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REFLEX BRONCHOMOTOR RESPONSES TO STIMULATION OF RECEPTORS IN THE REGIONS OF THE CAROTID SINUS AND ARCH OF THE AORTA IN THE DOG AND CAT

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It has been shown by many authors (Hering, 1927; Koch, 1931; Heymans, Bouckaert & Regniers, 1933; Schweitzer, 1937) that stimulation of the baroreceptors, by raising the pressure in the carotid sinus, causes, reflexly, a fall of blood pressure and a diminution of heart rate. The latter effect is brought about by an increase of vagal tone.

Other reflex effects have also been described. Schweitzer (1934) found that stimulation of the baroreceptors by raising the intrasinusal pressure in the dog produced an increase in tone and motility of the stomach. In the rabbit, bilateral carotid occlusion causes inhibition of motility of the small intestine (Kisch, 1931), whereas stimulation of the aortic nerve causes an increase of peristalsis (Bayliss, 1893). Koch (1932) has described reflex pupillary constriction on stimulation of the baroreceptors.

These experiments indicate that baroreceptor stimulation causes not only a generalized increase in vagal tone, but also an increase in activity throughout the parasympathetic system (Heymans *et al.* 1933; Schweitzer, 1937).

Since the bronchial musculature is also innervated by the vagus nerves (Einthoven, 1892; Dixon & Brodie, 1903; Dixon & Ransom, 1912) it might be expected that reflex changes in bronchial calibre would be brought about by altering the intrasinusal pressure. Houssay & Orias (1934*a*, *b*) investigated such reflexes and found that electrical stimulation of the carotid sinus nerve in dogs caused slight bronchoconstriction or occasionally bronchodilatation, whereas raising the intrasinusal pressure had little or no effect. They concluded that whereas it is easy to produce cardiovascular reflexes from the carotid sinus, it is difficult to elicit bronchomotor responses, and that, when they do occur, they are very weak.

Their method of measuring bronchomotor effects (Jackson, 1917) is open to the criticism that not only are changes in lung volume being recorded, but also concomitant changes in volume of other intrathoracic viscera.

This problem has therefore been investigated in cats and in dogs, and extended to include a study of the reflexes initiated from the receptors in the region of the arch of the aorta. Some of our observations have been reported (Daly & Schweitzer, 1951).

METHODS

Dogs, varying in weight from 2·7 to 8·0 kg., and cats, from 1·8 to 4·4 kg., were used in these experiments. The animals were anaesthetized with either chloralose (0·08–0·11 g./kg. body weight, intravenously) or pentobarbitone sodium (nembutal) (35–45 mg./kg. body weight, intraperitoneally). In some experiments, cats were decerebrated under ether anaesthesia.

The carotid sinus nerve was prepared for stimulation using an approach similar to that described by Euler, Liljestrand & Zotterman (1939). The aortic nerves were isolated in the neck at the site of their junction with the superior laryngeal nerve and with the vagus. Small shielded platinum wire electrodes mounted in perspex were used for stimulation of these nerves. A square wave electronic stimulator which allowed independent control of the voltage, frequency and the pulse duration of the stimulus was used.

In some dog experiments, the carotid sinus was isolated from the general circulation by ligating all branches of the common carotid artery and perfused with defibrinated ox blood by means of a Dale-Schuster pump (Dale & Schuster, 1928). The blood entered the sinus through a cannula in the common carotid artery and left through a cannula inserted into the external carotid artery. The outflow tube was fitted with a screw clip which allowed the resistance in the perfusion circuit to be altered. The pressure in the sinus was recorded from a mercury manometer connected to a side-arm of the inflow tubing. The blood was equilibrated with 95% O_2 and 5% CO_2 by means of a Hooker (1915) and Drinker *et al.* (1922) type of oxygenator in the perfusion circuit.

An alternative method consisted of isolating the carotid sinus from the general circulation by ligating all branches of the common carotid artery and finally tying off the common carotid itself. A glass cannula was then introduced into the common carotid artery and connected to a bottle containing 0·9% sodium chloride solution, which allowed rapid changes in pressure to be effected (Moissejeff, 1926; Koch, 1931; Schweitzer, 1937). The pressure in the sinus was recorded from a manometer connected to the side-arm of the cannula.

The chemoreceptors of the carotid body were stimulated by lobeline hydrochloride (E. Martindale) or sodium cyanide (B.D.H.) injected into the inflow tubing of the isolated perfused carotid sinus or injected via a cannula inserted into the superior thyroid artery. In the latter preparations the external carotid, internal carotid and sometimes the lingual arteries were ligated so that a high concentration of the drug would pass through the carotid body. The chemoreceptors of the aortic body were stimulated by these drugs injected via a catheter inserted into the left ventricle (Comroe, 1939). The position of the catheter was verified by post-mortem examination.

Bronchomotor effects were measured by recording with a small bell spirometer the volume of the tidal air of the animal under negative pressure ventilation with the chest of the animal opened in the mid-sternal line. The apparatus used was similar to that described by Daly & Mount (1951). Both phrenic nerves were cut so as to minimize the mechanical effects of diaphragmatic movements on the lungs.

A certain degree of bronchial tone is necessary for the demonstration of bronchodilator responses (Dixon & Brodie, 1903). In most experiments, the tone was found to be adequate; in a few, however, it was necessary to increase it artificially by the injection intravenously of eserine sulphate (B.D.H.), 0·1 mg./kg.

Blood pressure was recorded from the femoral artery with a mercury manometer. Changes in heart rate were measured by the method described by Daly & Schweitzer (1950), using a Gaddum drop timer (Gaddum & Kwiatkowski, 1938).

Heparin (Roche Products, Ltd.) was used as an anticoagulant in some experiments. Other drugs used in this investigation included: adrenaline chloride solution, 1 in 1000 with 0·5% chloretone

(Parke Davis and Co.), atropine sulphate (B.D.H.) and D-tubocurarine chloride (Burroughs Wellcome and Co.).

RESULTS

Electrical stimulation of the carotid sinus nerve

Cats

Pentobarbitone anaesthesia. Preliminary experiments made under nembutal anaesthesia showed that electrical stimulation of the carotid sinus nerve caused a fall of systemic blood pressure, cardiac slowing and changes in the calibre of the bronchi; in seven of eight experiments, bronchodilatation occurred, in the other, bronchoconstriction (Table 1). These responses also occurred in preparations in which the contralateral carotid sinus nerve had been cut.

