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THE SITE OF PULMONARY STRETCH RECEPTORS IN THE CAT

By J. G. WIDDICOMBE*

From the Nuffield Institute for Medical Research, Oxford

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Inflation of the lungs causes inhibition of inspiratory activity by the Hering-Breuer inflation reflex. In 1933, Adrian recorded action potentials from single vagal nerve fibres coming from the pulmonary stretch receptors for this reflex; the location of the receptors has not been identified. Weidmann, Berde & Bucher (1949), using rabbits, suggested that many of the endings lay in the visceral pleura, but this has little histological support. The intrapulmonary bronchi seemed a more likely site, not only because appropriate nerve endings have been described there (Larsell, 1921; Elftmann, 1943), but because stretch receptors in the *extrapulmonary* bronchi have properties similar to the pulmonary stretch receptors (Widdicombe, 1954*b*). This paper describes experiments attempting to localize the receptors for the Hering-Breuer inflation reflex, and a consideration of some of the factors which modify their activity.

A brief report of some of this work has already been given (Widdicombe, 1953).

METHODS

Thirty-seven cats were used; activity from pulmonary stretch fibres was recorded in twenty-five; and the Hering-Breuer inflation reflex investigated in twelve. They were anaesthetized with intraperitoneal pentobarbitone sodium, 32 mg/kg. Tracheal cannulae were inserted. Systemic blood pressure was recorded from a carotid artery, using a mercury manometer. Intravenous injections were made into an external jugular vein.

To record vagal nerve fibre activity the chest was first opened widely, the cat having artificial positive pressure ventilation. Both vagi were cut, and the peripheral end of the left nerve was placed on a small platform; strands containing one active afferent nerve fibre were isolated on electrodes. Action potentials were amplified and displayed on a cathode-ray oscilloscope. Fuller details of the electrical apparatus have been given elsewhere (Widdicombe, 1954*b*). Only those fibres coming from slowly adapting pulmonary stretch receptors were investigated.

Receptors were localized to a pulmonary lobe by preventing the expansion of each lobe in turn; gentle pressure at the root of the lobe blocked air entry without apparent damage to nervous or pulmonary tissue. The receptors were further localized by pressure on the lobe with a blunt probe or paint-brush. The pleura was then stripped off; this naturally resulted in haemorrhage and leakage of air. Lobes thus severely damaged had to be tied off at the root, so in any cat only three to four endings could be investigated with this technique.

* Present address: Microbiological Research Department, Ministry of Supply, Porton, Wilts.

To determine the action of bronchomotor drugs on the receptors the lungs were artificially ventilated, with a constant volume delivered at each pump stroke. The cats were usually enclosed in a body plethysmograph (Dawes, Mott & Widdicombe, 1951) from which a record of changes in lung volume was obtained by a float recorder writing on a smoked drum. Inflations with a syringe gave responses identical to those obtained with the pump. Intratracheal pressure was displayed on a cathode-ray oscilloscope by means of an electrical condenser manometer; the pressure changes were used as an index of bronchial tone, as the latter was believed to be the most important variable in causing changes in pulmonary resistance to inflation in these experiments.

The Hering-Breuer inflation reflex was elicited in cats with intact chests by inflating the lungs to approximately twice the tidal volume; the chosen inflation volume was used for the entire experiment in any particular cat. The inflation was made at the beginning of an expiratory pause, using a syringe; the next inspiratory effort was delayed by the reflex. In these experiments intratracheal pressure was measured by a tambour writing on a smoked drum. The activity of the Hering-Breuer inflation reflex was measured as the ratio of the time between the artificial inflation of the lungs and the next inspiratory effort to the time occupied by the preceding normal respiratory cycle. This ratio takes into account the rate of respiration and its slowing by the Hering-Breuer reflex, but not tidal volume and respiratory muscle tone. As such it could not be regarded as a comprehensive index of Hering-Breuer reflex activity, but it was convenient; changes in the ratio are expressed as a percentage to indicate either enhancement or depression of the reflex. The ratio was not applied if there were large changes in the spontaneous respiratory cycle.

To perfuse the bronchial arteries a short-circuit was first made round the segment of the aorta from which they arose. All the arteries in this segment were tied off except the branch to the bronchi; this also supplied a section of the oesophagus, part of the posterior chest wall, and some of the mediastinum. Thus only a proportion of a drug injected into it would reach the bronchi. The aortic segment was perfused from a carotid or internal mammary artery. Patency of the bronchial arteries was tested at the end of each experiment by injection of indian ink and direct observation. The cats were heparinized. Veratridine injections were made at intervals of 10–15 min in order to minimize tachyphylaxis.

Histamine acid phosphate was given in doses of 100–500 μg; acetylcholine 50–300 μg; eserine 300–600 μg; pilocarpine 50–500 μg; adrenaline 50–150 μg; atropine 1–3 mg.

