ACTA NEUROBIOL. EXP. 1973, 33: 21-31

Lecture delivered at Symposium "Neural control of breathing"
held in Warszawa, August 1971

RELATIVE ROLES OF IRRITANT, TYPE-J AND PULMONARY STRETCH RECEPTORS IN LUNG REFLEXES

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Abstract. Bilateral anodal block of both cervical vagus nerves of anaesthetized rabbits has been used to assess the relative role of afferent pathways with myelinated fibres (primarily from lung irritant receptors) and with nonmyelinated fibres (from J-receptors) in respiratory responses to some lung conditions. With inhalation of histamine aerosol the increase in breathing frequency is due to myelinated afferent fibres from irritant receptors. The similar response with inhalation of halothane is due to non-myelinated fibres from J-receptors. The reflex breathing response in lung oedema involves both pathways, but in the experimental conditions the myelinated pathway plays the larger part. The interaction of these two mechanisms, and the possible role of pulmonary stretch receptors, is discussed.

INTRODUCTION

About ten years ago it was thought that there must be at least six afferent pathways from the lungs to account for the diversity of respiratory reflexes that had been described. Today there are known to be three vagal afferent systems in mammals that have been studied by single fibre recording and the receptors of which have been identified histologically. In the present state of knowledge all the respiratory reflexes arising from the lungs can be explained on the basis of these three types of receptor. Other reflexes and receptors may be identified in future research, but there is at the moment no need to postulate them. This development has led to a welcome simplification of our understanding of lung reflexes, but new complications have arisen since it is now clear that it is usually no longer possible to account for one reflex response by only one afferent nervous pathway. Instead most physiological and pathological changes in

the lungs can be shown to produce reflex effects by interaction of the responses from two or three of the receptor and fibre groups. This means that the study of lung reflexes now demands a quantitative assessment of the relative roles of the afferent systems involved.

The three types of pulmonary receptor are:

1. *Pulmonary stretch receptors.* These are endings in the airway smooth muscle which are stimulated by inflations of the lungs, with both static and dynamic components to their response. Their reflex action is to inhibit inspiratory activity and to cause bronchodilatation. They are insensitive to "pathological" changes in the lungs such as microembolism, mild bronchoconstriction and inhalation of irritants and dust, but they are weakly sensitized by pulmonary congestion and oedema due to left heart failure. They have myelinated vagal nerve fibres of Aβ-γ diameter.

2. *Type-J receptors* (originally called "specific deflation receptors", Paintal 1963). These lie in the alveolar wall between epithelium and endothelium, and have nonmyelinated vagal afferent fibres. Their reflex action is to cause apnoea or rapid shallow breathing, hypotension and bradycardia. They may contribute to unpleasant respiratory sensation in man. They are stimulated by inhalation of strong irritant gases, including halothane, by increases in interstitial fluid volume due to pulmonary congestion and oedema, and by pulmonary microembolism.

3. *Lung irritant receptors* (also called deflation or collapse receptors, Koller, this Symposium). These are found in the epithelial layer of the intrapulmonary airways, and are similar in histological appearance to "cough receptors" in the tracheal epithelium. They have vagal myelinated nerve fibres of Aδ diameter. Their reflex action is hyperpnoea and hyperventilation, and bronchoconstriction. They may contribute to unpleasant respiratory sensation in man. They are stimulated or sensitized by intraluminal dust and chemical irritants; by contraction of underlying smooth muscle as in bronchoconstriction; by large inflations and deflations of the lungs, including pneumothorax; by increased elastic pull on the airway wall as in atelectasis; and by lung anaphylaxis, pulmonary congestion and microembolism.

Two other types of respiratory receptor may play a part in lung conditions in mammals: cough receptors in the tracheal epithelium, and pulmonary arterial baroreceptors. However, these, or most of them, are extra-pulmonary. The original literature describing all these receptors has been recently reviewed (Paintal 1963, Widdicombe 1964, 1971, Fillenz and Widdicombe 1971) and will not be detailed here.

