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ASSESSMENT OF THE PULMONARY ORIGIN OF BRONCHOCONSTRICTOR VAGAL TONE

BY Y. JAMMES AND N. MEI

From the Département de Neurophysiologie Végétative INP.01 C.N.R.S. 31 Chemin Joseph Aiguier, 13274 Marseille Cedex 2, France and the Laboratoire de Médecine Expérimentale, Faculté de Médecine, 27 Bld Jean Moulin, 13385 Marseille Cedex 4, France

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SUMMARY

1. In anaesthetized spontaneously breathing cats, the sensory component of the vagal nerves was sectioned at the level of nodose ganglion, using a method described previously (Mei, 1966; Mei & Dussardier, 1966).

2. The strength of the Hering–Breuer reflex (inhibitory ratio, i.e. T_1/T_0) provided a test for effectiveness of section of vagal afferents, particularly respiratory afferents. On the other hand, by studying the cardiac and bronchomotor effects induced by electrical stimulation of the supranodose portion of the vagal nerve, it was possible to test the integrity of the efferent vagal component.

3. Unilateral right sensory vagotomy was followed by a 29% reduction in total pulmonary resistance.

4. Section of the contralateral sensory vagal component (sensory bivagotomy), produced a weak supplementary effect (total decrease of total pulmonary resistance: 31%).

5. No additive bronchomotor effect could be observed after the bilateral section of efferent vagal fibres (total bivagotomy).

6. In intact cats, blockade of the two vagal nerves by procaine induced a decrease in pulmonary resistance similar to those produced by the sensory bivagotomy (23%). This bronchodilatator effect was concomitant with a complete disappearance of the C wave of the compound vagal potential.

7. Intravenous injection of phenyl diguanide, immediately after the blockade of the C vagal fibres by procaine did not modify bronchomotor tone. This result confirms that the C pulmonary afferents, which are activated by phenyl diguanide, are mainly involved in this mechanism.

8. The pulmonary irritant receptors seem to play a minor role. In fact, the I.V. administration of histamine under the same conditions, provides evidence that the corresponding neurones (small sized myelinated fibres) are potent during the procaine application.

9. From these results, it appears that bronchoconstrictor vagal tone has an exclusive peripheral origin and that pulmonary endings, in particular those connected with non-medullated fibres, are probably involved in this mechanism.

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INTRODUCTION

It is well known that the bronchomotor tone is mediated, at least in part, by vagal nerves (Colebatch & Halmagyi, 1963 for the sheep; Olsen, Dekock & Colebatch, 1967 for the cat; Karczewski & Widdicombe, 1969*a* for the rabbit). Widdicombe (1966) identified the efferent vagal fibres to the trachea and the lungs which are probably involved in the bronchoconstrictor tone; these fibres fired either continuously or periodically during the respiratory cycle (late in expiration and early in inspiration). Despite numerous studies on the nature of the central or peripheral origin of bronchomotor tone, as yet little direct evidence exists. Karczewski & Widdicombe (1969*a*) have described that afferent impulses originating from the pulmonary stretch receptors produce a bronchodilatator response, but the inability until recently to suppress selectively the afferent or efferent vagal components has hindered further progress. A method of selective vagotomy has been proposed at the level of nodose ganglion, which allows section of afferents by ablation of the ganglion itself (Mei, 1966; Mei & Dussardier, 1966).

In the present work, we have used this method in order to determine if pulmonary afferents are responsible for the bronchoconstrictor tone. In addition, we have attempted to identify the receptors which are involved in this mechanism.

METHODS

The experiments were performed on eight adult cats, weighing 2–4 kg. In all, anaesthesia was induced by halothane and maintained by an I.V. injection of barbiturate (pentobarbitone sodium (Nembutal) 30 mg/kg for two animals and thiopentone sodium (Nesdonal) 25 mg/kg for six cats). A tracheal cannula and femoral venous and arterial catheters were inserted. The added resistance of the tracheal cannula was 0·52 kPa.l^{-1}.sec. Blood pressure was recorded from the femoral artery through a polyethylene catheter connected to an electro- manometer (Telco).