RESULTS

Direct localization of receptors

Weidmann *et al.* (1949) have suggested that, in the rabbit, the majority of pulmonary stretch receptors lie in the visceral pleura; this possibility was tested in the cat. While recording from a pulmonary stretch fibre the lobe of the lungs containing the receptor was identified, and the position of the ending discovered by pressing on the pleura with a blunt probe. Rather heavy pressure was usually needed for stimulation, sufficient to indent the pleura several millimetres, and it was possible to delineate an area of maximum sensitivity to pressure about 5 mm or less in diameter. A corresponding area on the opposite side of the lobe was always found, although there was often an obvious difference in sensitivity between the two sides. Stroking these pleural areas with a paint-brush only stimulated the receptors when firm pressure was applied. Having determined the approximate site of a receptor the visceral pleura was stripped off both sides of the lobe for areas of more than 1 cm in diameter with centres at the points of maximum sensitivity to pressure.

Only one out of thirteen endings was destroyed by this procedure, although more than half the pleura was removed from several lobes.

After stripping the pleura overlying the receptor, dissection was continued into the lung parenchyma. The twelve endings all lay deep to the surface of the lung, and were usually very sensitive to traction on the bronchial tree; four were in or closely applied to large intrapulmonary bronchi (1–3 mm in diameter). In two experiments a probe was passed down small bronchi from the exposed peripheral ends, and the receptors were strongly stimulated by the resultant distension of the air passages. More precise localization of pulmonary stretch receptors proved difficult because of haemorrhage and leakage of air from the lungs. It had, however, been demonstrated that the majority of endings were not situated in the pleura.

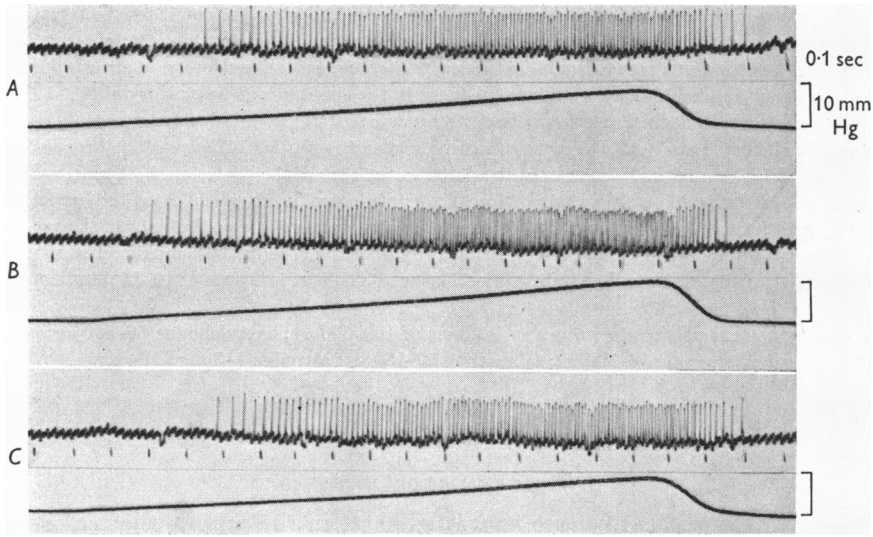

Fig. 1. The action of acetylcholine on a pulmonary stretch receptor. Upper trace: action potentials from a pulmonary stretch fibre. Lower trace: intratracheal pressure. *A*, *B* and *C* show the response to three inflations with the same volume of air; between *A* and *B* 200 μg acetylcholine was injected intravenously. In *B* the intratracheal pressure reaches a higher value than in *A* (indicating a bronchoconstriction), and the receptor discharges more frequently. *C* is 2 min later when the effect of the drug had worn off.

Bronchial tone and receptor activity

If the stretch receptors lay in the intrapulmonary bronchi their activity might be modified by drugs which altered bronchial tone. Acetylcholine was considered most suitable since its effects are transient and reproducible; intravenous doses were given which caused an increase in pulmonary resistance to inflation. Acetylcholine almost invariably caused an increased frequency of discharge from the receptors (Fig. 1); the volume of air entering

the lungs at each pump stroke was unchanged, but there was an increase in peak intratracheal pressure. The results for twenty-four endings are included in Fig. 2, which shows that there was no general correlation between the increase in discharge frequency and the change in intratracheal pressure. For any individual receptor, however, these two variables were closely related, and the time relationships of their changes were similar. Thus in Fig. 3 the peak discharge frequency of a receptor is plotted on the same time scale as the intratracheal pressure after an injection of acetylcholine; both responses lasted about 1 min.

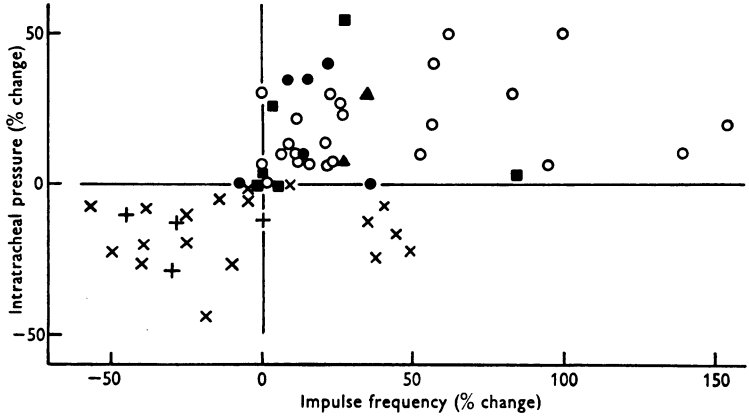

Fig. 2. The action of bronchomotor drugs on pulmonary stretch receptors. Ordinate: percentage change in intratracheal pressure. Abscissa: percentage change in peak discharge frequency at the height of inflation. ○, acetylcholine. ■, eserine; ●, histamine; ▲, pilocarpine; ×, adrenaline; +, atropine. Each point corresponds to the action of the appropriate drug on a single receptor; the maximum change in discharge frequency after the injection is compared with the change in intratracheal pressure at the same time, constant volume phasic inflations being used.