It is clear from these studies, based mainly on recording from vagal single afferent fibres from the appropriate receptors and summarized in Table I, that most of the test procedures activate more than one type of

TABLE I

Summary of the responses of three types of lung receptor in various physiological and pathologica conditions. The brackets mean weak or not clearly established effect.

Stimulus	Receptor response		
	Pulmonary stretch	Type-J	Irritant
Lung inflation	+	−	+
Lung deflation	−	−	+
Dust	−	−	+
Chemical irritants	−	+	+
Halothane	(+)	+	−
Ether	(+)	+	+
Phenyl diguanide	−	+	+
Bronchoconstriction	−	−	+
Microembolism	−	+	+
Pulmonary congestion	(+)	+	+

receptor and, in particular, that type-J and irritant receptors may be simultaneously stimulated in many of the pathological conditions investigated. The object of our research was twofold: to see if "pure stimuli" could be established which would indicate the reflex actions of each type of receptor uncomplicated by those of the other groups; and to try to apportion the role of type-J and irritant receptor reflexes in conditions where both were known to be involved.

METHODS

We have used rabbits, anaesthetized with pentobarbitone sodium, and tracheotomized. Femoral arterial blood pressure was recorded with a strain-gauge manometer, tracheal airflow and tidal volume with a Fleisch pneumotachograph and integrator (Godart), and end-tidal CO_2% with an infra-red analyser (Beckman). Arterial blood gas tensions were determined by blood-gas electrodes (Radiometer). Blood pressure, tidal CO_2% and tidal volume were recorded on UV paper (Honeywell). Total lung resistance and compliance were measured by the "subtractor" method of Mead and Whittenberger (1953), using an intrapleural catheter for transpulmonary pressure.

Three experimental conditions were studied.

1. Inhalation of an aerosol of a 5% solution of histamine acid phosphate in 0.9% saline. The aerosol (particle diameter 8μ) was produced by a commercial generator (B.O.C.) and the rabbits breathed in from a passing stream of the gas without measurable change in intratracheal pressure.

2. Inhalation of 4% halothane in air, by connecting a bag (5 litres capacity) filled with the gas to the tracheal cannula. The gas was given for 30 sec, which was too short a time for stimulation of breathing by blood gas changes.

3. Pulmonary congestion and oedema caused by intravenous injection of 0.08–0.1 ml of a solution of caprylic and capric acids in olive oil. This method has been shown to produce pulmonary oedema within 1–2 min of injection (Bost et al. 1969).

To separate the roles of irritant receptors and type-J receptors we used the anodal block method, similar to that described by Guz and Trenchard (1971), but applied to both cervical vagus nerves. With continuous (1/sec) monitoring of the compound electroneurograms of the two vagus nerves, currents of 40–180 μa were used to block completely the myelinated A-B waves (containing action potentials from pulmonary stretch and irritant fibres) while leaving intact the nonmyelinated C waves (containing action potentials from type-J receptor fibres). With anodal block at least 1–2 min was allowed to elapse before further tests to allow stabilization of the breathing pattern.

RESULTS

Histamine aerosol

Figure 1 shows the changes in frequency of breathing caused by inhalation of histamine aerosol for 1–3 min in rabbits with intact vagi, and in those with conduction in myelinated fibres in both nerves blocked. In the former group there was a consistant increase in breathing frequency; with anodal block the control frequency was slower (presumably due to block of conduction in fibres from pulmonary stretch receptors), and histamine no longer caused a significant increase in frequency. The differences in frequency, expressed in absolute units or as percentages, were statistically significant (Table II). Figure 2 shows the corresponding changes in tidal volume. There were nearly always decreases in tidal volume (possibly associated with changes in lung compliance) whether the vagal myelinated fibres were blocked or not, and there was no statistically significant difference between the two groups.

Halothane

Figure 3 shows the breathing frequency changes due to 4% halothane administered for 30 sec. With vagal conduction intact there were always increases in frequency usually starting within a few seconds, while with

anodal vagal block over half the rabbits still showed equivalent increases in frequency (Fig. 3). The corresponding results for tidal volume (Fig. 4) showed decreases with halothane whether the myelinated fibres were blocked or not.