TABLE 1. The effect of the anaesthetic upon the initial bronchomotor response to carotid sinus nerve stimulation in cats

	No. of experiments	Bronchomotor response: Broncho-constriction	Bronchomotor response: Broncho-dilatation	Bronchomotor response: Broncho-constriction followed by dilatation
Pentobarbitone	8	1	7	0
Decerebrate	6	4	0	2
Chloralose	5	4	1	0

In five of the experiments in which bronchodilatation was observed, the effect of eserine was investigated. In two of them there was an increase in the response, while in three, the subsequent effect of stimulation of the sinus nerve was either unchanged or bronchoconstriction resulted. Fig. 1 is representative of this type of experiment and shows that carotid sinus nerve stimulation may cause either bronchoconstriction or bronchodilatation; the interval between the injection of eserine and the subsequent observations was approximately 2½ hr. It is impossible to state in this instance whether the responses observed were conditioned by the preceding eserinization of the animal. However, in other experiments, similar results were obtained a few minutes after an intravenous injection of eserine. It will be noted that the last effect was produced by a stimulus of different frequency and pulse duration from the previous two, and it might be wondered whether the direction of the bronchomotor response is dependent upon the nature of the stimulus applied to the nerve. In several experiments carried out to elucidate this point, no such correlation has been found.

It must be pointed out that the apparently enhanced bronchodilator response observed in two experiments after eserine does not necessarily involve a cholinergic mechanism. Dixon & Brodie (1903) found that in anaesthetized or decerebrate animals, there was little or no bronchial tone, and that bronchodilator responses could best be demonstrated by first increasing the tone artificially

by the injection of muscarine or pilocarpine. It is therefore possible that eserine, by increasing the initial bronchial tone, creates conditions favourable for the demonstration of the bronchodilator effects of subsequent carotid sinus nerve stimulations.

Fig. 1 also shows that some of the blood pressure responses were of the same order of magnitude, so that the direction of the bronchomotor response is not in any way dependent upon this factor in this type of experiment.

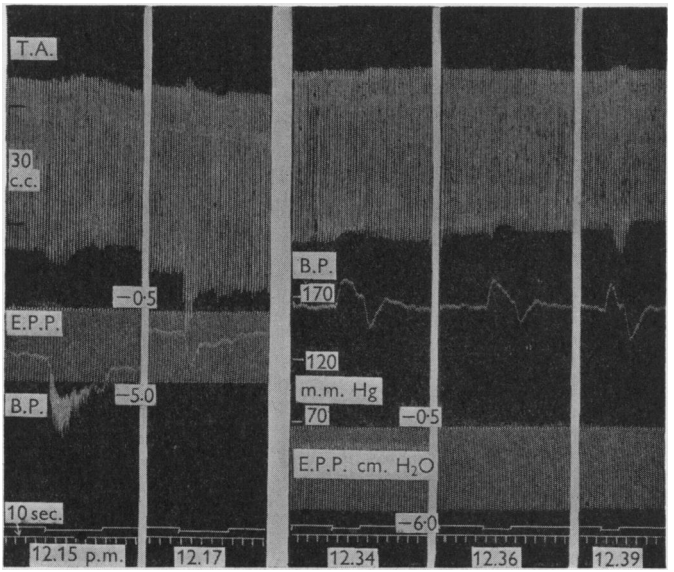

Fig. 1. Cat, ♂, 3·4 kg. Pentobarbitone. Eserine 0·25 mg. at 12.05 p.m. 12.15 p.m., right carotid sinus nerve stimulation, 6 V., 0·05 msec., 100 cyc./sec.; 12.17 p.m., right carotid sinus nerve stimulation, 6 V., 0·02 msec., 100 cyc./sec.; 12.34 p.m., left carotid sinus nerve stimulation, 4 V., 0·05 msec., 100 cyc./sec.; 12.36 p.m., left carotid sinus nerve stimulation, 4 V., 0·05 msec., 100 cyc./sec.; 12.39 p.m., left carotid sinus nerve stimulation, 5 V., 0·1 msec., 70 cyc./sec.

Records in this and in subsequent figs.: T.A. = tidal air volume (inspiration downwards); E.P.P. = extrapulmonary pressure; S.P. = carotid sinus perfusion pressure; B.P. = systemic blood pressure; H.R. = heart rate.

Decerebrate. Since carotid sinus nerve stimulation can cause either bronchoconstriction or bronchodilatation, it was necessary to see whether the direction of the response depended upon the anaesthetic, as does the blood pressure response in cats (Neil, Redwood & Schweitzer, 1949*a*). Experiments were therefore made on decerebrate cats. In four preparations, carotid sinus nerve stimulation caused bronchoconstriction. The effects after giving eserine were either potentiation of the bronchoconstriction, bronchodilatation (Fig. 10), or a diphasic response—bronchoconstriction followed by bronchodilatation. All three types

of response were seen in three of the experiments. In a further two experiments, the initial response to stimulation of the carotid sinus nerve was a diphasic one.

Chloralose anaesthesia. In cats under chloralose anaesthesia, stimulation of the carotid sinus nerve caused bronchoconstriction in four of five experiments, and bronchodilatation in one (Table 1).

It is apparent that in cats decerebrated or under chloralose anaesthesia, conditions favour bronchoconstrictor responses to carotid sinus nerve stimulation, whereas under pentobarbitone anaesthesia, bronchodilator responses predominate. There were opportunities, therefore, of investigating the nervous pathways through which these effects are mediated.

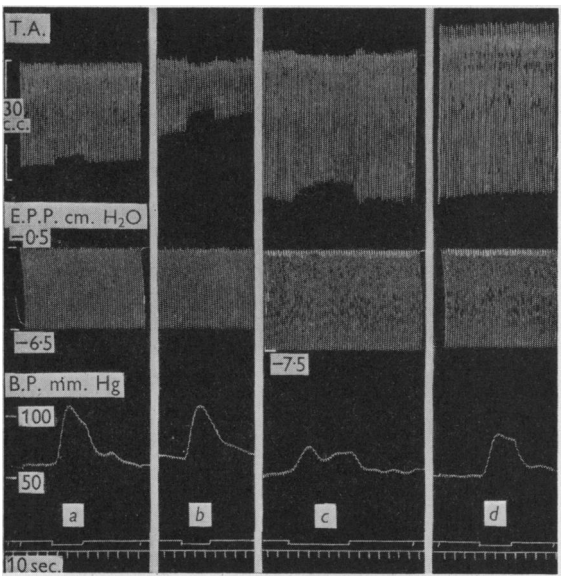

Fig. 2. Cat, ♀, 2·3 kg. Chloralose. *a*, *b*, *c* and *d*, stimulations of right carotid sinus nerve, 8 V., 0·1 msec., 100 cyc./sec. Between *a* and *b*, eserine 0·1 mg. Between *c* and *d*, atropine 0·5 mg. The extrapulmonary pressure was increased between *b* and *c*.

