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EFFECT OF ANAESTHETICS ON SYSTEMIC BARORECEPTORS

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Ether or chloroform vapour inhaled in high concentration causes a sharp fall in blood pressure and a slowing of the heart rate. This has been shown in dogs, cats and rabbits (MacWilliam, 1890; Embley, 1902; Schäfer & Scharlieb, 1904; Cattell, 1923). The mechanisms responsible for these effects have not been completely analysed. Chloroform and ether act directly on the heart, causing a rapid reduction in force of contraction and stroke volume (Sherrington & Sowton, 1904; Cattell, 1923), but there is also cardiac inhibition by increased vagal activity since slowing of the heart does not occur if the vagi have been cut (Embley, 1902). A reflex basis for this cardiac inhibition has not been demonstrated. Evidence on the contribution of vasomotor changes to the fall in blood pressure is conflicting, and there is no evidence that such changes as do occur are reflexly produced.

From observations on the effects of stimulating the carotid sinus region mechanically during chloroform anaesthesia, Hering (1927) suggested that in some stages of anaesthesia the sensitivity of the afferent mechanism of the reflex might be increased. Volatile anaesthetics are known to increase the sensitivity of pulmonary stretch receptors (Whitteridge & Bülbring, 1944), and the present studies were therefore undertaken to discover whether they have similar effects on carotid sinus and aortic baroreceptors. A preliminary account of this investigation has been published (Robertson, Swan & Whitteridge, 1955).

METHODS

Cats were used in these experiments, and the effects to be described were demonstrated in five experiments which were technically satisfactory. Anaesthesia was induced by ethyl chloride and ether, and maintained by chloralose 80 mg/kg given intravenously in a single injection. A tracheal tube was inserted at the beginning of the experiment. The technique employed to record activity in single units from the right aortic depressor or right carotid sinus nerves was similar to that described by Whitteridge (1948). Single unit preparations were obtained by dissecting the nerves with sharp razor-blade knives. A binocular microscope, giving a magnification of $\times 10$, was used in the later

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stages of dissection. The fine nerve strand containing the single active unit was laid on silver silver-chloride electrodes under paraffin at 38° C, and a conventional resistance-capacity coupled amplifier and cathode-ray tube was used to record impulse activity. The arterial blood pressure was registered by capacitance manometer using a circuit designed by Alexander (1951). The manometer was calibrated against a mercury manometer at frequent intervals during an experiment. Photographic records were made of impulse activity, together with blood pressure, the e.c.g. and a time-marker. In one experiment activity in a single unit from the left carotid sinus was recorded from the central end of the left aortic depressor nerve as described by Holmes (1954).

In four experiments the right carotid sinus was perfused while activity in a single unit of the sinus nerve was recorded, and effects were observed in two experiments where an adequate stimulus was used. The animal's own blood was used for perfusion and was led by polythene tubing from the femoral artery to a small pressure-reducing valve, similar to that described by Vane (1953). This was connected to the inlet of a small pump designed to have a low capacity and to avoid accumulation of stagnant blood. The total capacity of reducing valve, pump and connexion was 15 ml. The method of preparing the sinus for perfusion was similar to that described by Ead, Green & Neil (1952). The sinus was perfused through a polythene cannula in the common carotid artery, and all branches from the sinus were tied off except the external carotid: the superior thyroid artery and ramus musculus dorsalis from the common carotid were tied but left uncut, and helped to prevent the sinus from being pulled on by the cannula in the common carotid. Blood was led from the sinus by a polythene cannula in the external carotid, and pressures were recorded by capacitance manometer at a T-junction close to the sinus. From this T-junction, soft alkathene tubing returned the blood to the left external jugular vein, and peripheral resistance distal to the point where pressure was recorded was provided by a screw-clip on this tubing. The animals in these experiments were given heparin 1000 units/kg before perfusion was begun.

In the earlier experiments the animal breathed through light respiratory valves attached to the tracheal tube, and volatile anaesthetics were given from a draw-over bottle connected to the inspiratory valve inlet. In later experiments the animal was artificially ventilated by a Starling Ideal pump, and known concentrations of anaesthetic given by connecting an Oxford Vaporizer to the inlet of the pump. The Oxford Vaporizer was specially calibrated for use with cats.