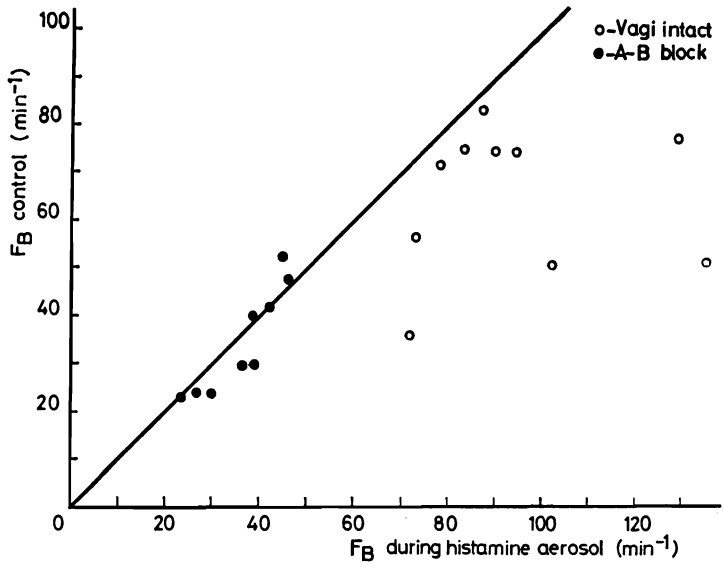

Fig. 1. Changes in frequency of breathing (F_B) during inhalation of a 5% solution of histamine acid phosphate. Ordinate, frequency before aerosol; abscissa, frequency during aerosol. The 45° line represents no change, and points to the right indicate an increase in frequency. Open circles, intact vagi; filled circles, anodal block of conduction in myelinated (A-B) vagal fibres.

TABLE II

Increases in breathing frequency (means and standard errors)

Vagi	5% histamine aerosol	4% halothane	Lung oedema
Intact	**25.3±5.79 min^{-1} **49.0±11.53%	**25.0±5.32 min^{-1} **38.3±8.95%	**32.4±7.02 min^{-1} *77.0±30.8%
A-B block	≠2.3±1.45 min^{-1} 6.7±5.05%	+*10.0±3.60 min^{-1} *31.9±11.40%	≠*5.2±1.62 min^{-1} 15.3±6.08%
Cut			≠* 5.8±1.83 min^{-1} *14.4±4.69%

* $p < 0.05$, ** $p < 0.01$ for significance of difference between mean and zero change.
\+ $p < 0.05$, ≠ $p < 0.01$ for significance of difference between cut or blocked vagi and vagi intact groups.

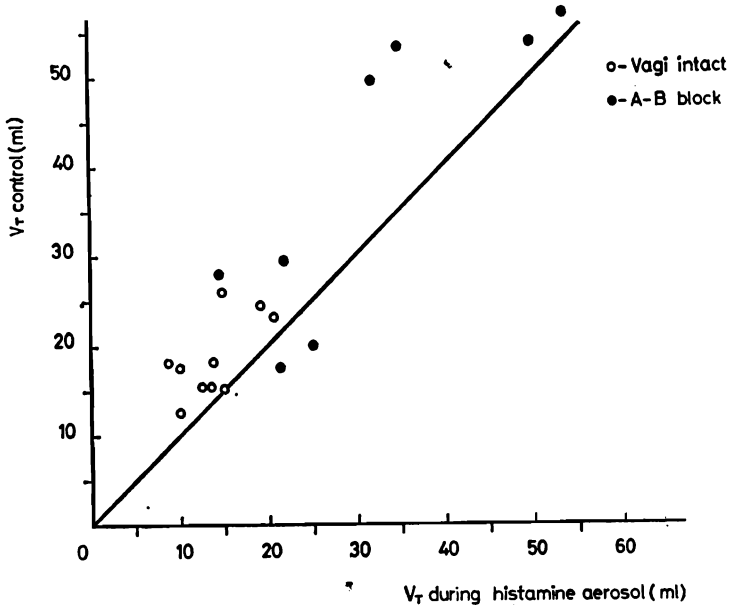

Fig. 2. As Fig. 1, but for changes in tidal volume (V_T) caused by inhalation of histamine aerosol.