(1) *Measurement of ventilatory variables*

A Fleisch pneumotachogram (number 0) was attached to the tracheal cannula and connected to a differential pressure transducer (Schlumberger ± 2 mbar); the signal was fed to an integration circuit. Outputs from the manometer gave the air flow rate (dV/dt) and from the integrator the tidal volume (V_T) and the ventilatory times (inspiratory, T_I, and expiratory, T_E, durations). Before and after each experiment, the system was calibrated with a syringe driven by hand for V_T measurements and by a water manometer for dV/dt calculations. The steady state dV/dt, pressure behaviour of the Fleisch flowmeter was assessed by measuring the pressure drop across it during steady state rates of flow produced by drawing gas at room temperature through the pneumotachograph with a flow generator. All data on V_T and dV/dt are corrected by b.t.p.s. coefficient and expressed in ml. b.t.p.s. or ml. b.t.p.s. sec^{-1} respectively. The transpulmonary pressure (P_{TP}, expressed in kPa) was measured from an air-filled catheter tied into a lower intrapleural space and from a polyethylene catheter connected to a needle inserted through the tracheal cannula. These two catheters were connected to a differential pressure transducer (Siemens, EMT 32c).

All variables, V_T, dV/dt, P_{TP} and arterial blood pressure, were recorded simultaneously on a multichannel recorder (Siemens, Mingograph).

Total pulmonary resistance (R_L) was calculated at points of equal volume (50 % V_T) during the expiratory phase of each cycle by the method of Amdur & Mead (1958). Thus the flow-resistive component of the transpulmonary pressure (called dynamic pressure = P_{dyn}) was related to the corresponding flow rate. P_{dyn} was assessed after subtracting from the total transpulmonary pressure the elastic component, measured between two successive moments where dV/dt was

zero. The resistance of the tracheal cannula was not subtracted. All measurements of pulmonary resistance are expressed in kPa.l^{-1} sec.

The ratio between the volume change (V_T) and the accompanying elastic pressure change gave a measure of lung compliance (C_L), expressed in ml..kPa^{-1}.

Our values of R_L and C_L are comparable to those previously measured in spontaneously breathing cats (Crosfill & Widdicombe, 1961; Spells, 1969).

Blood gas analysis. Partial pressures of O_2 and CO_2 and pH were analysed routinely during the experiment by taking blood samples from the catheter inserted in the femoral artery.

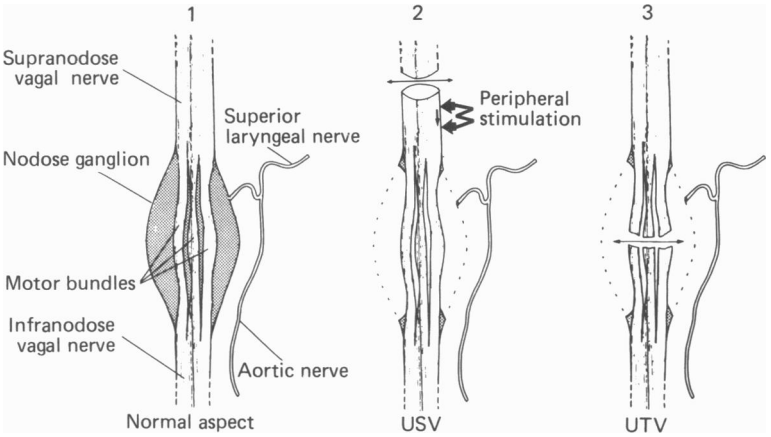

Fig. 1. Technique of the selective vagotomy used at the level of the nodose ganglion.

(1) Normal aspect: ventral view of the nodose ganglion. The motor bundles, the number of which is variable, are located on the ventral face of the ganglion.

(2) Selective unilateral sensory vagotomy (USV). The ganglion is dissected, and the motor bundles kept intact. The integrity of the efferent fibres is controlled by electrical stimulation of the vagal nerve on the supranodose level. In this case, the nerve is sectioned as it is shown in the Figure.