To study the behaviour of single units before and during exposure to anaesthetic, the peak frequency of discharge in a cardiac cycle was plotted against the peak of the pressure pulse in the same cycle. The peak frequency was calculated as the reciprocal of the mean of the three shortest time intervals between impulses in a single cycle. To record activity in a single unit over a range of pressure in the intact animal, the systemic pressure was lowered by brief inflation of the lungs and records taken as the pressure recovered after this manoeuvre.

RESULTS

In the single unit from the right aortic depressor nerve shown in Fig. 1A, there was a linear relation between peak frequency of discharge and peak systolic pressure over a range of pressure from 120 to 140 mm Hg. After the animal had inhaled ether from a draw-over bottle for 2 min, the same peak frequency of discharge occurred at a lower pressure than during the control period (Fig. 2). The concentration of ether vapour inhaled from a draw-over bottle in this way was probably between 10 and 15% (v/v). A frequency of 70 impulses/sec, which corresponded to a peak systolic pressure of 120 mm Hg before exposure, now occurred at a pressure of 102 mm Hg. With ether, activity in the unit was recorded over a lower range of peak pressure than during the control period, but the range of peak pressure was not low enough to determine

whether the threshold pressure at which discharge began was lower during exposure to this anaesthetic.

Chloroform (Fig. 3) and trichlorethylene also caused an increased frequency of discharge in this unit. After the animal had inhaled chloroform for 2 min, a peak frequency of 70 impulses/sec occurred at a peak systolic pressure of 95 mm Hg compared with a peak systolic pressure of 122 mm Hg during the control period. With chloroform and also with trichlorethylene the increase in frequency for a given peak pressure increment was less at higher pressures.

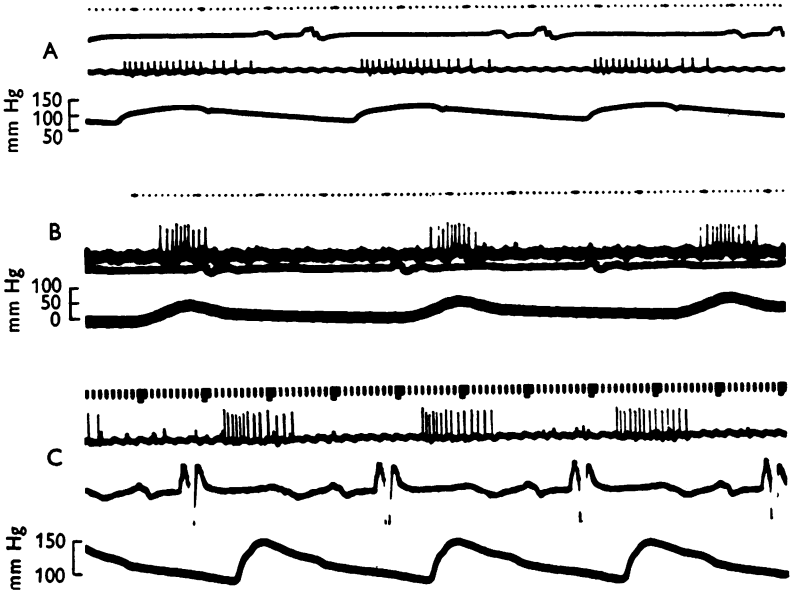

Fig. 1. (A) Single unit of the aortic depressor nerve. From above downwards, time in $\frac{1}{10}$ and $\frac{1}{100}$ sec; the e.c.g.; aortic depressor fibre; arterial pressure. (B) Activity in a single baroreceptor unit of the right carotid sinus nerve from a perfused sinus. From above downwards, time in $\frac{1}{10}$ and $\frac{1}{100}$ sec; carotid sinus fibre; the e.c.g.; intrasinus pressure. (C) Single baroreceptor unit from the right carotid sinus nerve in an animal with intact circulation through sinus. From above downwards, time in $\frac{1}{10}$ and $\frac{1}{100}$ sec; carotid sinus fibre (spikes retouched); the e.c.g.; arterial pressure.

