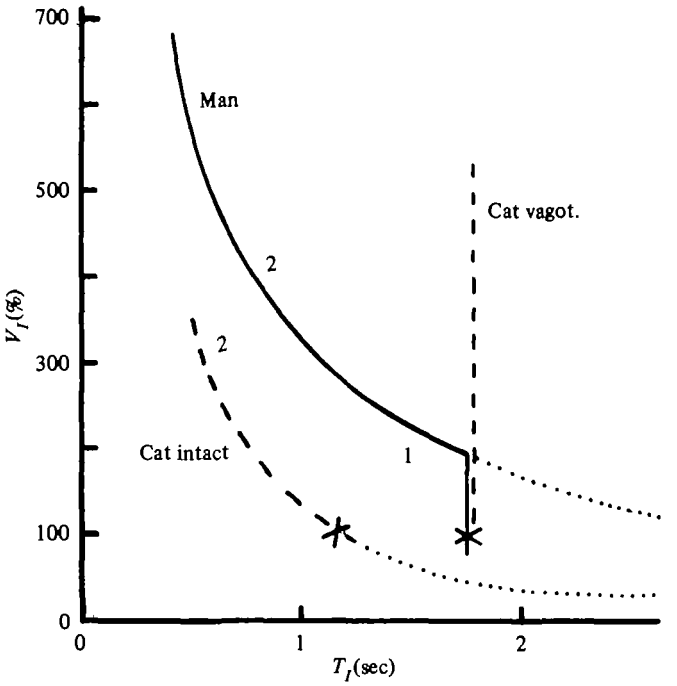

Fig. 3. The relationship between volume of inspiration (ordinate, V_I, as a percentage of eupnoeic tidal volume) and time of inspiration (abscissa, T_I). The lines labelled (2) show the hyperbolic relationship between the two variables when the Breuer–Hering reflex limits inspiratory duration; larger inspiratory volumes correspond to shorter inspiratory times and therefore more rapid breathing. The vertical lines (1) correspond to constant-frequency breathing when the time of inspiration is limited not by the Breuer–Hering reflex but by the intrinsic activity of the respiratory complex of the brainstem. The crosses show eupnoeic points. For the cat (– – –) only vagotomy produces constant time of inspiration and frequency. For man (——) the eupnoeic point is on the vertical line and the Breuer–Hering reflex has not reached its central threshold. (Modified from Clark & Euler, 1972.)

single fibres, that slowly adapting lung stretch receptors have properties appropriate to mediate this reflex. More recently, Clark & Euler (1962) and others have analysed further the effects of the receptors on the pattern of breathing.

Since inflation of the lungs inhibits inspiration, it prolongs expiratory time (t_E). This effect is abolished by vagotomy, it has a low volume threshold and can be long maintained. It is a mechanical and not a chemical effect, since it is present in dogs with cardiopulmonary bypass and constant blood gas tensions (Bartola *et al.* 1974). It results in a sensitive inverse relationship between expiratory lung volume (FRC) and breathing frequency, mediated by the slowly adapting lung stretch receptors.

The effect of the receptors on inspiration (t_I) is more complex. Their stimulation during inflation of the lungs is initially ineffective but, once a sufficient level of discharge (or volume threshold) has been achieved, inspiratory motoneurone discharge is rapidly terminated (Clark & Euler, 1972). This is a 'phasic' action of the receptors. If they are sensitized, or if their discharge is enhanced for example by more rapid inflation, the result will be a shorter t_I and quicker breathing. Since receptor discharge is