(3) Unilateral total vagotomy (UTV). The motor bundles are sectioned.

(2) *Assessment of lung reflexes*

(*a*) The activity of lung stretch receptor afferents was assessed by studying the apnoeic response caused by lung inflation. Changes in tracheal pressure were used to measure the duration of the apnoea as previously reported by Bouverot, Crance & Dejours (1970). The total duration of the apnoeic breath (T_1) was compared to the mean value of the ventilatory period of the three preceding cycles (T_0). The T_1/T_0 ratio, called 'inhibitory ratio', assessed the strength of the Hering–Breuer reflex. All lung inflations were performed with a 20 ml. syringe both before and after suppression of vagal afferent conduction.

(*b*) The function of other lung receptors was assessed by measuring the bronchomotor response to intravenous injections of histamine (100 μg/kg) or phenyl diguanide (100 μg/kg). Responses to these two drugs showed the integrity of bronchomotor vago-vagal reflexes.

(3) *Selective afferent vagotomy and total bivagotomy*

The afferent pathways were selectively suppressed according to a previously described procedure (Mei, 1966; Mei & Dussardier, 1966). At the level of the nodose ganglion, the vagal motor fibres are scattered in several ventral superficial bundles (Fig. 1). Thus, using an operating microscope, it is possible to section either the efferent or the afferent fibres. In these experiments, we made successively an unilateral sensory vagotomy, a bilateral sensory vagotomy and a total bivagotomy (Fig. 1). After selective sensory vagotomy, we tested the integrity of the motor component by electrical stimulation of the vagus nerve above the nodose ganglion (10 Hz, 30 V, 1 msec, for 20–30 sec) and by recording of respiratory variables, arterial blood pressure and heart rate.

TABLE 1. Strength of the Hering–Breuer reflex, assessed by the ratio of the inspiratory duration (T_I) following a 20 ml. lung inflation and the mean value from control cycles (T_O), total pulmonary resistance (R_L) and lung compliance (C_L) measured in four successive states: control, unilateral sensory vagotomy (USV), bilateral sensory vagotomy (BSV) and total bilateral vagal section (TB). Each mean value is given with its standard error (10–20 cycles are measured for each cat in control state and 6–17 in each other situation). Changes in R_L or C_L are expressed in % of respective value measured in control state

	Control state			USV		BSV			TB
Cat	T_I/T_O	R_L (kPa.l^{-1}.sec)	C_L (m (b.t.p.s..kPa^{-1})	T_I/T_O	R_L (%)	T_I/T_O	R_L (%)	C_L (%)	R_L (%)
1	3·29 (0·72)	2·27 (0·08)	188·5 (7·0)	1·71 (0·06)	−36	1·00 (0·00)	−54	+1	−51
2	1·91 (0·58)	3·36 (0·20)	139·0 (6·2)	0·86 (0·00)	−40	0·86 (0·08)	−30	+37	
3	3·46 (0·30)	3·60 (0·13)	129·0 (2·1)	3·84 (0·03)	−27	1·19 (0·04)	−35	+1	−50
4	2·19 (0·13)	3·87 (0·16)	101·2 (2·1)	1·48 (0·02)	−33	1·00 (0·00)	−21	+66	−28
5	2·23 (0·11)	3·50 (0·06)	126·1 (3·0)	0·44 (0·05)	− 5	0·42 (0·08)	−16	+6	+ 5
6	7·49 (0·36)	3·17 (0·07)	120·3 (2·0)	1·34 (0·06)	−18	1·34 (0·06)	−18	+2	
7	3·22 (0·09)	1·45 (0·03)	128·0 (3·1)	1·88 (0·00)	−21	1·00 (0·00)	−19	+14	−20
8	1·98 (0·09)	4·46 (0·02)	112·7 (5·0)	1·33 (0·08)	−50	0·88 (0·04)	−49	+31	