The concentrations of chloroform and trichlorethylene vapour in the inspired air were probably in the range 2–4% (v/v). In pulmonary stretch receptors Whitteridge & Bülbring (1944) found that prolonged exposure to volatile anaesthetics resulted in a progressive decrease in the maximum frequency of response followed by complete failure of the ending to respond to inflation of the lungs. Chloroform caused this effect most rapidly; a concentration of 4% (v/v) produced some reduction of the maximum frequency of response with 10 sec of exposure. Trichlorethylene, while less rapid than chloroform, caused a reduc-

tion in maximum frequency of response in a concentration of 3–4% (v/v) within 70 sec of exposure. In these experiments the baroreceptors were exposed to anaesthetic for periods of 2 min, and it is probable that the smaller increases in frequency at higher pressures seen during exposure to chloroform and trichlorethylene indicate a similar effect of the anaesthetics in reducing the maximum frequency of response of the unit. With the baroreceptors, as with pulmonary stretch receptors, this effect was seen earliest with chloroform and trichlorethylene; and with ether was only seen after longer exposure to much higher concentrations (Fig. 5).

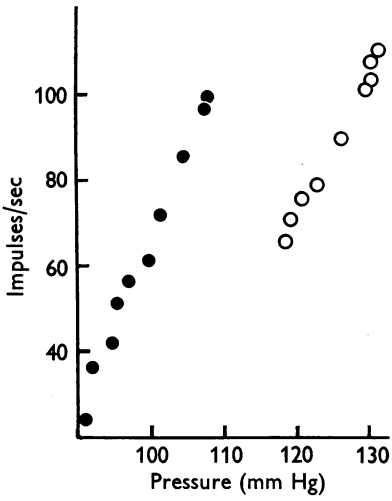

Fig. 2.

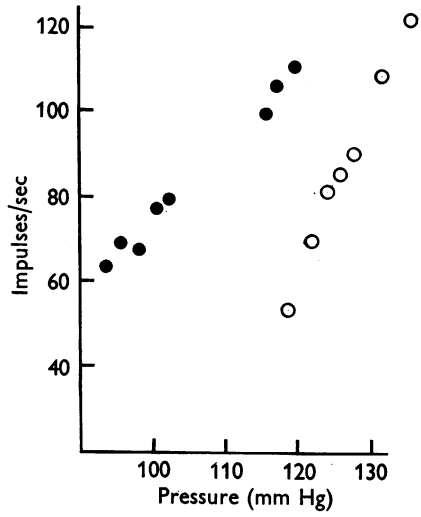

Fig. 3.

Fig. 2. Effect of ether on the activity of a single unit of the aortic depressor nerve. ○, control observations; ●, observation after the animal had inhaled ether vapour for 2 min.

Fig. 3. Effect of chloroform on the activity of the same unit of the aortic depressor nerve as in Fig. 2. ○, control observations; ●, observations after the animal had inhaled chloroform vapour for 2 min.

During exposure to trichlorethylene of the unit of the aortic depressor nerve shown in Fig. 1A, discharge began at a lower pressure than during the control period, indicating a lowering in the threshold of the ending. There was no change in the behaviour of this unit after the animal had inhaled 30% cyclopropane in oxygen for 2 min from a bag connected to the inspiratory inlet (Fig. 4): and 80% nitrous oxide in oxygen given in the same way for 2 min was also without effect.

Changes in intrathoracic pressure, by altering the effective pressure on the aortic endings, may alter the relation between peak frequency of discharge and systolic pressure in units of the aortic depressor nerve, and mechanical changes

at the root of the lung may also affect the behaviour of the endings (Whitteridge, 1948). Since the volatile anaesthetics may all produce changes in the pattern of respiratory movements in animals breathing spontaneously, alterations in intrathoracic pressure and mechanical changes cannot be excluded as factors responsible for the altered behaviour of aortic endings observed during exposure to anaesthetics.