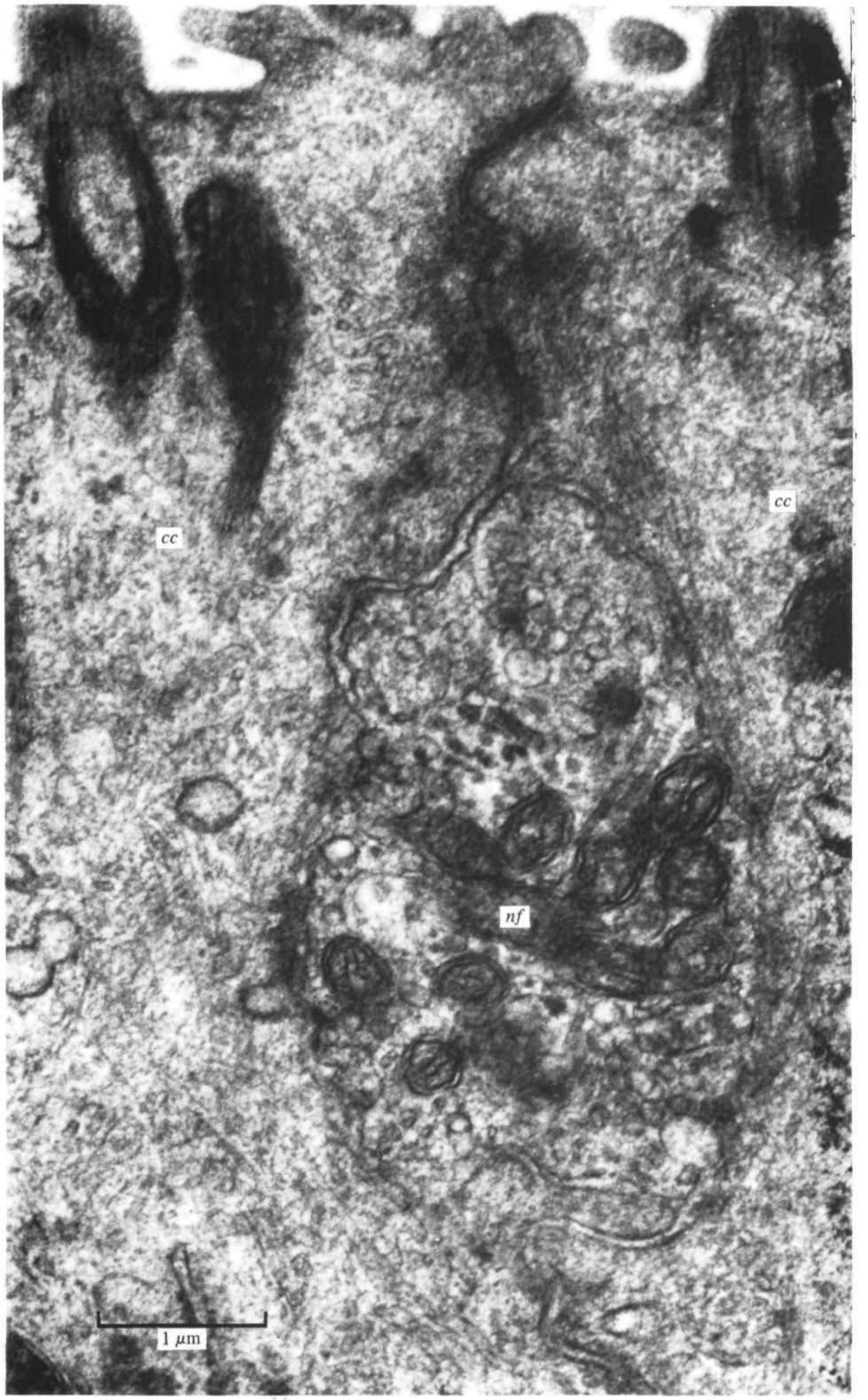

Fig. 4. Luminal edge of airway epithelium, showing a nerve fibre (*nf*) containing numerous inclusions. The nerve lies between ciliated cells (*cc*) with a double cell membrane (fixed with glutaraldehyde and osmium tetroxide; stained with uranyl acetate and lead citrate; original magnification: × 50000).

positively related to lung volume, the relationship between tidal volume (V_T) and t_I has an approximately hypobolic form (Fig. 3). Thus by a reflex feedback from the lungs an increase in inspiratory drive in each breath will lead to an increase in inspiratory frequency. Models of the respiratory control complex in the brainstem have been devised to explain these relationships (Bradley, 1977). It has been suggested that the lung stretch receptors monitor changes in the mechanical conditions of the lungs to optimise the pattern of breathing in terms of mechanical work (Widdicombe, 1964). In recent studies DiMarco *et al.* (1981) have shown that slowly adapting pulmonary stretch receptors have in addition a facilitatory action on inspiration early in the inspiratory phase, but the importance of this mechanism in the control of the pattern of breathing has yet to be demonstrated.

In man, the Breuer–Hering reflexes can be demonstrated but they are weaker than in other mammals studied (Widdicombe, 1961); this can be shown by comparing in man and other species the effects of lung inflation or by blocking the vagus nerves with local anaesthetic (Guz *et al.* 1970). Increased inspiratory drive due to exercise or hypercapnia does not cause the same hyperbolic relationship between V_T and t_I until a volume threshold of about 1·0 l or more has been exceeded (equivalent to an increase of inspiratory tidal volume to 200% of control in Fig. 3).