Bronchoconstrictor responses. The bronchoconstrictor response is potentiated by eserine (five experiments) and abolished by atropine (four experiments) (Fig. 2). It is also abolished by section of both cervical vagus nerves. We therefore conclude that this type of response is mediated through the vagus nerves.

Bronchodilator responses. Evidence as to the pathway through which the bronchodilator responses to carotid sinus nerve stimulation are mediated has been more difficult to obtain. Owing to the absence of any bronchial tone in some experiments, it had to be increased artificially by the injection of eserine. In several experiments, stimulation of the carotid sinus nerve caused a slight

bronchodilatation, but after eserine, the same stimulus produced either bronchodilatation or bronchoconstriction, although the tone had been increased. The probable explanation of this phenomenon is that eserine, although increasing the bronchial tone, also potentiates the bronchoconstrictor response; the latter effect may be, under these experimental conditions, the more powerful, and therefore mask the appearance of the bronchodilator effect.

However, in four experiments in which consistent bronchodilator effects of carotid sinus nerve stimulation were obtained, the response in one of them was abolished by cutting the sympathetic supply to the lungs, involving section, on both sides, of the rami communicantes, T_1 and T_2, and of the sympathetic chain immediately below T_2. In this experiment, the animal was adrenalectomized, and therefore the initial bronchodilator responses could not have been due to the secretion of adrenaline. Although adrenaline can be secreted reflexly from the suprarenal medulla in response to a lowered intrasinusal pressure (Heymans, 1929), and probably also in response to chemoreceptor stimulation (Gernandt, Liljestrand & Zotterman, 1946), the part it plays in these responses has not been determined. In the second experiment, sympathetic denervation of the lungs caused only a slight reduction in the bronchodilator response. It seemed unlikely that this was due to the secretion of adrenaline as there was a latent period of less than 5 sec. between the beginning of the stimulus and the onset of the response. This was confirmed in the third experiment in which the animal was adrenalectomized; the bronchodilator response in this case was unaffected by bilateral sympathetic denervation of the lungs. In one further experiment, sectioning the sympathetic nerves resulted in the bronchodilator response being converted to bronchoconstriction.

We are, at present, unable to give any satisfactory explanation of these results. If the persistence of the bronchodilator responses after cutting the sympathetic nerves is due to a decrease in vagal tone, then it is difficult to correlate this with the fact that there was a concomitant fall of blood pressure and bradycardia. It may be that the reflex fall in systemic blood pressure, produced by carotid sinus nerve stimulation, decreased the vagal tone through an action on the baroreceptors which had not been denervated, viz. those in the arch of the aorta. Another possible explanation may be that the sympathetic denervation of the lungs was not complete, for it has been found that some fibres issue from the ganglia of the sympathetic chain ($T_1 - T_4$) and proceed medially to the lung hilum (Ionescu & Enachescu, 1928). Although our experiments in dogs support the view that the bronchodilator response is mediated through the sympathetic system, further evidence must be obtained before a final interpretation of these results can be made.

Dogs

In three dogs under chloralose anaesthesia, stimulation of the carotid sinus nerve invariably produced a fall of arterial blood pressure, bradycardia and bronchoconstriction. In one experiment bronchodilatation was observed, and in another, the effect was diphasic, bronchoconstriction followed by bronchodilatation. These results confirm those of Houssay & Orias (1934*a*, *b*).

Similarly, stimulation of the carotid sinus nerve under pentobarbitone anaesthesia produced a fall of systemic blood pressure, bradycardia and bronchoconstriction. No evidence of bronchodilatation was observed, and in this respect, the results differ from those obtained in the cat.

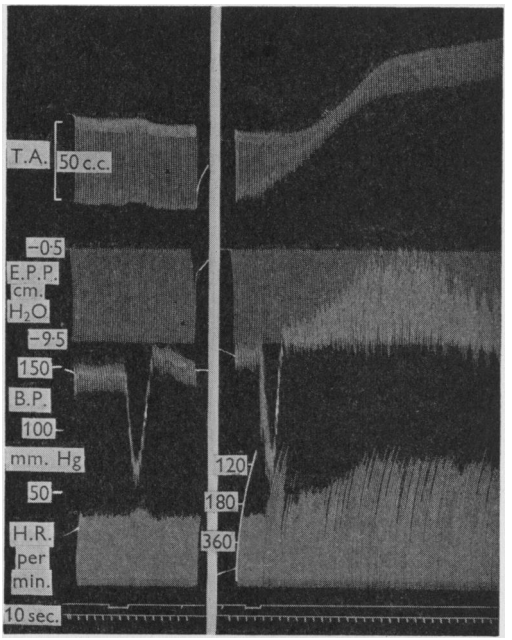

Fig. 3. Dog, ♂, 7·75 kg. Chloralose. Stimulation of the right carotid sinus nerve, 4 V., 0·5 msec., 50 cyc./sec., before and after eserine, 1·0 mg.

No opportunity was available, therefore, for investigating the nervous pathway through which the bronchodilator response on sinus nerve stimulation is mediated; some evidence on this point has been obtained using other techniques.

The bronchoconstrictor response to stimulation of the carotid sinus nerve has been shown to be mediated through the vagus nerves. It is potentiated by eserine (Fig. 3), abolished by atropine (two experiments) and also abolished by section of both cervical vagosympathetic nerves. Further experiments have shown that these responses can occur in preparations in which the contralateral carotid sinus nerve has been sectioned. The experiment from which Fig. 3 is

taken is of particular interest. The reduction of the tidal air volume due to carotid sinus nerve stimulation was so great that the oxygen uptake by the animal had been hindered, as indicated by the upward slope of the limiting lines of the tidal air record. The gradual rise of blood pressure and slowing of the heart rate after the end of the stimulus was almost certainly due to asphyxia; this chemical stimulus to the chemoreceptors was, apparently, not of sufficient strength to elicit bronchodilatation against the artificial background of eserine (*vide infra*). This potentiating action of eserine may be, in part, of central origin. We have, at present, no evidence which would enable us to discriminate between the central and peripheral effects of this drug in respect of these responses.

Electrical stimulation of the aortic nerve

It is generally held that the carotid sinus and aortic nerves form a functional entity. Consequently, the effects of stimulation of the aortic nerves have been examined in cats and dogs.