This suggested that the increased frequency of discharge observed after acetylcholine might not be a direct action on the receptor but a secondary result of bronchoconstriction. This was supported by observations with other drugs. Histamine, eserine and pilocarpine all increased the pulmonary resistance to inflation and the discharge frequency of pulmonary stretch endings (Fig. 2), and again the time courses of the two changes were similar (Fig. 3). Adrenaline and atropine, on the other hand, usually caused a decrease in the discharge frequency of the receptors, which was concurrent with a decrease in intratracheal pressure (Fig. 2); there was not the same consistency as with acetylcholine, and several receptors discharged more rapidly after adrenaline in spite of a decrease in intratracheal pressure. Before adrenaline would lower the discharge frequency of the receptors it was usually necessary to increase

bronchial tone with eserine or pilocarpine. Figs. 3 and 4 illustrate results with adrenaline. The fact that all six drugs changed the activity of the stretch receptors, and that for any single receptor this change ran parallel in size and time with the alteration in intratracheal pressure (and hence probably with bronchial tone) suggested that the two were causally related. This was supported by the fact that, in four instances, atropine blocked the action of acetylcholine.

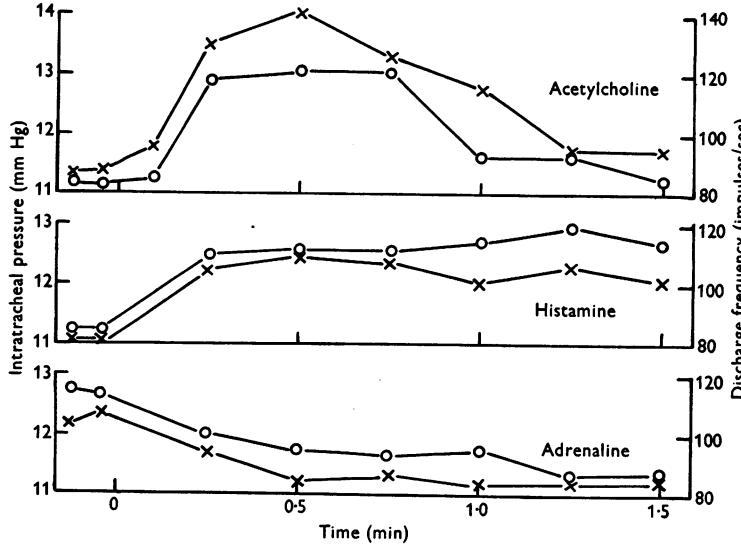

Fig. 3. The time relationships of the actions of acetylcholine (150 μg), histamine (200 μg) and adrenaline (50 μg) on the discharge of a single pulmonary stretch receptor and on intratracheal pressure. — × —, peak discharge frequency of the receptor at the height of phasic constant volume inflations; —○—, peak intratracheal presssure at the same instants. Abscissa: time in minutes, reckoned from the times of injection of the drugs. There was a 5 min interval between the injections of acetylcholine and histamine; the adrenaline was administered while the response to histamine was still apparent.

These observations might have been attributed to changes in the expiratory volume (functional residual air) of the cats, which would alter total lung volume at the peak of inflation. This was excluded by recording changes in expiratory volume by means of the body plethysmograph; they were often too small to measure, and never greater than 5 ml. For some receptors impulse frequency/lung volume curves were drawn before and after administration of the drugs; Fig. 5 shows two such curves, one before and one after injection of 200 μg acetylcholine. With a 25 ml. inflation the peak frequency of the receptor increased from 40 to 52 impulses/sec after the drug; the increase in expiratory volume which would have produced an equivalent change was about 14 ml. For a 100 ml. inflation the increase in discharge frequency after acetylcholine