Other reflex actions

The slowly adapting pulmonary stretch receptors cause a reflex bronchodilatation. They have complex actions on the larynx, in general leaving the glottis open with some degree of abductor muscle tone. They probably cause reflex cardio-acceleration. These reflexes have been analysed in experimental animals, but their role in man is uncertain (Widdicombe, 1981).

Rapidly adapting lung stretch receptors

After the observation by Keller & Loeser (1926) that the vagus nerves contained fibres from lung receptors that responded to lung inflation and deflation with a rapidly adapting discharge (unlike the slowly adapting receptors described by Adrian in 1933), Knowlton & Larrabee (1946) analysed the receptor properties by single fibre recording. The receptors were shown to have a high volume threshold, to respond to both inflation and deflation and to probing the airway mucosa, to have an irregular pattern of discharge and to be connected to vagal myelinated nerve fibres. For reasons which will become apparent, they are now often referred to as cough or irritant receptors (Sant'Ambrogio, 1982).

Structure and localization

Since the studies of Larsell (1922) many histological papers have been published demonstrating by light microscopy that nerve fibres can be found under and in the epithelium of the lower respiratory tract (see Sant'Ambrogio, 1982). Most histologists have considered that the receptors are responsible for coughing, both because of the superficial situation and because they are concentrated at the points of tracheal and bronchial bifurcation, sites from which the cough reflex could most readily be elicited.

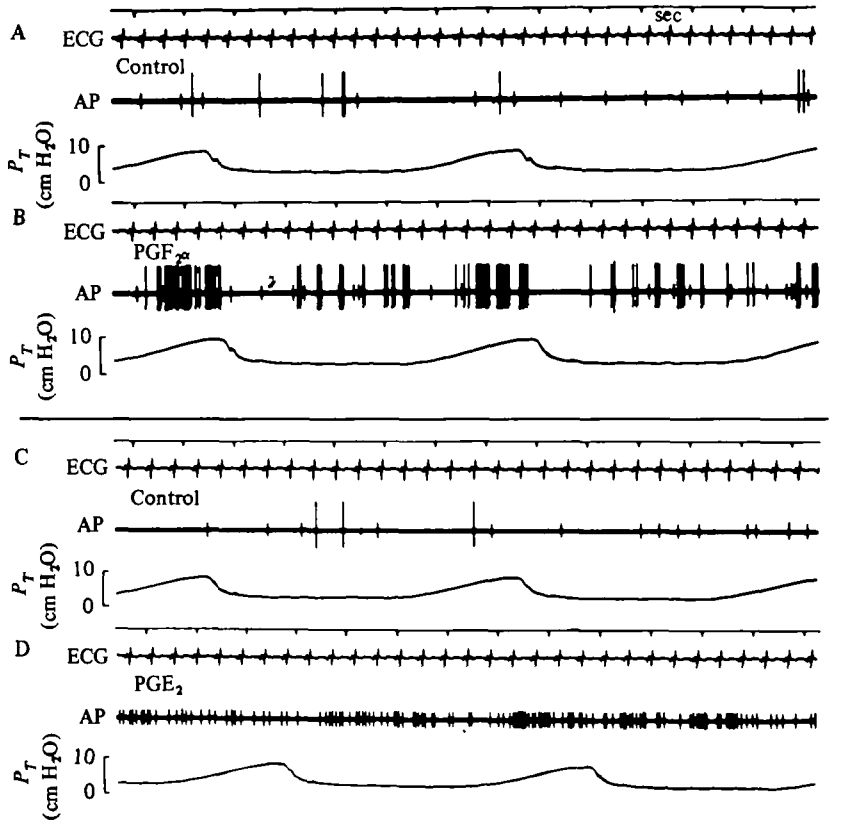

Fig. 5. Response of a rapidly adapting (irritant) receptor (large spikes) and a C-fibre ending (small spikes) to prostaglandins. Dog, open-chest, artificially ventilated. Both endings were located in the lower lobe of the left lung. A, Before, and B, 16 s after right atrial injection of prostaglandin $F_{2\alpha}$ (4 μg. kg^{-1}). Interval of 6 min between B and C. C before, and D, 42 s after right atrial injection of PGE_2 (20 μg. kg^{-1}). From above down in each record, 1 s time trace; ECG, electrocardiogram; AP, action potentials recorded from a filament of the left vagus nerve; PT, tracheal pressure. (From Coleridge *et al.* 1976.)