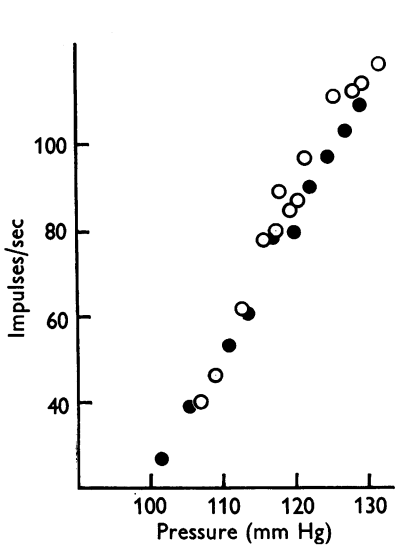

Fig. 4.

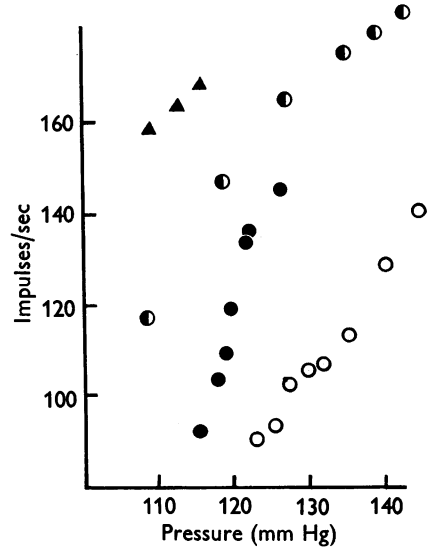

Fig. 5.

Fig. 4. Activity in unit of aortic depressor nerve during exposure to 30% (v/v) cyclopropane. ○, control observations. ●, observations after the animal had inhaled 30% (v/v) cyclopropane in oxygen for 2 min (same unit as shown in Figs. 2 and 3).

Fig. 5. Effect of 20% (v/v) ether vapour on single unit of the carotid sinus nerve. Animal artificially ventilated by Starling Ideal pump. Ether vapour given from Oxford vaporizer. ○, control observations; ●, after administration of 20% (v/v) ether vapour for 30 sec; ◐, after administration of 20% (v/v) ether vapour for 1½ min.; ▲, after administration of 20% (v/v) ether vapour for 4½ min.

These factors can, however, be excluded when activity in units from the carotid sinus is observed while ventilating the animal artificially by pump. When the animal was ventilated with air containing 20% ether (Fig. 5), there was an increase in the activity of the endings within 1 min from the beginning of exposure and a frequency of 120 impulses/sec which corresponded to a peak systolic pressure of 135 mm Hg during the control period now occurred at a pressure of 120 mm Hg. After 1½ min exposure this frequency of discharge was found at a still lower peak systolic pressure, 110 mm Hg. After 4½ min exposure the peak frequency corresponding to this peak systolic pressure of 110 mm Hg increased to 160 impulses/sec.

Landgren (1952*a*) has shown that in carotid sinus baroreceptors the frequency of the unadapted discharge, which has been the frequency measured in the present studies, depends on the rate at which the pressure rises as well as the final level reached. Large differences in rate of rise were required, however, to show this effect in the unit for which he gives data. At a final pressure level of 100 mm Hg, the rate of rise to this level had to be increased to 10 times its previous value to double the frequency of the unadapted discharge. In these experiments on animals with intact circulation, where activity was recorded in

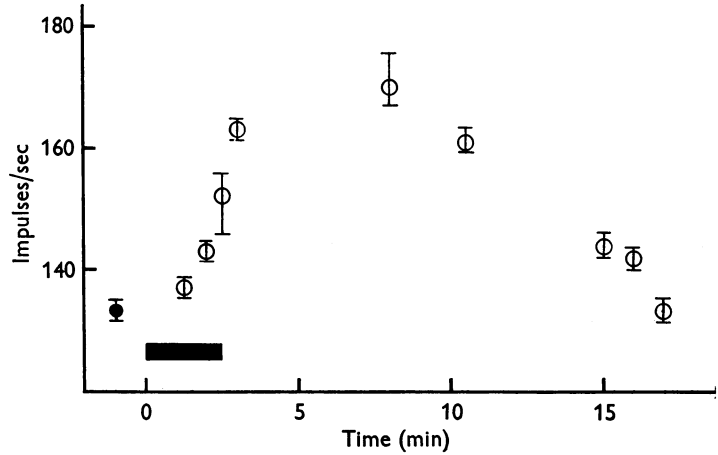

Fig. 6. Effect of ether on single unit of the carotid sinus nerve from a perfused sinus. Pump rate and peak pressure constant (55 mm Hg). Plotted points are means of peak frequencies in four successive pump cycles at each period. Vertical lines through the points indicate the range of peak frequencies for each mean value. Horizontal black bar indicates period during which animal inhaled ether vapour from a draw-over bottle.