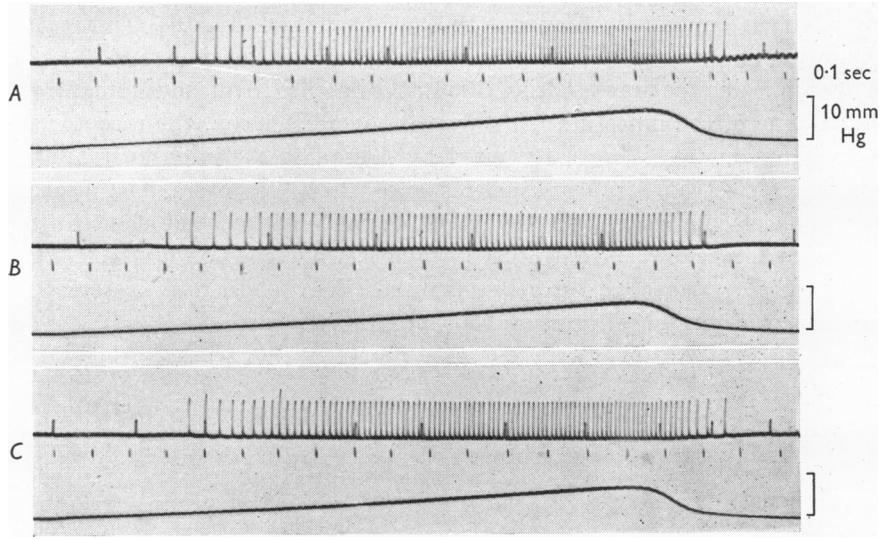

Fig. 4. The action of adrenaline on a pulmonary stretch receptor shown as in Fig. 1. Between *A* and *B* 100 μg of adrenaline was injected intravenously. The discharge of the receptor decreased, and the intratracheal pressure was less (constant volume inflation). In *C* the effect of the drug has worn off.

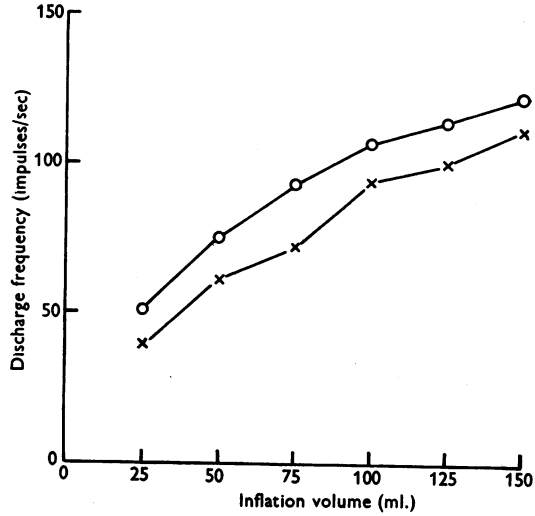

Fig. 5. Volume response curves of a pulmonary stretch receptor before (— × —) and after (—○—) administration of 200 μg acetylcholine.

(94–107 impulses/sec) would require an increased expiratory volume of 40 ml. The increase in expiratory volume measured from the plethysmograph record was about 2 ml. and was constant throughout the test inflations.

Three receptors whose discharge frequency was increased by acetylcholine abruptly ceased activity towards the end of inflation (Fig. 6). During each expiration the sensory unit recovered. This is somewhat similar to the effect of over-inflating the lungs (Adrian, 1933); the impulse frequency increases with the volume of the lungs until, with severe overdistension, the receptor suddenly 'cuts-out'; this was attributed by Adrian to a Wedensky inhibition. Histamine also caused an unusual response in two receptors. The discharge rate of these endings was first increased during inflation, and then the peak frequency fell below the control level while the frequency of discharge during the expiratory pause was greatly enhanced (Fig. 7). In both instances the increase in intratracheal pressure was exceptionally large.

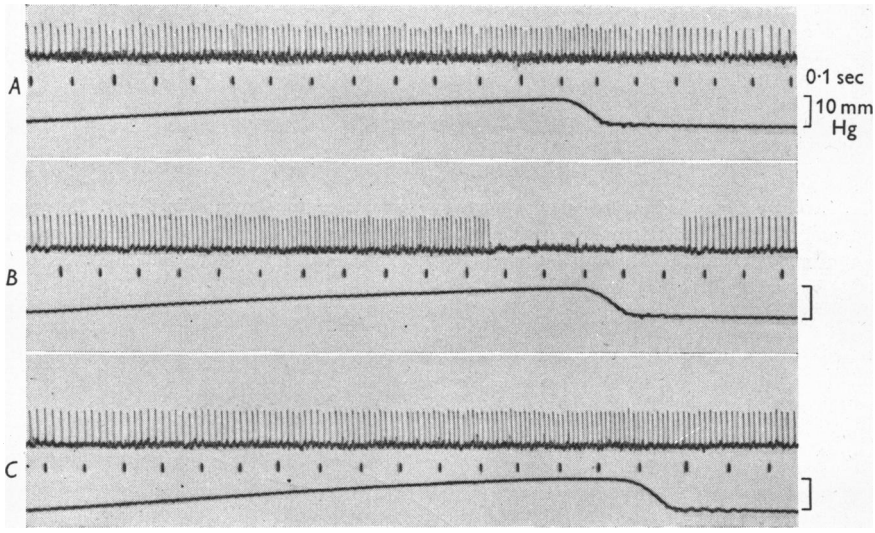

Fig. 6. An atypical response of a pulmonary stretch receptor to acetylcholine (150 μg injected between *A* and *B*), shown as in Fig. 1. The drug caused an increased discharge by the receptor early during inflation, but the activity ceased as the peak of inflation was reached (*B*); in *C* both the increased discharge and the cessation of activity have disappeared.

The drugs were also injected during maintained distension of the lungs. The lungs were inflated until the receptor was excited to a continuous discharge, the tracheal cannula was closed and the drug then injected. With very slowly adapting endings the discharge rate was nearly constant before the injection was made; with more rapidly adapting receptors the action of the drugs was seen on the spontaneously declining discharge. Observations with four drugs are included in Table 1. With one exception acetylcholine caused a decrease in the discharge rate of the receptors. This usually lasted a few seconds and started 5–10 sec after the injection. In three instances there was a short com-

plete inhibition. The other drugs yielded inconstant results. The two endings with histamine were those mentioned in the paragraph above. There was no measure of bronchial tone in these experiments, but the same quantities of the drugs caused normal changes in bronchial tone both before and after the experiments.