Electronmicroscopy has confirmed that nonmyelinated nerves exist in the airway epithelium, both near the basal lamina and also close to the lumen just deep to tight junctions (Jeffery & Reid, 1973; Das, Jeffery & Widdicombe, 1978; Fig. 4). Counts of these nerves in cat and rat show that they are more frequent in extra-pulmonary airways, with greatest concentration at the carina, and are rare or absent in the intra-pulmonary airways (*loc. cit*). Degeneration experiments establish that most of the fibres are afferent (Das, Jeffery & Widdicombe, 1979), a conclusion supported by their ultrastructural features.

Receptor properties

The rapidly adapting 'irritant' receptors have been extensively studied by recording from vagal single fibres (see Sant'Ambrogio, 1982, for references). In quiet breathing they have little discharge, but they are stimulated in hyperpnoea and by vigorous inflations and deflations of the lungs. They are probably more sensitive to rate of

airflow than to volume change *per se*. Their concentration at the carina and hilum of the lung has been confirmed for cat (Widdicombe, 1954*a*) and dog (Mortola, Sant'-Ambrogio & Clement, 1975). For the trachea, they are found at all parts of the circumference, unlike the slowly adapting endings which are mainly restricted to the posterior smooth muscle. In the dog, each receptor complex may extend over an area as large as 1 cm^2; removal of the mucosa abolishes the sensitivity to mechanical probing, which supports the view that they have superficial terminals; however the response to inflation and deflation remains intact, indicating that each receptor may also have deeper branches (Sant'Ambrogio *et al.* 1978).

As well as their response to lung volume changes, the rapidly adapting receptors are stimulated or sensitized in a variety of lung pathological conditions including pulmonary congestion and oedema, atelectasis, microembolism, anaphylaxis and bronchoconstriction (Mills, Sellick & Widdicombe, 1969; Sellick & Widdicombe, 1969). The extent to which these receptor changes depend on mechanical factors or chemical changes is not clear. The receptors can be stimulated by many mediators known to be released locally in lung disease and damage, e.g. histamine, prostaglandins (Fig. 5) and 5-hydroxytryptamine (Sampson & Vidruk, 1975; Coleridge *et al.* 1978*b*); some of these mediators may act mechanically by contracting the smooth muscle underlying the receptor, as indicated for example by the fact that the response to histamine can be prevented by administration of a bronchodilator drug such as isoprenaline.

The rapidly adapting receptors are also stimulated by a number of inhaled irritant chemicals and aerosols –hence the fact that they are often called 'irritant receptors'. These stimuli include sulphur dioxide, ammonia, cigarette smoke and carbon dusts, but the receptors vary greatly in their sensitivities to these stimuli (Mills *et al.* 1969; Sant'Ambrogio, 1982).

Thus the rapidly adapting receptors appear to be polymodal; their activation in diseases and by chemical irritants suggests that their main role may be nociceptive. Nonetheless, as will be described below, they seem to have a physiological role, at least in anaesthetized animals.

Reflex actions on breathing

The stimuli that excite these receptors will, when applied to the trachea and extrapulmonary bronchi, cause coughing (Widdicombe, 1974*b*). Much indirect evidence supports the concept that these endings are cough receptors, including their localization. However the same stimuli applied deeper in the lungs do not usually cause coughing but instead hyperpnoea. Although there are fewer rapidly adapting receptors deep in the lungs, it is probable that they are responsible for this hyperpnoea, although receptors with C-fibres (see below) may also be involved.