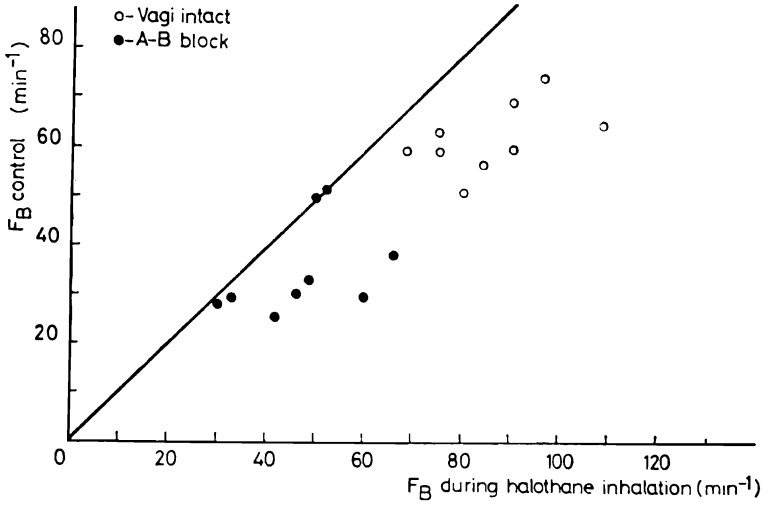

Fig. 3. As Fig. 1, but for changes in frequency of breathing caused by inhalation of 4% halothane in air.

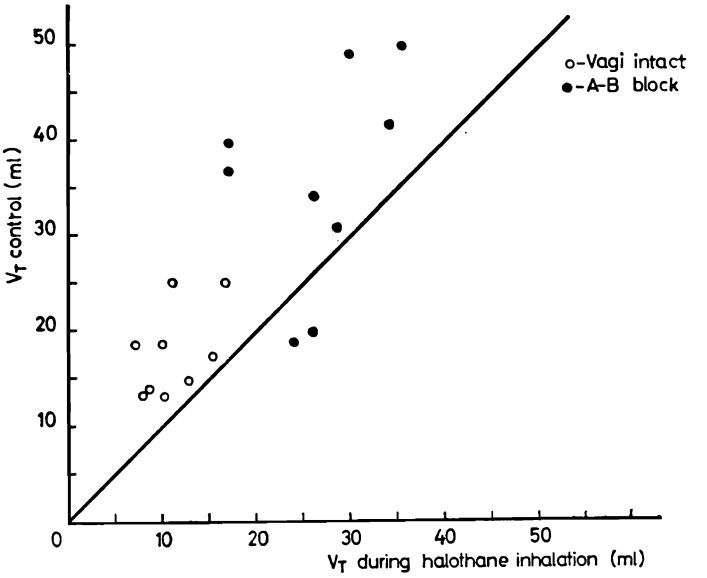

Fig. 4. As Fig. 3, but for changes in tidal volume due to halothane.

Pulmonary oedema

By carefully adjusting the dose of fatty acids in oil it was possible to produce clear changes in breathing due to oedema, and also a temporary arterial hypotension (used as an index of an effective dose), which allowed