Cats

Under chloralose or pentobarbitone anaesthesia, stimulation of the left or right aortic nerve caused a rise in systemic blood pressure (cf. Neil *et al.* 1949*b*), and bronchoconstriction (three experiments). In one further experiment under chloralose anaesthesia, however, bronchodilatation resulted. These responses can also occur in animals after denervation of both carotid sinuses. The bronchoconstrictor response is still observed after section of the ipsilateral cervical vagus nerve at a level caudal to the electrode, so that it is not due to current spreading to the vagus nerve (Fig. 4*b*). It also precludes the possibility that the bronchomotor responses, observed on aortic nerve stimulation, might have been caused by way of an axon reflex from fibres in the aortic nerve making connexion with efferent fibres of the vagus. The bronchoconstrictor response is potentiated by eserine and abolished by atropine (Fig. 4). It is also abolished by section of both cervical vagus nerves.

Dogs

Similar results have been obtained in dogs under chloralose anaesthesia. Stimulation of the aortic nerve causes a fall in systemic blood pressure, bradycardia and bronchoconstriction. The bronchoconstrictor response occurs after section of the ipsilateral cervical vagosympathetic nerve at a level caudal to the electrode. It is potentiated by eserine, and abolished by atropine and by section of both cervical vagosympathetic nerves. No bronchodilator responses have been observed.

Since the aortic nerves in cats and dogs contain both chemo- and baroreceptor fibres, it might be expected that bronchoconstrictor and bronchodilator responses to stimulation of these nerves would be observed, similar to those on

carotid sinus nerve stimulation. In only one experiment, however, has a bronchodilator response to stimulation of the aortic nerve been obtained.

It would appear, therefore, that of the two types of bronchomotor effects initiated on stimulation of either the carotid sinus or the aortic nerve, the bronchoconstrictor response predominates and tends to mask the bronchodilator one. This is more evident in the dog than in the cat.

It appeared to us that the most plausible explanation of the mechanism by which these bronchomotor responses are brought about would be as follows: It is generally accepted that stimulation of the baroreceptors in the carotid sinus causes a reflex fall of systemic blood pressure and bradycardia, the

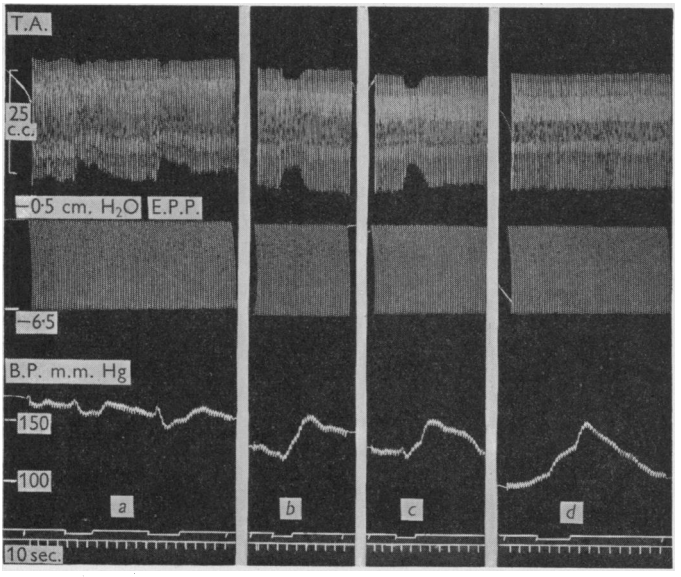

Fig. 4. Cat, ♀, 2·6 kg. Chloralose. Stimulations of the left aortic nerve in *a*, 3·5 V., 0·1 msec., 50 cyc./sec., and at *b*, *c* and *d*, 4 V., 0·1 msec., 50 cyc./sec. Between *a* and *b*, section of the left cervical vagus nerve caudal to the electrode. Between *b* and *c*, eserine, 0·1 mg. Between *c* and *d*, atropine, 1·0 mg.

latter effect being due to an increase in vagal tone. On the other hand, stimulation of the chemoreceptors of the carotid body produces a reflex rise in blood pressure due to increased activity of the sympathetic system (Heymans, Bouckaert, Euler & Dautrebande, 1932; Bernthal, Motley, Schwind & Weeks, 1945).

The carotid sinus nerve is a mixed afferent nerve containing afferents from the baroreceptors of the carotid sinus and from the chemoreceptors of the carotid body. In our own experiments, therefore, it might be expected that stimulation of the baroreceptor fibres, by reflexly increasing vagal tone, would

cause bronchoconstriction, whereas stimulation of the chemoreceptor fibres, by reflexly decreasing vagal tone and increasing sympathetic tone, would cause bronchodilatation. The direction of the bronchomotor response elicited on stimulation of the carotid sinus nerve would therefore depend upon the conditions of the experiment existing at that time and the prepotence of the afferents stimulated. Subsequent experiments were therefore designed to test the validity of this hypothesis.

It is apparent that complete analysis of these effects can only be made by initiating each type of response separately and without the interference of the other.

Isolated perfused carotid sinus experiments

The object of these experiments was to provide further evidence as to the role of the baroreceptors and chemoreceptors in the initiation of the bronchomotor responses observed on electrical stimulation of the carotid sinus and aortic nerves. For this purpose, two types of carotid sinus preparation have been used.

The isolated carotid sinus was subjected to changes in static internal pressure (Moissejeff, 1926; Koch, 1931; Schweitzer, 1937). Dogs under chloralose anaesthesia were used. It was found that sudden raising of the pressure from 65 to 180 mm. Hg caused a lowering of the systemic blood pressure, a diminution of heart rate and bronchoconstriction (Fig. 5). No bronchodilator responses were observed in these experiments.

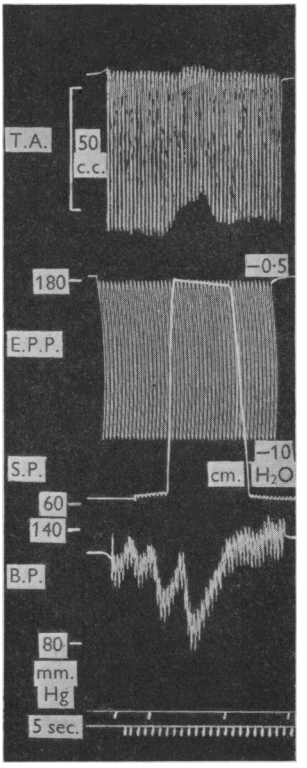

Fig. 5. Dog, ♀, 5·0 kg. Chloralose. Isolated right carotid sinus preparation. Effect of altering the intrasinusal pressure (non-pulsatile).