TABLE 2. Tidal volume (V_T) and respiratory frequency (f_R) measured in the four successive experimental states described in Table 1. Each mean value is given with its standard error. Changes in V_T and f_R are highly significant in all cats after USV

	Control state		USV		BSV		TB	
Cat	V_T (ml. b.t.p.s.)	f_R (min^{-1})	V_T (ml. b.t.p.s.)	f_R (min^{-1})	V_T (ml. b.t.p.s.)	f_R (min^{-1})	V_T (ml. b.t.p.s.)	f_R (min^{-1})
1	22·2	13·8	23·5	11·0	24·8	8·5	22·2	8·8
	(0·2)	(0·1)	(0·2)	(0·1)	(0·3)	(0·4)	(0·3)	(0·4)
2	25·7	17·8	34·9	15·6	33·1	14·8		
	(0·6)	(0·2)	(0·8)	(0·2)	(1·0)	(0·2)		
3	33·2	27·4	33·3	47·2	41·2	23·7	51·8	16·5
	(0·6)	(1·8)	(0·3)	(0·4)	(0·7)	(1·0)	(0·7)	(0·2)
4	32·5	11·3	34·2	9·2	46·4	5·7	47·0	5·8
	(0·3)	(0·1)	(0·5)	(0·4)	(1·0)	(0·1)	(0·6)	(0·3)
5	37·5	17·9	49·1	16·6	52·8	14·0	40·3	15·5
	(0·5)	(0·1)	(0·8)	(0·2)	(0·4)	(0·8)	(0·4)	(0·1)
6	50·9	42·1	57·1	24·0	57·1	24·0		
	(0·7)	(1·3)	(0·9)	(0·7)	(0·8)	(0·7)		
7	46·0	45·6	49·5	33·5	71·0	21·7	66·3	23·1
	(0·5)	(2·6)	(0·3)	(0·3)	(0·4)	(0·1)	(0·6)	(0·2)
8	54·4	21·1	95·8	9·0	119·3	8·6		
	(0·8)	(0·2)	(7·1)	(0·6)	(1·8)	(1·0)		

(4) *Vagal blockade by procaine application*

At the mid cervical level, both vagus nerves were dissected and isolated with a rubber film in order to apply the procaine solution (1 or 5 %). Nerves were stimulated caudal to this level via a pair of silver wires. The resulting compound action potentials were recorded in two ways: (1) on the nerve trunk just above the nodose ganglion, using a pair of silver wires; (2) on the nodose ganglion with a silver wire ending with a small sphere. In the latter case, afferent potentials were recorded alone, whereas in the former situation both motor and sensory fibre activity was monitored.

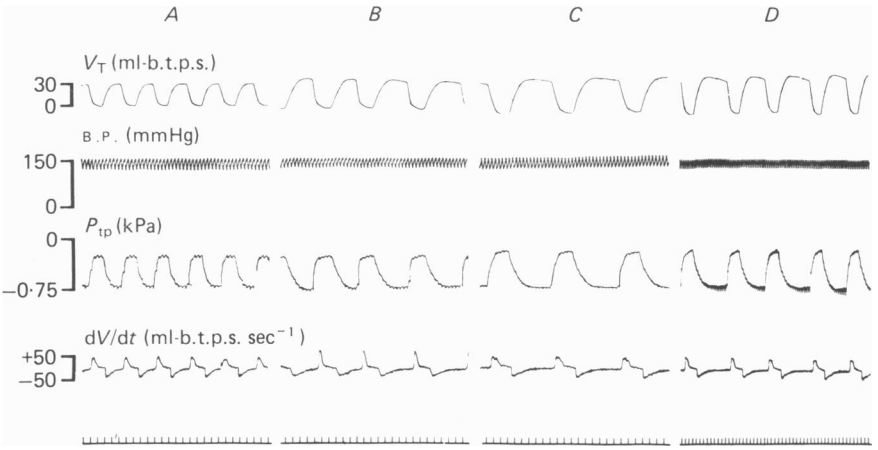

Fig. 2. Successive effects of selective or complete bivagotomy on respiratory and cardiovascular variables. Simultaneous recording of tidal volume (V_T), transpulmonary pressure (P_{tp}), air flow rate (dV/dt) and arterial blood pressure (B.P.).