baroreceptor units, exposure to anaesthetic produced changes in heart rate or pulse pressure or both together. Reliable information about the maximum rate of rise of pressure in a pressure-pulse cannot be inferred from measurements of heart rate and pulse-pressure, but the size of the differences in these measurements between controls and observations during exposure to anaesthetic made it unlikely that there were large differences in rate of rise of pressure.

By perfusing the carotid sinus, however, pulse-pressure, mean pressure and the rate of the pump could be kept constant while recording activity in a baroreceptor unit from the sinus, and in this way changes in rate of rise of pressure could be excluded as a cause of the increased discharge seen in the presence of a volatile anaesthetic. In the unit shown (Fig. 6) the peak pressure was constant at 55 mm Hg and the peak frequency of discharge corresponding to this varied between 136 and 139 impulses/sec. After the animal had inhaled

ether from a draw-over bottle for $2\frac{1}{2}$ min, the discharge frequency increased and a maximum frequency of 170 impulses/sec, a 25% increase, was reached 7 min from the beginning of ether inhalation. The impulse frequency did not return to the control level until 17 min from the start of inhalation. Chloroform given in the same way had a smaller but more rapid effect, and the maximum increase in frequency (16%) was seen at the end of the period of inhalation.

DISCUSSION

These experiments show that exposure to volatile anaesthetics results in an increased activity of baroreceptors. In strands dissected from the carotid sinus nerve, von Euler, Liljestrand & Zotterman (1941) found that there were often large differences in amplitude of action potential between baroreceptor units, when several were active together in the same nerve-strand. Units with large action potentials are easiest to isolate in the carotid sinus nerve since they apparently survive dissection best, and it has been assumed that they are the fibres of largest diameter in the nerve (Landgren, 1952*a*). In the present experiments single units with the largest amplitude of action-potential were isolated on all occasions, and, although Paintal (1953) has shown by measurement of conduction velocities that spike height alone is not a reliable criterion of fibre size when action potentials are recorded in fine nerve-strands, it is probable that all the units studied were fibres of large diameter.

Contraction of the smooth muscle of the carotid sinus, produced by adrenaline applied directly to the wall (Heymans & van den Heuvel-Heymans, 1950; Landgren, Neil & Zotterman, 1952; Landgren, 1952*b*; Witzleb, 1953) or by stimulation of the sympathetic nerve supply from the superior cervical ganglion (Palme, 1943; Kezdi, 1954), results in increased baroreceptor activity. But only Landgren has attempted to correlate changes in the distensibility of the sinus with changes in the behaviour of single large baroreceptor units. After adrenaline he found that the sinus was less distensible at low pressures (below 60 mm Hg) though more distensible at high pressures. 'If the large baroreceptor spikes are assumed to be elicited from stretch receptors acting in parallel with the contractile elements of the sinus wall, they must be expected to show a lower frequency after adrenaline application when stimulated by a pressure rise from 0 mm Hg. This is indeed the case...' (Landgren, 1952*b*). In our experiments in the perfused sinus, where the pressure was raised by each pump stroke from 0 to 55 mm Hg, exposure to anaesthetic resulted, on the contrary, in an increased baroreceptor discharge (Fig. 6). We conclude, therefore, that in these experiments at least there is no reason to believe that contraction of the arterial wall plays any part in the production of this sensitization. In the intact animal, conditions are so much more complex that we are unable to offer a reliable interpretation of the very large observed increase in discharge with anaesthetics.