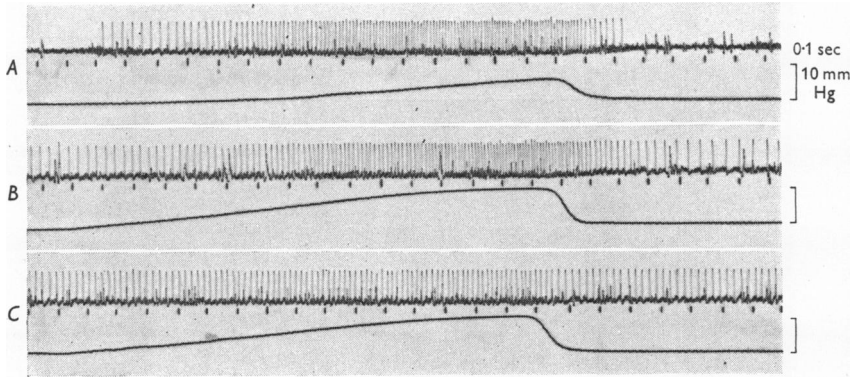

Fig. 7. An atypical response of a pulmonary stretch receptor to histamine (500 μg injected between *A* and *B*), shown as in Fig. 1. The drug first caused increased activity by the receptor (*B*), but then the discharge rate at the peak of inflation fell considerably (*C*), although the discharge rate during the expiratory pause was increased. Note the great increase in intratracheal pressure during inflation.

TABLE 1. The changes in activity of pulmonary stretch receptors in response to bronchomotor drugs. The receptors were stimulated by a maintained inflation of the lungs, and the drugs injected intravenously. The maximum change in impulse frequency after the injection is expressed as a positive or negative percentage; −100% corresponds to cessation of firing. In calculating the percentages the impulse frequency which showed maximum change after the drug was compared with the average of the impulse frequencies before the injection and that after the response to the injection was complete.

	Percentage change in frequency of discharge after			
Receptor	Eserine	Acetylcholine	Histamine	Adrenaline
1	71	—	82	−28
2	11	—	—	0
3	4	—	60	—
4	−15	−100	—	0
5	—	23	—	0
6	—	−8	—	−57
7	—	−55	—	—
8	−6	−100	—	0
9	0	−14	—	—
10	0	−15	—	—
11	—	−100	—	194
12	—	−20	—	—

Action of veratridine

Veratridine causes pulmonary stretch receptors to discharge continuously (Dawes *et al.* 1951); the necessary intravenous dose is about 10–20 μg for an adult cat. If the receptors lie in the intrapulmonary bronchi they may receive

a large proportion of their blood supply from the bronchial arteries; the effective doses of veratridine when injected into the bronchial circulation were therefore determined and are shown in Table 2. The two central columns show

TABLE 2. Doses of veratridine needed to sensitize pulmonary stretch receptors. The doses of veratridine injected into the perfused bronchial circulation and external jugular vein respectively are given. The 'effective' doses are the smallest which caused sensitization by each route; the 'ineffective' are the largest which caused no change in receptor activity.

	μg of veratridine into			
	Bronchial artery		External jugular vein	
Fibre	Ineffective	Effective	Ineffective	Effective
A	—	1	2·5	5
B	—	1	10	—
C	—	1	10	—
D	—	1	10	—
E	1	2·5	5	10
F	1	2·5	10	—
G	2·5	5	12·5	—
H	—	5	5	10
I	—	10	10	20
J	5	12·5	12·5	—
K	—	50*	100*	—
L	—	100*	100*	—
M	—	150*	150*	—

* Veratrine.

the smallest effective doses of veratridine when injected into the bronchial circulation, and the largest ineffective doses given intravenously. For thirteen receptors smaller doses caused sensitization via the bronchial arterial route, and in three experiments (B, C and D) the difference was at least tenfold. Nine endings (not included in Table 2) did not show any difference in sensitivity; eight of them had a high threshold to veratridine by both routes and were not studied further when test doses (of 10–25 μg veratridine) proved ineffective. Fig. 8 shows the effect of 1 μg veratridine injected into the bronchial circulation compared with 5 μg given intravenously (receptor A); there is a continuous high-frequency discharge after the former injection, but only a minimal sensitization after the latter.

The drug concentrations at the receptors were not known. There was a large dead space in the aortic segment and cannula, and the latency between injection and sensitization was usually over 30 sec for the bronchial arterial route; this dead space would lower considerably the blood concentration of veratridine. In addition, the aortic segment supplied other structures as well as the bronchi; a proportion of the drug would not reach the bronchi, and the difference in sensitivity between the two routes may have been greater than it seemed.