Isolated carotid sinus preparations were perfused by means of a Dale-Schuster pump with defibrinated ox blood. Experiments under these conditions confirmed the results obtained by the first method, viz. a rise in intrasinusal pressure caused a fall in blood pressure, usually bradycardia, and bronchoconstriction (Fig. 6*a*). Again, in no instance was a bronchodilator response observed on stimulation of the baroreceptors. The bronchoconstriction is still apparent after denervation of the contralateral carotid sinus, and may in some instances be increased. This is probably due to the loss of the buffering action following denervation of the contralateral carotid sinus. The results of Houssay & Orias (1934*a*, *b*) who found no bronchomotor effect upon raising the intra-

sinusal pressure in pulsatile perfused carotid sinus preparations cannot therefore be confirmed.

Stimulation of chemoreceptors of the carotid body. The chemoreceptors have been stimulated by the injection of lobeline hydrochloride or sodium cyanide into the inflow tubing of isolated perfused carotid sinus preparations. Fig. 6 is taken from one such experiment. It shows that the injection of lobeline causes bronchodilatation, whether the intrasinusal pressure is high (*b*) or low (*c*). Other experiments have shown that this response can occur in adrenalectomized preparations. It is therefore not due to a reflex secretion of adrenaline acting

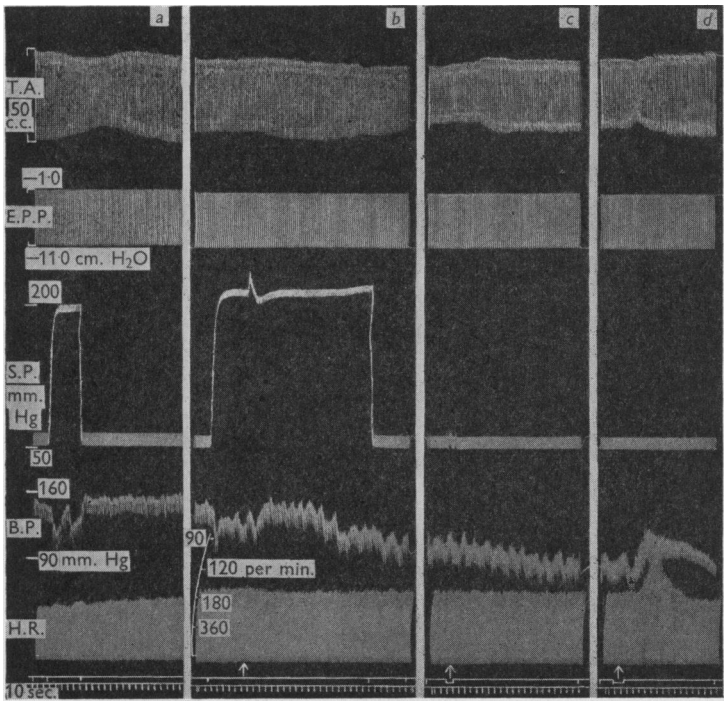

Fig. 6. Dog, ♀, 7·0 kg. Chloralose. Left common carotid ligated. Perfusion of right carotid sinus. Eserine, 0·2 mg. *a*, effect of altering the intrasinusal pressure; *b* and *c*, lobeline, 3 mg., injected into perfusion inflow tubing at arrow ↑ ; *d*, lobeline, 3 mg., intravenously.

directly on the bronchial musculature. The intravenous injection of lobeline (*d*) causes bronchoconstriction followed by bronchodilatation. It also causes slowing of the heart rate. The analysis of this response is difficult, for lobeline has nicotine-like actions, and the initial bronchoconstriction is therefore probably due to stimulation of the vagal ganglia and the vagal centres. The bronchodilator phase may be due, in part, to stimulation of the chemoreceptors of the aortic bodies, stimulation of the sympathetic ganglia and to a decrease

of peripheral vagal action. With regard to the last effect, Bjorkman (1926) has shown that the excitability of the bronchial muscle to parasympathomimetic drugs is decreased by lobeline. These effects are apart from any which lobeline may exert on the bronchial musculature itself.

The mechanisms, however, which might have operated after an intravenous injection of the drug, could not have been the cause of bronchodilatation observed in these experiments where lobeline was injected into the carotid sinus isolated from the general circulation.

These experiments show, therefore, that stimulation of the baroreceptors by increasing the intrasinusal pressure causes bronchoconstriction, whereas the injection of lobeline, which specifically stimulates chemoreceptors (Zotterman, 1944), causes bronchodilatation. These results give strong support to our hypothesis and, moreover, account for the fact that stimulation of the carotid sinus nerve containing afferent fibres serving two functions can produce either bronchoconstriction or bronchodilatation.

Several points emerge from these experiments which are worthy of note. A comparison of the bronchomotor responses in experiments involving stimulation of the carotid sinus nerve in dogs and cats showed that in both species, bronchoconstriction was more readily obtained than bronchodilatation. This may, in part, be due to the fact that the bronchoconstrictor *reflex* (as it has been shown to be) is prepotent to the bronchodilator, or that in a majority of the experiments, there was little bronchial tone. Furthermore, the responses in dogs were usually less clear and less well maintained than those in cats. A similar state of affairs has been found when, by means of isolated perfused carotid sinus preparations, the responses are initiated by altering the intrasinusal pressure or by stimulating the chemoreceptors. Again, the bronchodilator response is the more difficult to elicit.

In dogs, it was found that the factor contributing most to the falling off of the bronchoconstrictor response was the presence of lobeline in the perfusion system. The usual routine in our experiments was to observe the effects of altering the intrasinusal pressure alternately with those of stimulating the chemoreceptors with lobeline. It was noticed that, once lobeline had been injected, the bronchoconstriction, fall of blood pressure and cardiac slowing produced on raising the intrasinusal pressure, gradually fell off and finally disappeared. The responses were diminished when the concentration of lobeline was 1 in 160,000 and abolished with concentrations of 1 in 40,000. A possible explanation of this phenomenon would be that the abolition of the responses to a rise in intrasinusal pressure was merely due to loss of sensitivity of the baroreceptors. It occurred, however, only in experiments in which lobeline was used; in those in which it was not used, the blood pressure responses remained unchanged, although the bronchomotor effects did diminish to some extent throughout the course of the experiment. These results confirm those of Euler

et al. (1941) who found that, in cats, lobeline injected into isolated perfused carotid sinus preparations in concentrations up to 1 in 200,000 caused insignificant changes in the reaction of the blood pressure to alterations in the intrasinusal pressure; in concentrations of 1 in 50,000, the reactions diminished and finally disappeared. They attributed these results to a direct paralysing action of lobeline on the baroreceptors.

The demonstration of bronchodilator responses on stimulation of the chemoreceptors has proved more difficult. These responses depend essentially on an adequate degree of bronchial tone. This had to be increased artificially in many experiments by injecting eserine intravenously, and even then the increase in bronchial tone was often small, while in other experiments the drug was ineffective.