Liljestrand (1953) and Landgren, Liljestrand & Zotterman (1953), recording activity in multifibre strands of the carotid sinus nerve in cats, found that ether and chloroform, as well as ethyl alcohol and a number of related substances given by intracarotid injection in Ringer's solution, reduced or abolished the activity in baroreceptor fibres while stimulating chemoreceptor activity. With this method it is not possible to estimate the concentration of substance reaching the carotid sinus receptors during the brief period of its maximum effect, but it is likely that this was many times greater than the blood concentrations achieved in our experiments where the anaesthetic was given by inhalation, for the concentrations of ether and chloroform in the fluids injected were 2·8 and 0·5% (w/v) respectively. This difference between the results of Landgren *et al.* (1953) and our own is most probably due to the different concentrations of anaesthetics used in the two sets of experiments, for in perfusion experiments the reflex effects of increased intrasinus pressure were abolished when the sinus was perfused with Ringer's solution containing ether in a concentration of 0·3–0·4% (w/v) (Robertson & Swan, unpublished).

The increase in baroreceptor discharge during exposure to anaesthetics would have corresponded to an increase in blood pressure of 30–45% and came on rapidly, within 30 sec of exposure. It is probable, therefore, both from the size of the effects and their rapidity of onset, that in the intact animal, where all the baroreceptors are simultaneously affected, sensitization of baroreceptors is the principal afferent mechanism responsible for the reflex slowing of the heart observed with chloroform by Embley (1902) and with ether in sympathectomized dogs by McAllister & Root (1941). Harris (1939) has shown that in rabbits stimulation of the nasopharynx alone with ether vapour will produce a reflex slowing of the heart, but this and the accompanying fall in blood pressure are small in comparison with the effects of sudden inhalation in the cat and dog. McAllister & Root (1941) attributed the reduction in heart rate and the fall in blood pressure which they observed in response to ether inhalation in dogs with both carotid sinuses denervated to a reflex from the nasopharynx, but in none of their experiments in which a fall in blood pressure was observed were all the baroreceptors eliminated.

Reflex vasodilation from increased activity of baroreceptors must also contribute to the fall in blood pressure, but the vasomotor effects of the volatile anaesthetics are complex. Bhatia & Burn (1933) found that ether in decerebrate and spinal cats produced a stimulation of the sympathetic nervous system in the absence of the adrenals, resulting in an increased heart rate and in splenic contraction. Cattel (1923) had shown earlier that the rate at which ether was given to cats under basal chloralose anaesthesia determined whether or not a fall in blood pressure occurred, and Root & McAllister (1941) found that in conscious dogs, where the rate of administration of ether was necessarily more limited, a fall in blood pressure only occurred in sympathectomized

animals or in chronic spinal animals with transection at the level of T_6 or above. In normal dogs and in chronic spinal animals with the level of section below T_{10}, although there was a rise in blood pressure on inhalation of ether, there was also a reduction in heart rate, which in the light of the present work may well have been the reflex effect of an increased sensitivity of baroreceptors.

The varying initial effects of volatile anaesthetics on the blood pressure in intact animals may therefore depend on the relative rates at which sensitization of baroreceptors and stimulation of the sympathetic nervous system develop. With sudden exposures to high concentrations of anaesthetic, sensitization of baroreceptors apparently exerts its effect before sympathetic stimulation occurs. It is probable, therefore, that in the intact animal the effects of sensitization of baroreceptors are most important during the early stages of induction of anaesthesia.

SUMMARY

1. Inhalation of ether, chloroform or trichlorethylene results in an increase in sensitivity of carotid sinus and aortic baroreceptors. Cyclopropane does not produce this effect.

2. The effect has been observed in single units from the perfused carotid sinus where mechanical factors, such as changes in the form of the pressure-pulse wave, can be excluded.

3. Receptors in the perfused carotid sinus show an increased discharge in conditions in which contraction of smooth muscle of the arterial wall has been shown by others to decrease the discharge.

4. The role of sensitization of baroreceptors in the vasomotor response of the intact animal during induction of anaesthesia with volatile anaesthetics is discussed.

We wish to thank the Association of Anaesthetists of Great Britain and Ireland for a grant to one of us (J.D.R.) for the conversion of the Oxford Vaporizer used in these experiments. The vaporizer was calibrated by Dr H. Epstein of the Nuffield Dept. of Anaesthetics, Oxford. We are grateful to Mr W. T. S. Austin for much technical help.

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