Bronchial tone and the Hering-Breuer inflation reflex

Since bronchoconstriction (as judged by changes in intratracheal pressure) was associated with an increased response of the pulmonary stretch receptors

to phasic constant volume inflations, the action of bronchomotor drugs on the Hering-Breuer inflation reflex was determined. Acetylcholine was not used since its effect was too transient; the results with the other drugs are summarized in Fig. 9. An enhancement of the inflation reflex was produced by drugs which caused an increase in intratracheal pressure (bronchoconstriction) and depression of the reflex by drugs which lowered intratracheal pressure. Interpretation of the results was complicated because the drugs often

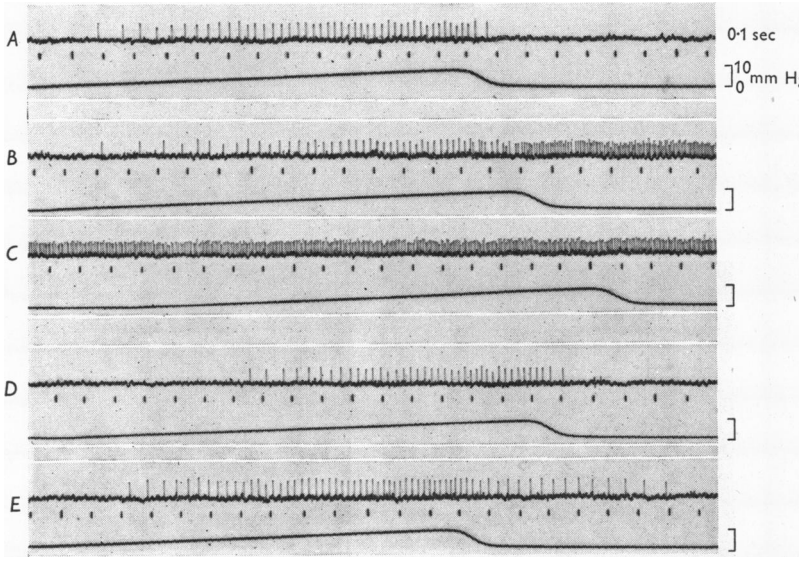

Fig. 8. Sensitization of a pulmonary stretch receptor by veratridine administered into the bronchial circulation (*A*, *B* and *C*) and intravenously (*D* and *E*). Traces as in Fig. 1. All inflations of the same volume. Between *A* and *B*, 1 μg veratridine was injected into the perfused bronchial arteries; *B* and *C* (continuous) show the great sensitization which resulted. Between *D* and *E*, 5 μg of the drug were given intravenously, with a slight change in activity only. 15 min between *C* and *D*.

caused changes in the respiratory cycle; these could not always be eliminated but doses were chosen as small as possible in the hope of altering bronchial tone with little effect on the respiratory cycle. In Fig. 9 only those results are included in which there was no change in expiratory, tidal and minute volumes or in which the change in the inflation reflex was much larger than any alteration of respiration. This made it less likely that the changes in the reflex were due to direct action of the drugs on the respiratory centre. Fig. 10 illustrates two experiments. In the first, a 50 ml. inflation caused a large rise in intratracheal pressure; the next inspiratory effort during this artificial inflation caused a fall in intratracheal pressure and at this instant the trachea was opened to atmospheric pressure; thus the duration of the artificially raised

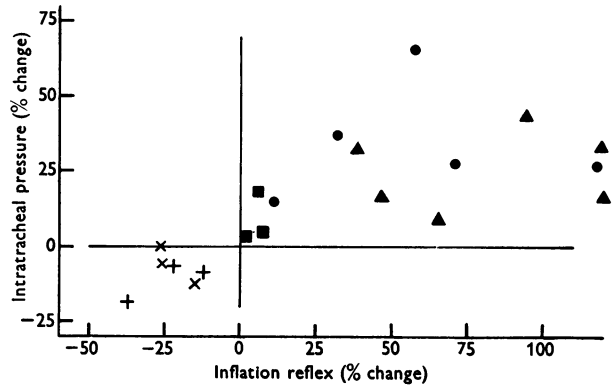

Fig. 9. The action of bronchomotor drugs on the Hering-Breuer inflation reflex. Ordinate: percentage change in intratracheal pressure on a large positive pressure inflation of the lungs. Abscissa: percentage change in the inflation reflex elicited by the same inflations. ■, eserine; ●, histamine; ▲, pilocarpine; ×, adrenaline; +, atropine. Each point corresponds to a single experiment.