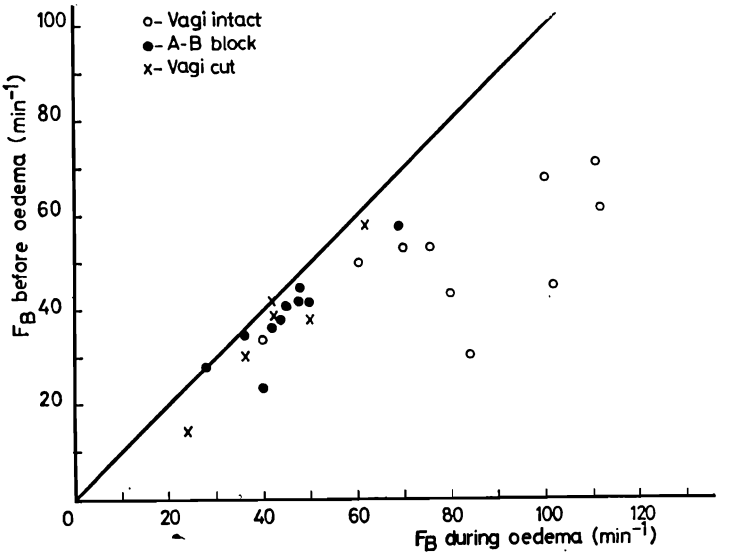

Fig. 5. As Fig. 1, but for changes in frequency of breathing caused by induction of pulmonary oedema. Crosses, after bilateral vagotomy.

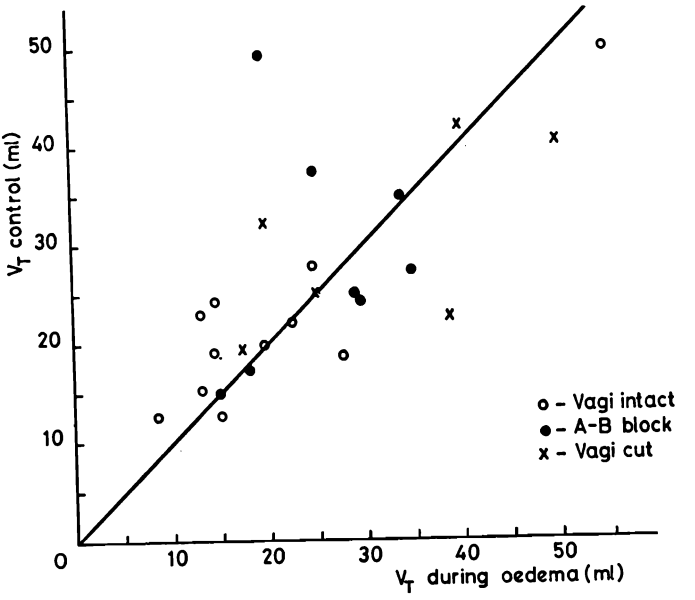

Fig. 6. As Fig. 5, but for changes in tidal volume due to pulmonary oedema.

the rabbits to live for at least 30–60 min before they were killed for post mortem examination. Histological studies showed lung congestion, haemorrhage and oedema.

Figure 5 shows the breathing frequency changes and includes a group of rabbits in which oedema was induced after bilateral vagotomy. With vagal conductions unimpaired there was a consistant increase in frequency, but with anodal block or vagotomy the increase was very greatly reduced (Table II) and there was no significant difference between the

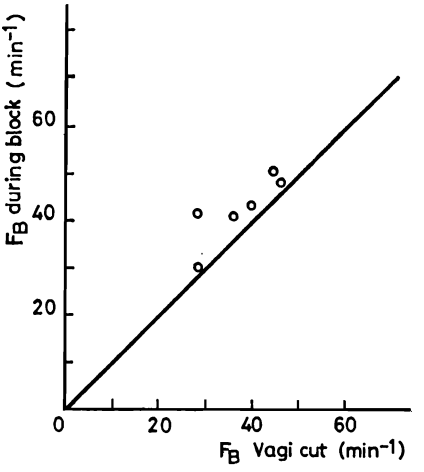

Fig. 7. The effect of bilateral vagotomy on the frequency of breathing (F_B) during pulmonary oedema with anodal block of myelinated fibres in both vagus nerves.

two latter groups. Tidal volume showed very variable changes in the three groups of rabbits (Fig. 6).

In a further group of rabbits oedema was first induced and anodal block of conduction in myelinated fibres was then started. After some minutes when the animals' breathing patterns were stable, both vagus nerves were cut below the block. Figure 7 shows that this vagal section produced a small but consistent decrease in the frequency of breathing.