Another method of stimulating the carotid chemoreceptors has been used in this investigation. Lobeline or sodium cyanide has been injected through a cannula inserted into the superior thyroid artery. The internal carotid, external carotid and occasionally the lingual arteries were ligated so that most of the injected drug passed through the occipital artery from which the carotid body takes its main blood supply (Comroe & Schmidt, 1938).

When using lobeline as the stimulant, the usual response was bronchoconstriction. In some experiments, however, a small bronchodilatation followed by severe bronchoconstriction with concomitant cardiac slowing was observed. From the results obtained in isolated perfused carotid sinus experiments, it would appear probable that lobeline, by stimulating the carotid body, caused bronchodilatation, but that when it entered the general circulation, its stimulation of the vagal ganglia produced bronchoconstriction. These findings are in agreement with those already described following intravenous injection of the drug. Such side effects as these ruled out any possibility of obtaining consistent results with this drug.

Sodium cyanide injected into the superior thyroid artery has given more consistent results. It causes initial bronchoconstriction followed by bronchodilatation with concomitant rise in systemic blood pressure (Fig. 7*a*). After section of the ipsilateral carotid sinus nerve, the same dose of sodium cyanide caused only slight bronchoconstriction and a smaller rise in blood pressure (*b*). The injection of adrenaline intravenously (*c*) caused bronchodilatation, showing that bronchial tone was still present.

This experiment illustrates yet another difficulty when attempting to elicit bronchodilator responses from the chemoreceptors, for the concomitant rise in blood pressure itself stimulates the baroreceptors, thereby causing bronchoconstriction. Therefore, the ultimate direction of the bronchomotor response in these experiments depends essentially on the magnitude of the stimulus applied to the chemoreceptors and the degree of rise in blood pressure produced. In the experiment from which Fig. 7 is taken, the contralateral carotid sinus was

not denervated, and it is probable that some of the injected sodium cyanide entered that sinus by passing retrogradely down the ipsilateral common carotid artery in which the blood stream had been greatly slowed by ligation of its major branches. This would account for the persistence of the blood pressure response after denervation of the ipsilateral carotid sinus (*b*). We interpret the slight bronchoconstrictor response as being due to this rise in blood pressure. This contention is supported by the coincidence of the hyper-

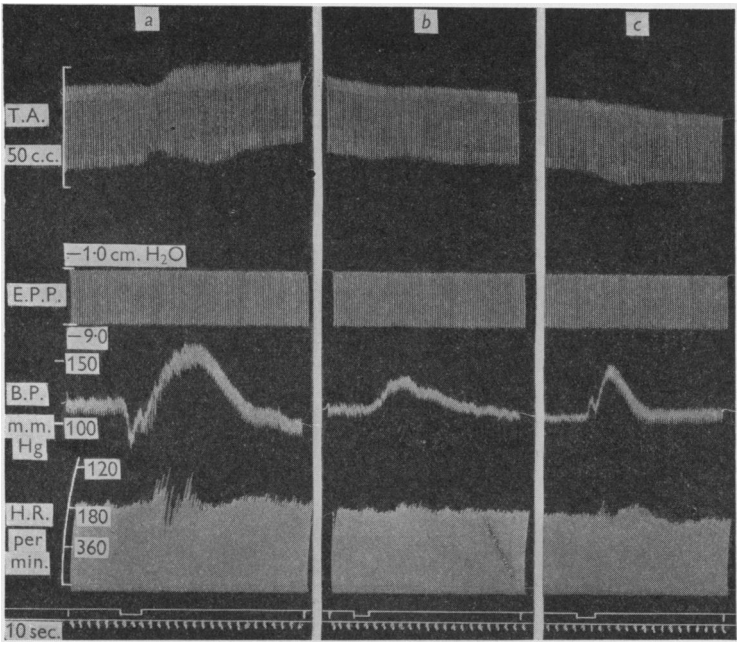

Fig. 7. Dog, ♀ 3·7 kg. Chloralose. External carotid, lingual and internal carotid arteries ligated on right side. *a* and *b*, sodium cyanide, 0·5 mg. in 0·5 c.c., injected into right superior thyroid artery; between *a* and *b*, right carotid sinus nerve divided; *c*, adrenaline, 10 μg., intravenously.

tensive effect of the drug and the bronchoconstrictor response which is evident on analysis of the records.

It is therefore apparent that, in order to eliminate secondary effects from the action of the injected drug, the use of the isolated perfused sinus is the preparation of choice for eliciting bronchomotor responses from the carotid body. But even with this preparation, secondary effects on the bronchi due to the concomitant rise in systemic blood pressure can only be eliminated by sectioning the remaining three buffer nerves, unless a blood pressure compensating device is used.

Stimulation of aortic chemoreceptors by intraventricular injection of lobeline or sodium cyanide

Stimulation of the aortic nerve has been shown to cause bronchoconstriction or occasionally bronchodilatation. As the bronchodilator effects of carotid sinus nerve stimulation are due to stimulation of the chemoreceptor fibres, it might be expected that specific stimulation of the aortic chemoreceptors would cause a similar effect. Our results support this view.

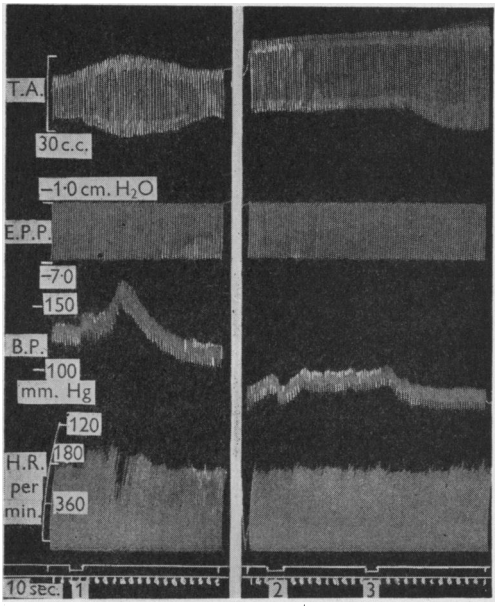

Fig. 8. Dog, ♂, 3·2 kg. Chloralose. Both carotid sinus nerves cut. Intraventricular injections of sodium cyanide, 0·025 mg., before (1) and after (2) the intraventricular injection of acetic acid, 1 c.c. 0·5 N; (3), atropine, 1·0 mg., intravenously.

In these experiments, the aortic chemoreceptors have been stimulated by the intraventricular injection of sodium cyanide (Comroe, 1939; Gernandt, 1946). The injections were made into the left ventricle through a catheter inserted via the left common carotid artery, the tip of the catheter being pushed through the aortic valve. Before the introduction of the catheter both carotid sinuses were denervated.