In anaesthetized rabbits activation of the rapidly adapting receptors by short pressure pulses (while the slowly adapting lung receptors have been blocked by sulphur dioxide) shortens t_E and accelerates breathing by a vagal reflex (Davies *et al.* 1978; Davies & Roumy, 1982), and it is likely that the tonic action of lung rapidly adapting receptors in these conditions is to maintain breathing frequency. This conclusion may explain a long-standing paradox concerning the breathing response to

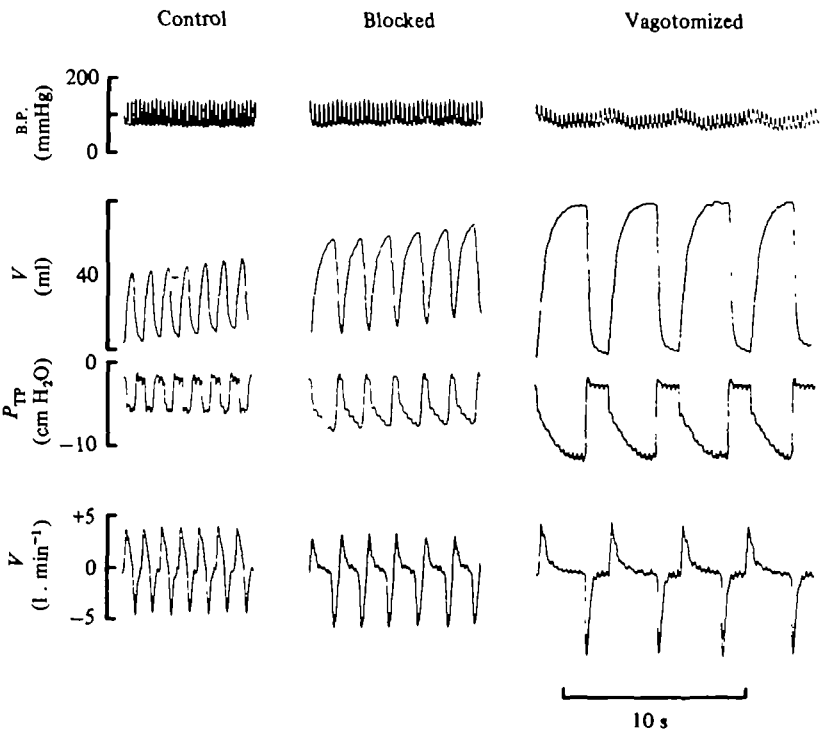

Fig. 6. Effect of stretch receptor block by SO_2 and vagotomy on, from above downwards; blood pressure, tidal volume (with some integrator drift), transpulmonary pressure and airflow. Records from a spontaneously breathing rabbit. (From Davies *et al.* 1978.)

vagotomy; this intervention slows and deepens breathing with a conspicuous *increase* in t_E. Yet the abolition of the activity of slowly adapting lung receptors, which prolong t_E, should by itself lead to a shortening of t_E. The fact that the opposite is seen can be explained by the converse reflex effect on t_E of rapidly adapting receptors. This view is supported by the observation that specific block of slowly adapting stretch receptor activity by SO_2 causes deep breathing with *shortened* t_E; subsequent vagotomy (abolishing reflex effects of rapidly adapting and C-fibre receptors) then leads to a lengthened t_E (Fig. 6; Davies *et al.* 1978).

A further effect of rapidly adapting receptors on breathing is the triggering of augmented breaths, the occasional deep sighing breaths shown by mammals which reverse the tendency of the lungs to collapse. These breaths are abolished or infrequent in vagotomized animals, so they depend largely on a vagal reflex. They can be initiated by the same stimuli that activate rapidly adapting stretch receptors, including short pressure pulses and large inflations; after each augmented breath the mechanism is refractory for some minutes, preventing repetition of the deep breath (Davies & Roumy, 1982).