A: *control state*: f_R = 10 min^{-1}, R_L = 3·87 kPa.l^{-1}.sec, P_{aO_2} = 13·7 kPa, P_{aCO_2} = 3·5 kPa and pHa = 7·38.

B: *after unilateral sensory vagotomy*: the respiratory frequency and the tidal volume are changed: f_R = 8·6 min^{-1}; R_L = 2·40 kPa.l.$^{-1}$.sec; B.P. is not modified.

C: *after bilateral sensory vagotomy*: the previous effects on V_T and f_R are enhanced. R_L = 3·05 kPa.l^{-1}.sec, P_{aO_2} = 13·2 kPa, P_{aCO_2} = 3·2 kPa and pHa = 7·37.

D: *after total bivagotomy*: the f_R is slightly diminished and R_L = 2·80 kPa.l^{-1}.sec (Pa_{O_2} = 13·2 kPa, Pa_{CO_2} = 3·7 kPa, pHa = 7·37) (time calibration: 1 sec between two successive vertical marks).

RESULTS

The mechanical properties of the lungs and the resting values of ventilatory variables are summarized in Tables 1 and 2, which also illustrate the effects of unilateral and bilateral sensory vagotomy and total bilateral vagotomy through surgical transection. The values of T_1/T_0 in the intact preparations (Table 1) show the persistence of the lung stretch afferents with both anaesthetics used.

Unilateral sensory vagotomy. Sensory vagotomy was performed by sectioning the right vagus initially (seven of our eight cats). Table 1 and Fig. 2 show changes in total pulmonary resistance following such a unilateral transection. In seven cats the decrease in total pulmonary resistance was significant (mean decrease = 28·8 %) and was accompanied by small variations of tidal volume and respiratory frequency (Table 2). The Hering–Breuer reflex was diminished in six cases and completely abolished in two cases.

Bilateral sensory vagotomy. The effects of bilateral sensory vagotomy were observed

in each cat for between 2 and 3 hr. In six cats, the decrease of total pulmonary resistance following unilateral vagal section was not enhanced, despite great changes of tidal volume and respiratory frequency produced by the bilateral section (Table 1 and Fig. 2). The Hering–Breuer reflex was abolished in six animals and greatly reduced in the others. A significant increase ($2P < 0{\cdot}05$) in lung compliance was

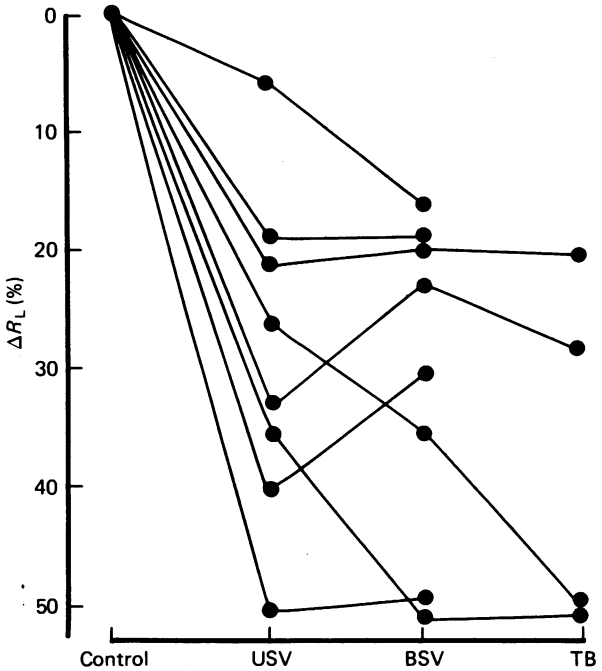

Fig. 3. Relative changes (%) in the total pulmonary resistance (R_L) after unilateral sensory vagotomy (usv) bilateral sensory vagotomy (BSV) and total bivagotomy (TB). The effect is maximal after unilateral sensory vagotomy (four animals) or after bilateral sensory vagotomy (three animals). After total bivagotomy the R_L changes are comparable for three cats and greater for one.

found after bilateral sensory vagotomy in five cats (see Table 1). In four cats the integrity of the efferent vagal component was assessed by measuring changes in total pulmonary resistance and heart rate during electrical stimulation above the nodose ganglion. A mean increase in total pulmonary resistance (+32%) and a fall in heart rate (−56%) were noted.