DISCUSSION

Histamine aerosol

Histamine is said not to act on J-receptors (Paintal 1970), and the size of the aerosol particles (8μ diameter) should have prevented them from reaching the alveoli. However histamine aerosol stimulates lung irritant receptors in the rabbit (Mills et al. 1969). Our results are consistant with this, and indicate the increase in breathing frequency due to the histamine is mediated by myelinated fibres, presumably from irritant receptors. The usual decreases in tidal volume may be due to the effect of a decreased lung compliance; they were generally present with histamine during anodal vagal block, and in this condition are unlikely to be due to a J-receptor reflex since the latter always causes an increase in rate of breathing.

Halothane

This is known to stimulate J-receptors (Paintal 1970), but has no action, or even a weak inhibition, on irritant receptors (Mills et al. 1970). With anodal block we usually found that halothane caused as much rapid shallow breathing as when vagal conduction was intact, which is consistent with a J-receptor mechanism. Although in four rabbits the frequency increase due to halothane was absent during anodal block, this could be due to tachyphylaxis which proved troublesome with halothane. Halothane has a complicated action on pulmonary stretch receptors but, in so far as we found responses in five rabbits during anodal block, these could not be due to conduction in myelinated fibres from either pulmonary stretch or irritant receptors.

Pulmonary oedema

Pulmonary congestion caused by occlusion of the aorta and oedema caused by alloxan stimulate J-receptors in the cat (Paintal 1969), and mild pulmonary congestion caused by left atrial obstruction stimulates irritant receptors in the rabbit (Sellick and Widdicombe 1969). Our results with a severe pathological lesion including congestion, haemorrhage and oedema indicate that by far the larger part of the reflex increase in breathing

frequency is mediated by receptors with myelinated fibres. The size of the response suggests that these are probably irritant receptors, but a rather weak sensitization of pulmonary stretch receptors has also been shown in pulmonary congestion (Marshall and Widdicombe 1958), and in lung oedema (Widdicombe 1961, Dziewanowska-Kunert et al. 1971). The variability of tidal volume changes is not surprising in view of the lung pathology. Although the results of Fig. 7 indicate that nonmyelinated fibres (from J-receptors) contribute to the increased frequency of breathing, their role must be small. Comparison between the vagotomized and anodal blocked groups (Fig. 5, Table II) shows no significant difference, whereas there is a significant large difference between the vagi intact and anodal block groups.

GENERAL CONCLUSIONS

Single fibre recording shows that both type J and lung irritant receptors are stimulated in several lung pathological conditions. Our results show that in at least one of these conditions, pulmonary oedema, the irritant receptors play the larger part in the changes in breathing frequency. Presumably both reflexes interact also in microembolism, since this condition stimulates both J-receptors (Paintal 1970) and lung irritant receptors (Sellick and Widdicombe 1969). However the relative roles of the two reflexes will be influenced by conditions such as anaesthetic and possibly by the species. In these experiments the use of halothane and phenyl diguanide (not described here) indicated that the J-receptor reflex was effective, and the use of histamine aerosol indicated that the irritant receptor reflex was effective. It is clearly impossible to say what the relative importance of the two reflexes would be in other species, including man, or in unanaesthetized animals. As with nociceptive endings in the skin so for the lungs there are two types of receptor, with δ-myelinated and nonmyelinated fibres respectively, and both presumably interact to produce their reflex and sensory responses in various physiological and pathological conditions.

Nor should the pulmonary stretch receptors be ignored. Even if they are not directly stimulated by the lung conditions their discharge will be altered by any changes in the pattern of breathing. Their normal role seems to be to adjust the pattern of breathing; their inactivation by anodal block or vagotomy could limit the range of responses to other respiratory reflexes.

Maria Głogowska was supported by a personal grant from the Smith Kline and French Foundation. Some of the apparatus used was brought with grants from the Royal Society and the Medical Research Council.

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