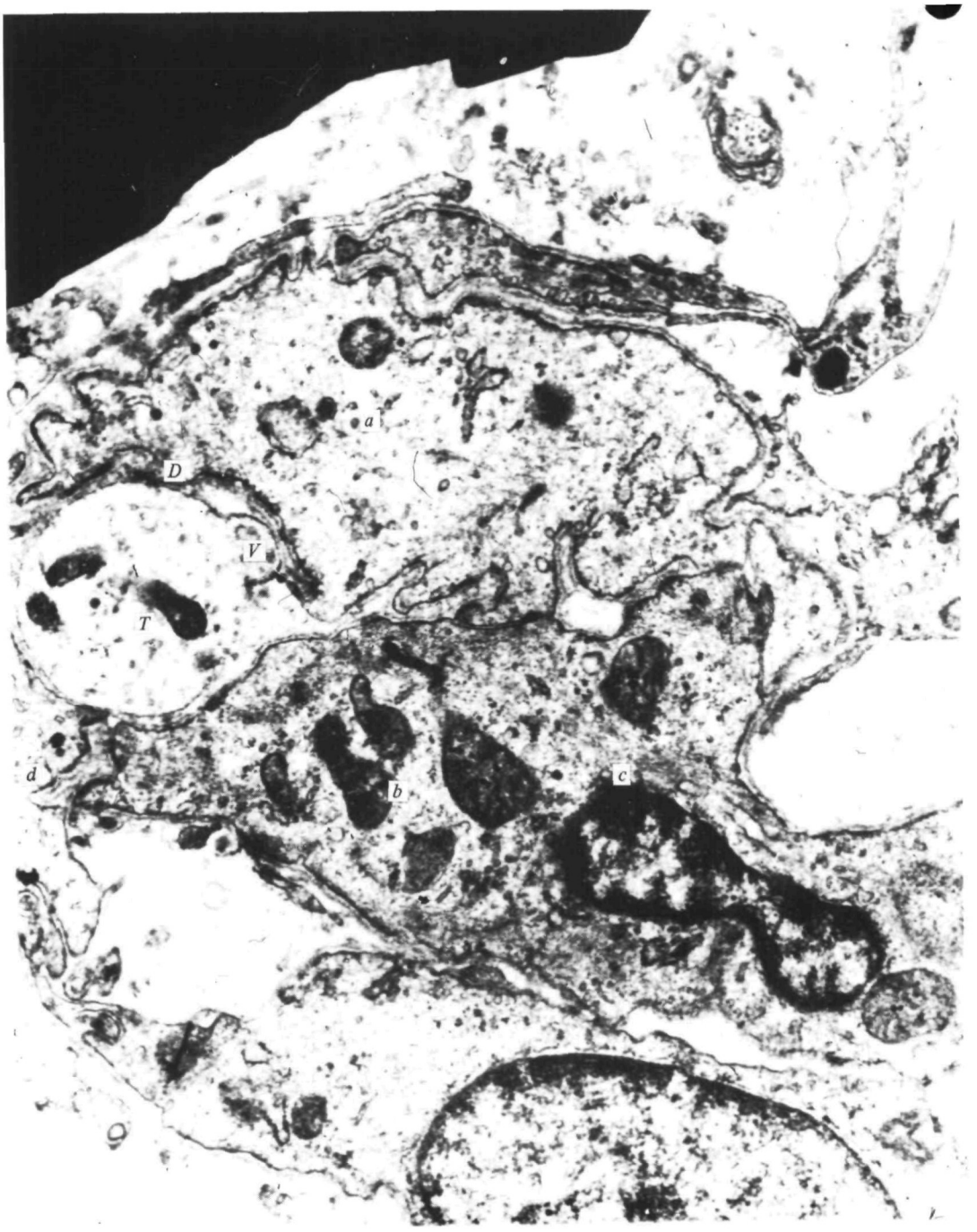

Fig. 7. Section of a nerve terminal (*T*) showing bulb-like varicosity containing tubules and vesicles (*V*). This is surrounded by 'guard' cells (*a–d*) with basement membranes joined by a desmosomoid structure (*D*). A distinct basement membrane (BM) to the varicosity is seen at arrow. An axon is emerging from a Schwann cell sheath and basement membrane at top right-hand corner. (× 14500). (From Meyrick & Reid, 1971.)

Other reflex actions

The rapidly adapting receptors have been shown to cause reflex bronchoconstriction, laryngoconstriction and airway mucus secretion. These are all responses associated with coughing, and also with the hyperpnoea due to lung irritant stimulation. Cardiovascular reflexes are less well established, but the rapidly adapting receptors in the trachea can produce a reflex hypertension (see Widdicombe, 1977, 1981).

Pulmonary and bronchial C-fibre receptors

Paintal (1955), with cats, first recorded impulses in vagal afferent nonmyelinated fibres from the lungs, and later Coleridge, Coleridge & Luck (1965) extended these studies to the dog. Paintal (1969) concluded that the receptors attached to the nerve fibres were 'juxta-pulmonary capillary', and termed them 'J-receptors'. Subsequent studies have shown that some receptors respond to chemical changes mainly via the pulmonary circulation, and others via the bronchial circulation, so it is now usual to refer to pulmonary and bronchial C-fibre receptors (Coleridge & Coleridge, 1977).