Total bilateral vagotomy. The effects of total bilateral vagotomy were studied in five animals and followed for 1 hr (Table 1, Fig. 2). The bronchodilatation that had followed bilateral sensory vagotomy was not enhanced by total vagotomy and the ventilatory patterns were not further modified, except for cat 3 in which total suppression of vagal afferents had not been achieved by previous procedures (see Table 1, $T_1/T_0 = 1{\cdot}19$ after bilateral sensory vagotomy). For cat 5, total vagal section provoked a strong and long lasting stimulation of both efferent activity (increase in total pulmonary resistance) and afferent activity (decrease of tidal volume and slight tachypnoea). Figs. 2 and 3 summarize all the effects of the successive operating procedures on total pulmonary resistance, ventilatory variables and blood pressure.

Effects of bilateral vagal blockade by procaine on total pulmonary resistance. Six tests were performed in three cats to assess the effects of procaine (as a 1 or 5 % solution) on pulmonary resistance. After 11–17 min, there was a complete suppression of C fibre activity and a marked decrease in the AδB waves (Fig. 3). In contrast, afferents from the broncho-pulmonary stretch receptors (A$\beta\gamma$ fibres) were always transmitted to the central nervous system during the procaine block, as is shown by the measurement of the T_1/T_0 ratio (Table 3 and Fig. 4). Concomitant with the disappearance of the C wave, a significant decrease of total pulmonary resistance was observed. This

TABLE 3. Total pulmonary resistance (R_L), expressed in kPa.l.$^{-1}$.sec ± one standard error (Abs. for absolute value), measured in control state, after application on the vagal nerves of a procaine solution (1 % in cat 6*A* and cat 7; 5 % in cat 6*B*) and after recovery. Changes in R_L are expressed in % of its value measured in control state. The T_1/T_0 ratio was measured during the three states (control, total blockade of C fibres by procaine and recovery). Values in parentheses indicate times in minutes from the beginning of procaine application. All changes in R_L after C blockade were significant ($2P < 0.001$).

		Control	Procaine application	Recovery
CAT 6A	T_1/T_0	7·49	2·00 (11)	5·33 (24)
	R_L Abs.	3·31	2·21	3·37
		0·08	0·04	0·06
	%	—	−33 %	+1·8 %
CAT 7	T_1/T_0	3·22	2·00 (17)	2·00 (25)
	R_L Abs.	1·45	1·27	1·34
		0·03	0·02	0·03
	%	—	−13 %	−7·5 %
CAT 6B	T_1/T_0	7·50	5·71 (12)	(26)
	R_L Abs.	3·37	2·56	3·21
		0·06	0·07	0·11
	%	—	−24 %	−4·7 %

TABLE 4. Bronchomotor effects of histamine or phenyl diguanide after total disappearance of C wave action potential due to bilateral application of a 5 % procaine solution. All changes in R_L were highly significant ($2P < 0.001$) after histamine injection, but phenyl diguanide induced no significant effect. Changes in R_L are expressed in % of its value measured during the previous state

	Control	Procaine application	Drug injection histamine
CAT 6 R_L Abs.	3·50	3·10	6·53
	0·04	0·13	0·18
%	—	−12 %	+111 %
			Histamine
CAT 8 R_L Abs.	4·46	3·12	4·90
	0·02	0·03	0·13
%	—	−30 %	+57 %
			Phenyl diguanide
CAT 7 R_L Abs.	1·34	1·03	1·07
	0·03	0·01	0·04
%	—	−23 %	+4 %

effect was not proportional to the concentration of procaine and was completely reversible when the C action potential has recovered, 5–10 min after washing out the procaine solution.