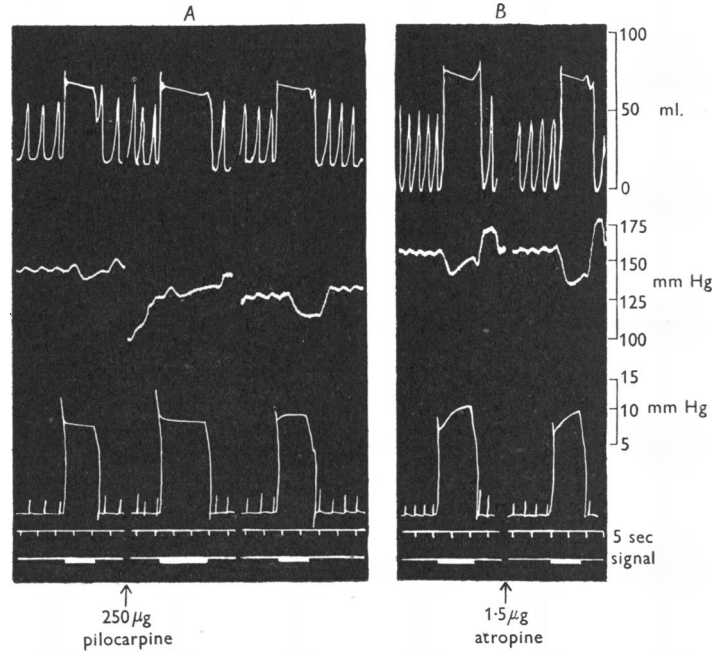

Fig. 10. Cat, 3·3 kg. The actions of pilocarpine (*A*) and atropine (*B*) on the Hering-Breuer inflation reflex. Uppermost trace: lung volume changes. Middle trace: systemic blood pressure. Lowest trace: intratracheal pressure. The inflation reflex was elicited by artificial inflations of the lungs, indicated by the large rises in intratracheal pressure and by the signal marks. The durations of the artificial inflations indicate the time during which respiration was inhibited by the inflation reflex. Pilocarpine caused an increase in the respiratory pause due to inflation of the lungs, the effect wearing off after some minutes (third signal mark). Atropine caused a decrease in the respiratory pause due to inflation. For further description see text. The mountings have been retouched.

intratracheal pressure (9 sec) compared with the previous respiratory interval (5 sec) is a measure of the delay in the respiratory cycle caused by the Hering-Breuer reflex. After administration of pilocarpine there was a small decrease in expiratory volume and an increase in respiratory rate and in minute volume (interval 3·5 sec), but a 50 ml. inflation caused a longer delay (14 sec) than previously. Thus in spite of a respiratory stimulation by pilocarpine, inflation of the lungs was more effective in slowing the respiratory cycle than before the drug. The second experiment, illustrated in Fig. 10, shows a depression of the Hering-Breuer inflation reflex by atropine, although the drug caused slight respiratory inhibition, with no change in expiratory volume.

As with the experiments on stretch receptors, those drugs which cause bronchoconstriction gave more consistent results than those which cause bronchodilatation; the latter usually diminished the reflex response to inflation only if the resting bronchial tone had previously been increased by eserine or pilocarpine, so that the drugs could produce a substantial decrease in resistance to inflation. In two cats in which large doses of histamine and pilocarpine were used an immediate enhancement of the inflation reflex was followed by a depression which lasted several minutes.

DISCUSSION

In the cat the pulmonary stretch receptors were not destroyed by stripping the overlying pleura. Weidmann *et al.* (1949) have concluded that in the rabbit the receptors lie in the pleura; they found that many of them were inhibited by 2% procaine solution painted on the lung, while intravenous injections of procaine were ineffective. However, the depth of penetration of the drug when applied to the pleura was not measured and the intravenous procaine must have reached all parts of the lung including the pleura. Histological evidence is against the pleural site. The 'encapsulated receptors' of McLaughlin (1933) were described as non-nervous structures by Larsell (1935). Those pleural receptors which have been observed are infrequent and are connected to small nerve fibres (Larsell, 1922); the pulmonary stretch fibres are relatively large (Paintal, 1953). A species difference is possible, but does not seem likely since the receptors behave in identical manner in cat and rabbit (as judged by records of the activity of vagal nerve fibres). The pleura of both species is thin and serous, unlike the fibrous layer of larger animals.

In considering how bronchomotor drugs can influence the activity of pulmonary stretch receptors, several possibilities can be eliminated.

(1) The drugs might be acting *directly* upon the sensory endings; but it is unlikely that all six drugs have a direct action upon the receptors. In addition, acetylcholine increased the discharge of the receptors on phasic positive pressure ventilation, but *inhibited* the continuous discharge of the endings due to a maintained inflation; this is difficult to explain by a direct drug action.

(2) The changes in receptor activity might be secondary to cardiovascular effects; but there was no constant relationship between the two. For example, an increase in the discharge of the receptors was seen both after pilocarpine which usually caused a large secondary increase in systemic blood pressure and heart rate, and after histamine and acetylcholine which produced a fall in blood pressure and heart rate. Changes in the pulmonary vascular bed were not recorded, but Bülbring & Whitteridge (1945) have shown that these have little effect on the activity of pulmonary stretch receptors in cats with opened chests.

(3) It is improbable that mucus secretion caused the transient increase in receptor activity seen after acetylcholine, for the removal of any mucus would be slow (in the absence of the cough reflex); and this could explain neither the actions of adrenaline and atropine, nor the changes in discharge on injection of the drugs during maintained inflation of the lungs.

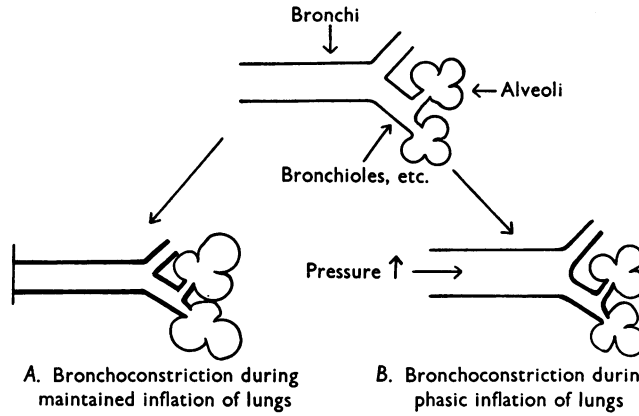

Fig. 11. Diagrams of the air passages and alveoli to explain suggested mode of action of bronchomotor drugs on the pulmonary stretch receptors. For description see text.