Structure and localization

Light microscopy does not give very clear pictures of nonmyelinated fibres and receptors. Electron microscopy shows nonmyelinated fibres in rat (Fig. 7) (Meyrick & Reid, 1971) and human alveolar walls (Fox, Bull & Guz, 1980), but they are infrequent. They are thought to be identical with pulmonary C-fibre or J-receptors. For the bronchi, nonmyelinated fibres have been identified in the epithelium and, although these are thought to be irritant receptors (see above) the possibility that some may have nonmyelinated vagal afferents has not been ruled out. Similar fibres can be seen in the lamina propria. Punctate stimulation of the airway mucosa of the dog can cause discharges in vagal C-fibres from bronchial receptors (Coleridge & Coleridge, 1977). It should be stressed that degeneration studies show that the majority (75%) of vagal afferent fibres from the lungs are nonmyelinated (Agostoni *et al.* 1957).

Receptor properties

In the eupnoeic anaesthetized animal C-fibre receptors usually have a sparse irregular discharge. They are not very sensitive to lung volume changes, but can be stimulated by large lung inflations in dogs (Coleridge *et al.* 1965) and by forced lung deflations in cats. Pulmonary vascular congestion is a strong stimulus, and Paintal (1969) believes that the main 'physiological' stimulus to the receptors is an increase in interstitial fluid in the alveolar wall. Drugs that cause pulmonary oedema strongly stimulate the pulmonary C-fibre receptors. The receptors are excited by an increase in pulmonary blood flow, which raises the possibility that they may play a role in the respiratory changes in exercise (Paintal, 1973).

Many chemicals have been shown to stimulate the receptors. These include foreign substances such as phenyl diguanide and capsaicin, much used in their study, and also natural mediators such as histamine, bradykinin, some prostaglandins (Fig. 5) and 5-hydroxytryptamine. There are differences in sensitivity of pulmonary and bronchial C-fibre receptors to various mediators (Coleridge & Coleridge, 1977). The receptors

Table 2. *Responses of lung irritant and C-fibre receptors*

Stimulus	Receptor response	
	Lung irritant	C-fibre
Lung inflation	++	+
Lung deflation	++	o
Chemical irritants	+	+
Histamine	++	+
Prostaglandins	+	+
Bradykinin	o	+
5-Hydroxytryptamine	?	+
Microembolism	+	++
Congestion	+	++
Anaphylaxis	+	?

are also stimulated by inhalation of strong irritants such as chlorine, and by high concentrations of volatile anaesthetics such as halothane and ethyl ether (Paintal, 1973).

It will be apparent that, in general, lung irritant and C-fibre receptors are affected by the same types of stimuli, and therefore would be activated by the same types of lung pathological change (Table 2). However the irritant receptors are probably more sensitive to lung volume changes, and there are some clear differences in responses to mediators such as prostaglandins.

Reflex actions of C-fibre receptors

Chemical stimulation of pulmonary C-fibre receptors causes apnoea followed by rapid shallow breathing in the cat and dog. In the rabbit there is also a large increase in FRC (Dawes, Mott & Widdicombe, 1951). These changes are abolished by vagotomy. In man, indirect evidence suggests that the receptors increase breathing frequency (Jain *et al.* 1972).

Activation of C-fibre receptors cause laryngeal constriction that, in the cat, amounts to complete glottal closure during the reflex apnoea (Stransky, Szereda-Przestaszewska & Widdicombe, 1973). There is also reflex bronchoconstriction (Russell & Lai-Fook, 1979) and tracheal mucus secretion (Richardson & Phipps, 1978). These responses are quantitatively similar to those seen with stimulation of lung irritant receptors. However, in addition C-fibre receptors cause reflex hypotension and bradycardia, and a long-lasting depression of spinal reflexes (Paintal, 1973; Deshpande & Devanandan, 1970).

Interaction of lung reflexes

It has been stressed that many mechanical and chemical stimuli activate both lung irritant and C-fibre receptors, and that there are similarities in the reflex responses from the two groups of ending. It is therefore probable that in many pathological conditions, such as microembolism, pulmonary congestion and oedema, and antigen-antibody reactions in the lungs with release of mediators, both groups of receptor and their reflexes are involved. The precise pattern of responses will depend on the balance of stimuli affecting the receptors, and the interplay of the reflex motor changes. This

complexity of mechanism is not surprising, since other visceral and somatic tissues have similarly complicated innervations. However it makes the interpretation of experiments with isolated components of the system difficult, and points to the need for quantitative analysis of reflex interactions in pathophysiological conditions, including in man.

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