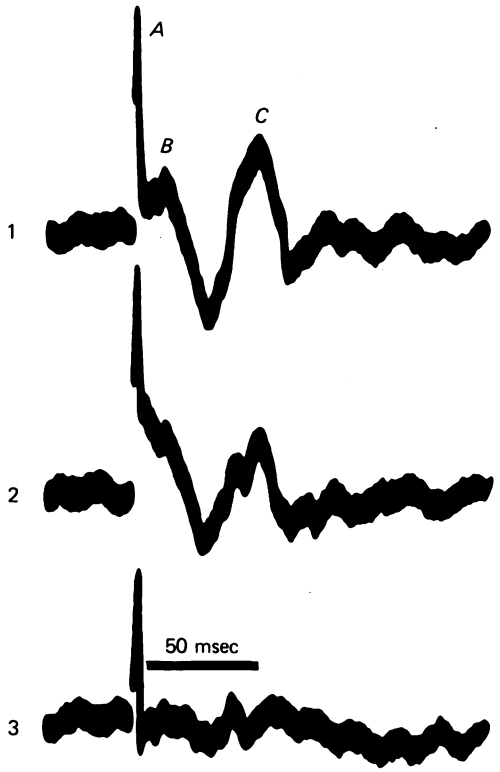

Fig. 4. Effect of local application of procaine solution (5 %) on the action potential recorded in the nodose ganglion (cat 7).

(1) *Control recording:* note the three waves *A*, *B* and *C*. It is not possible with this sweep rate to distinguish the Aδ group. At this moment, the Hering–Breuer reflex was potent ($T_I/T_0 = 2{\cdot}00$) and R_L value was $1{\cdot}34 \pm 0{\cdot}03$ kPa.l^{-1}.sec.

(2) *14 min after application of procaine:* the *C* wave was diminished whereas *A* and *B* waves were practically unchanged $T_I/T_0 = 1{\cdot}81$ and $R_L = 1{\cdot}03 \pm 0{\cdot}03$ kPa.l^{-1}.sec (relative decrease = 23 %).

(3) *3 min later:* the *C* wave disappeared completely as well as the *B* one, whereas the *A* wave was still present. $T_I/T_t = 1{\cdot}81$, and $R_L = 1{\cdot}07 \pm 0{\cdot}03$ kPa.l^{-1}.sec (relative decrease = 20 %).

Bronchomotor effects of histamine and phenyl diguanide injected during the procaine block. When the C fibre action potential had disappeared, an I.V. injection of histamine induced a strong increase in total pulmonary resistance (+57 to +111 %). This effect was quantitatively identical to that measured in control conditions (mean increase in total pulmonary resistance = +89 %), but was much greater than the bronchoconstriction induced by histamine after bilateral sensory vagotomy (increase in total pulmonary resistance = +15 to +25 %). Conversely, an I.V. administration of phenyl diguanide during C wave suppression did not change lung resistance, although weak ventilatory changes were present (a short apnoea of 15–20 sec followed by a small decrease of tidal volume and increase in respiratory frequency). All results are reported in Table 4.

DISCUSSION

Selective sensory vagotomy allowed us to demonstrate that in cats bronchoconstrictor vagal tone resulted exclusively from peripheral afferents. The disappearance of the bronchoconstrictor tone was concomitant with the suppression of the Hering–Breuer reflex which has been used to assess the complete elimination of pulmonary afferents. Furthermore, when bilateral sensory vagotomy was only partial (T_1/T_0 greater than unity) the total vagotomy enhanced bronchial and ventilatory effects. By addition since the cardiac and bronchomotor effects following electrical stimulation above the nodose ganglion remained after bilateral sensory vagotomy, the efferent pathway had not been damaged by our surgical procedure. A subsequent surgical section of these efferent fibres after bilateral sensory vagotomy did not enhance the primary bronchodilatation.