(4) Changes in expiratory volume might have accounted for some of the results, but this has been eliminated.

A direct relationship between bronchial tone and receptor activity seems the most likely explanation, since for any receptor the timing and size of the change in discharge frequency ran parallel to the alteration in resistance to inflation. Any consideration of these results must account for the fact that during constant volume inflations of the lungs, drugs that caused bronchoconstriction *enhanced* the Hering-Breuer inflation reflex and pulmonary stretch receptor activity, while during maintained inflation of the lungs acetylcholine *reduced* the receptor response. A possible explanation is illustrated in Fig. 11. During maintained inflation acetylcholine would constrict the entire bronchial tree, with a displacement of gas into the alveoli. Under these

conditions stretch endings in the airways might be less active. With phasic inflations, however, there is an increased peak pressure, and this might cause a greater transmural pressure and distension of the larger bronchi (in spite of the muscular contraction in their walls) concurrently with a bronchiolar constriction; this assumes that the main increase in resistance to inflation occurs in the smaller air passages. There is no direct evidence for such an increase in diameter of the larger bronchi, but in the absence of a more likely explanation, this site is suggested for many of the 'pulmonary stretch receptors'.

Some results may be due to unequal changes in the lungs; for example the experiment illustrated in Fig. 7 is consistent with almost complete blockage of air entry to a partially distended pulmonary unit, so that there is a raised resting discharge rate with only a small increase on inflation. Similarly, the increased expiratory discharge in Fig. 6 could be due to hindered deflation of the appropriate unit. That only five out of twenty-four receptors had behaviour of this type suggests that unequal ventilation of the respiratory units concerned was uncommon; and the uniformity of experiments on the Hering-Breuer inflation reflex supports this view.

The presence of smooth muscle spindles in the bronchi with 'large' afferent nerve fibres, has been described by Larsell (1921) and by Elftmann (1943). From their situation the receptors might be expected to show many of the properties described in this paper, including a relative sensitivity to drugs injected into the bronchial arterial circulation. Stretch receptors in the *extrapulmonary* bronchi and the trachea have many properties in common with the pulmonary stretch receptors. Both are slowly adapting, and both inhibit inspiratory activity (Widdicombe, 1954*a*, *b*). One difference is that the great majority of the former are stimulated by deflation of the air passages, which is unusual with pulmonary stretch receptors.

If the stretch receptors lie in the intrapulmonary bronchi two further observations may be explained. Knowlton & Larrabee (1946) have shown that after an over-distension of the lungs the response of the receptors to a given volume inflation of the lungs is reduced (fig. 16 of their paper). This is accompanied by a fall in resistance to inflation of the lungs, and in intratracheal pressure. They suggested that the endings have adapted to the over-inflation; it seems more probable that the lowered inflation pressure stretches the walls of the larger bronchi less than before, since the resistance to distension of the alveoli and bronchioles has decreased. Aviado, Li, Werner, Schmidt, Turnbull, Peskin, Hess & Weiss (1951) have shown that veratridine causes exaggerated reflex respiratory responses when it is injected into the pulmonary veins with retrograde perfusion through the lungs, compared with injection into the pulmonary artery with normal direction of flow; the pulmonary stretch receptors are sensitive to veratridine (Dawes *et al.* 1951), and if they receive a large

proportion of their blood supply from the bronchial arteries, and the latter drain ultimately into the pulmonary veins, then a retrograde injection may reach a greater number of receptors by a more direct route than an injection into the pulmonary arteries.

While it has been concluded that the majority of the stretch receptors lie in the intrapulmonary bronchi, this site is clearly not exclusive. The pulmonary stretch receptors have been studied only by recording activity from afferent nerve fibres, and considerable variations in adaptation rate, response to deflation, fibre size, cardiac modulations of rhythm, and responses to drugs have been found. In the absence of investigations more directly applied to the receptors themselves it would be dangerous to assume complete uniformity either in location or in reflex activity.

SUMMARY

1. Experiments have been carried out to localize the pulmonary stretch receptors in the cat.

2. Removal of the visceral pleura did not destroy the great majority of endings, and it was concluded that they were not pleural receptors.

3. Drugs which altered bronchial tone (as measured by changes in resistance to inflation of the lungs) influenced the responses of the receptors to phasic constant volume inflations with positive pressure; bronchoconstriction was accompanied by an increased discharge from the receptors, and bronchodilatation by a reduced discharge.

4. Endings stimulated by a maintained inflation of the lungs were inhibited by acetylcholine.

5. The Hering-Breuer inflation reflex was more active after administration of drugs known to cause bronchoconstriction, and less active after drugs known to cause bronchodilatation.

6. Smaller doses of veratridine sensitized the pulmonary stretch receptors when injected into the bronchial arterial circulation than into the pulmonary arteries.

7. Possible explanations of these results are discussed. It is concluded that the activity of pulmonary stretch receptors is related to bronchial tone, and that many of the endings lie in the intrapulmonary bronchi.

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