As Fig. 8 (*1*) shows, the intraventricular injection of sodium cyanide causes a rise in systemic blood pressure (confirming Comroe, 1939; Gernandt, 1946), and bronchodilatation. After inactivation of the chemoreceptors by the intraventricular injection of acetic acid, a second injection of sodium cyanide had no effect on the bronchi (*2*). It might be argued that the absence of a response

was due to there being little or no bronchial tone. This was not so, since a subsequent intravenous injection of atropine caused bronchodilatation (*3*).

These results could also be criticized on the grounds that the observed bronchodilatation was due to a direct action of sodium cyanide on the bronchi. This is improbable, for intra-aortic injection of the same dose of sodium cyanide, which does not produce stimulation of the aortic chemoreceptors (Comroe, 1939; Gernandt, 1946), produced no bronchomotor effect. It is therefore concluded that, as with stimulation of the carotid body, stimulation of the aortic chemoreceptors causes bronchodilatation.

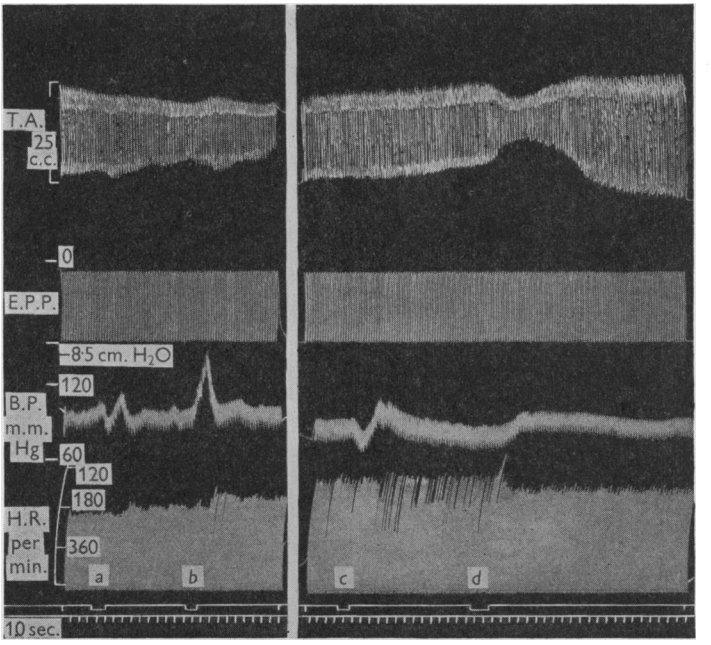

Fig. 9. Dog, ♀, 3·0 kg. Chloralose. Both carotid sinus nerves cut. Eserine, 0·3 mg. Intraventricular injections of sodium cyanide at *a*, 0·025 mg., and at *b* and *c*, 0·05 mg.; between *b* and *c*, sympathetic nerve supply to lungs cut on both sides; *d*, atropine 1·0 mg., intravenously.

In experiments involving stimulation of the carotid sinus nerve, evidence was obtained that the bronchodilator responses were partly or wholly mediated through the sympathetic system. The results obtained on stimulating the aortic chemoreceptors have given added weight to this view.

In one experiment (Fig. 9), the aortic chemoreceptors were stimulated by the intra-ventricular injection of sodium cyanide. A bronchodilatation resulted which disappeared after bilateral section of the sympathetic nerves innervating the lung. The subsequent intravenous injection of atropine caused initial bronchoconstriction followed by bronchodilatation and resulted in a tidal air

42% greater than its original volume, showing that a considerable degree of tone had existed. A possible explanation of the initial bronchoconstrictor response after the atropine injection is that it was due to a direct stimulating effect on the vagal nuclei.

Although lobeline has been used to stimulate the aortic chemoreceptors by Comroe's method, the experiments were unsatisfactory. This was due to the fact that lobeline invariably produced bronchoconstriction and bradycardia, probably by stimulating the vagal ganglia, and so masked any bronchodilator effect which might have been present.

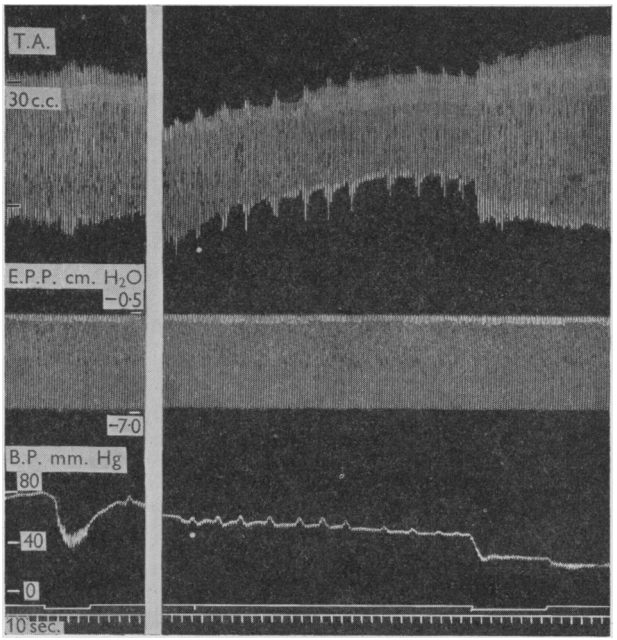

Fig. 10. Cat, ♂, 2·1 kg. Decerebrate. D-tubocurarine chloride, 1·0 mg.; eserine, 0·25 mg.; stimulation of right carotid sinus nerve, 6 V., 0·1 msec., 100 cyc./sec., at signals. Note variations in tidal air volume coincident with the Mayer waves in the blood pressure.

It has been reported recently (Dawes, 1947; Aviado, Pontius & Schmidt, 1949) that there are present veratridine sensitive receptors in the pulmonary vascular bed and in the distribution of the coronary arteries. In our own experiments, therefore, it is possible that such receptors supplied by the coronary arteries were also stimulated, but no attempt has been made to distinguish the effects of their stimulation from those of stimulation of the aortic body. Since sodium cyanide injected into the arch of the aorta causes no bronchomotor effect, it seems unlikely that the pulmonary receptors play any part in the effects observed by us.