The assessment of the peripheral origin of the bronchoconstrictor tone raises the question of the receptors involved in this mechanism. We can eliminate extrapulmonary afferents, such as baroreceptors and gastro-intestinal receptors since their stimulation has been shown to induce a bronchodilatation (Nadel & Widdicombe, 1962; Jammes, Delpierre, Vanuxem, P., Vanuxem, D. & Grimaud, 1975; Mei, 1976). The work of Nadel & Widdicombe (1962) has, however, shown that the stimulation of carotid body chemoreceptors provoked a bronchoconstriction. Chemosensitive vagal afferents are known to arise from the arch of the aorta in cats, but their activation produces weak ventilatory effects (Comroe, 1939). Thus, it is doubtful that they play a marked role in the control of the bronchomotor tone.

According by elimination, it would seem that the receptors involved in the vagal bronchoconstrictor tone must be located in the bronchopulmonary area. In this case, we can exclude the lung stretch receptors, since firstly their stimulation produces a reflex increase in tracheal volume (Widdicome & Nadel, 1963) and secondly cooling their fibres provokes a persistant bronchoconstriction, revealing a primary bronchodilator effect (Karczewski & Widdicombe, 1969*a*). Laryngeal receptors can be also eliminated since our cats were tracheotomized. There are, however, two classes of bronchopulmonary endings that could be involved in this mechanism: the irritant receptors, connected with small sized medullated fibres (Aδ and B) and receptors innervated by non-medullated fibres (type C), in particular J receptors. Stimulation of these two groups of receptor produces a strong bronchoconstriction (Mills, Sellick & Widdicombe, 1969; and Fillenz & Widdicombe, 1971 for irritant receptors and Karczewski & Widdicombe, 1969*b* for type J ones).

Recent work by Armstrong & Luck (1974) confirms that the spontaneous discharge of these two kinds of receptors is sparse, irregular and that they do not fire in phase with the breathing rhythm. Is such an erratic activity responsible for the bronchoconstrictor tone? We consider this likely on the basis of the present results relating to the blockade of vagal nerves. We observed a marked decrease of total pulmonary resistance ($-22{\cdot}5\%$) after procaine application. In this condition, the previous reports (Nathan & Sears, 1961) and our present observations on the vagal compound potential show that the non-medullated fibres are preferentially blocked. The decrease in pulmonary resistance following procaine application must then be attributed mainly to the blockade of vagal afferent fibres and not of the motor fibres

equally affected by the procaine block since it was identical to the change in total pulmonary resistance produced by the bilateral sensory vagotomy (−31·1 %).

From the results of the procaine block experiments, it is not possible to exclude the participation of small myelinated fibres in bronchomotor control. In order to further study the respective role of the two kinds of receptors, we injected intravenously histamine, which stimulates chiefly the irritant receptors, and phenyl diguanide, a more specific stimulus of C fibres (Guz & Trenchard, 1971; Armstrong & Luck, 1974). After blockade of C fibres by procaine, the total disappearance of the bronchomotor effect of phenyl diguanide shows that non-medullated pulmonary afferents were functionally suppressed by local anaesthesia. This further indicates that they are involved in the maintenance of the bronchoconstrictor tone. The bronchomotor effects of histamine are more difficult to interpret because it acts on bronchial muscle both reflexly through a powerful stimulation of irritant and type J receptors and directly (Karczewski & Widdicombe, 1969*b*; Sellick & Widdicombe, 1971; Islam, Zimmermann & Ulmer, 1975). Our experiments show that the bronchoconstriction due to the direct effect can be estimated as 15–25 % (values obtained after bilateral sensory vagotomy), whereas in the intact animal the mean increase in total pulmonary resistance was +89 %. After the procaine block of vagal nerves, the effect was comparable. This provides evidence that the irritant receptors are potent in this condition. Therefore, from both electrophysiological and pharmacological studies, we suggest that irritant receptors do not play a major role in the control of broncho-constrictor tone.

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