Rhythmical variations in tidal air volume. The causes of certain rhythmical changes in lung volume and in tidal air volume under conditions of artificial respiration have been previously described (Dixon & Brodie, 1903; Daly, 1938). During this investigation, variations in tidal air volume have been observed on a few occasions in both cats and dogs. These usually occurred when the general condition of the animal was poor, and were accompanied by Mayer waves in the blood pressure and also by periodic changes in heart rate. A record from such an experiment is shown in Fig. 10. It will be noted that the periodic increase in the tidal air volume coincided with the ascending phase of the Mayer waves in the blood pressure. Such changes could not have been caused by mechanical effects due to movements of the diaphragm or the thorax, for the animal was fully curarized, and the absence of such movements was noted at the time. Andersson, Kenney & Neil (1950) have suggested that Mayer waves are due to rhythmic excitation of the chemoreceptor mechanism. Since our experiments have shown that chemoreceptor stimulation causes bronchodilatation, it would appear probable that the observed periodic fluctuations in tidal air volume, coincident with the Mayer waves, would also be due to such a mechanism. No experiments have as yet been made to test the validity of this view.

DISCUSSION

We have shown that electrical stimulation of the carotid sinus and aortic nerves cause bronchoconstriction or bronchodilatation. These nerve trunks in the dog and cat contain afferent fibres from both baroreceptor and chemoreceptor regions of the carotid bifurcation and arch of the aorta. The difficulties encountered in the study of reflex actions following stimulation of mixed afferent nerves were well recognized by Sherrington: 'The laboratory usage for obtaining reflexes is often direct stimulation of bared afferent nerves, a plan which eschews selective excitation of specific receptors and precise knowledge of the receptive field, and thus renounces serviceable guides to the functional purpose of the reflex.' He further points out that each afferent nerve presents a dominant reflex and that the reaction when the nerve is stimulated may obscure others concomitantly excited (Creed, Denny-Brown, Eccles, Liddell & Sherrington, 1932). These conclusions, based on the study of somatic reflex arcs, may well be applied to our present investigation.

The results of an analysis of our observations by means of isolated perfused carotid sinus experiments, have shown that stimulation of the baroreceptors causes reflex bronchoconstriction which is mediated through the vagus nerves. Chemoreceptor stimulation causes a reflex bronchodilatation which occurs also in adrenalectomized preparations and appears, partly or wholly, to be mediated through the sympathetic nerves innervating the lungs. Our experiments show moreover that the bronchomotor responses to stimulation of the carotid sinus and aortic nerves are abolished by section of the efferent nerves supplying the

bronchial musculature. When the baroreceptors and chemoreceptors are stimulated, with the carotid sinus isolated from the general circulation, the bronchomotor effects are abolished by inactivation of the receptors and by section of the carotid sinus nerve. Similarly, the effects of stimulation of the aortic chemoreceptors are abolished by their inactivation. These results show that the observed bronchomotor phenomena are beyond doubt reflex in nature.

Our interpretation of these results may be criticized on the grounds that the observed changes in tidal air volume may be complicated by concomitant changes in pulmonary vasomotor activity. Using the perfused left lung preparation (Daly & Duke, 1948) to study the reflex pulmonary vasomotor reactions in response to sino-aortic nerve stimulation, we have shown that, under negative pressure ventilation, pulmonary arterial pressure changes may occur in the absence of changes in tidal air volume; these experiments are being made the subject of a separate communication by us. The reflexes acting on the pulmonary circulation and on the ventilation can therefore be regarded as independent of one another; Konzett & Hebb (1949) arrived at a similar conclusion on the basis of pharmacological experiments.

The bronchomotor responses which we have observed must introduce a complicating factor into any experiments designed to study the effect of respired mixtures of gases on the bronchial musculature. For gas mixtures containing excess carbon dioxide or little oxygen may not only influence the bronchial calibre directly (Löhr, 1924; Nisell, 1950), but also exert their effects by an action on the vagal nuclei (Einthoven, 1892; Dixon & Brodie, 1903). Moreover, as our own experiments have shown, stimulation of the baroreceptors causes reflex bronchoconstriction. Therefore, any alteration in blood pressure resulting from inhalation of such gas mixtures might in itself produce secondary bronchomotor effects. Some of the older observations quoted above will therefore have to be reconsidered in the light of our results.

The existence of such a powerful reflex causing bronchoconstriction in animals appears to us to justify speculation as to whether a similar mechanism may not be active under certain conditions in man. We refer in particular to certain forms of paroxysmal dyspnoea due to bronchospasm. It seems remarkable that in certain subjects, an attack of asthma should be precipitated by an emotional stimulus, which might reasonably be expected to be accompanied by a general increase in sympathetic activity, together with the secretion of adrenaline. Of the many causes of asthma which have been postulated, most are supposed to involve the parasympathetic system since stimulation of the vagus nerve causes bronchoconstriction (Longet, 1842; Dixon & Brodie, 1903; Dixon & Ransom, 1912).

Our experiments have clearly demonstrated that stimulation of the baroreceptors of the carotid sinus by a rise of intrasinusal pressure causes reflex bronchoconstriction. We suggest, therefore, that this reflex may exist in man;

thus a rise of systemic blood pressure, produced by general sympathetic activity on receipt of an emotional stimulus, could activate the baroreceptors and so cause reflex bronchospasm, in spite of the potential direct bronchodilator effect of the adrenaline released.

Subjects receiving intravenous infusions of adrenaline (5–20 μg./min.) frequently suffer, in the initial stages, a considerable respiratory distress which is usually described as a sensation of tightness in the chest (Barcroft, 1950). These symptoms appear to be related to the rise in systemic blood pressure. In the light of our observations, it might be reasonable to suggest that this respiratory distress is due to a sino-aortic bronchoconstrictor reflex. The eventual disappearance of these disturbances could be explained by the direct dilator effect which a mounting concentration of adrenaline in the blood would exert on the bronchi.

SUMMARY

1. Electrical stimulation of the carotid sinus nerve in dogs and cats causes bronchoconstriction or bronchodilatation.

2. The bronchoconstrictor responses are potentiated by eserine and abolished by atropine. They are also abolished by section of both cervical vagosympathetic nerves in the dog or of both cervical vagus nerves in the cat.

3. The bronchodilator responses to carotid sinus nerve stimulation occur in bilaterally adrenalectomized animals and are either diminished, abolished or reversed to bronchoconstriction on sectioning the sympathetic nerves innervating the lungs.

4. An analysis of these bronchomotor responses by means of isolated perfused carotid sinus experiments shows that a rise of intrasinusal pressure causes only bronchoconstriction and that stimulation of the chemoreceptors by lobeline or sodium cyanide causes bronchodilatation.

5. Stimulation of the carotid body by injection of sodium cyanide into the common carotid artery causes a bronchodilatation which is abolished by section of the ipsilateral carotid sinus nerve.

6. Stimulation of the aortic bodies causes bronchodilatation which is abolished by inactivation of these chemoreceptors or by section of the sympathetic nerves innervating the lungs.

7. These bronchomotor effects are reflex in nature.

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