PREGANGLIONIC SYMPATHETIC ACTIVITY AND THE EFFECTS OF ANAESTHETICS

BY

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SUMMARY

Preganglionic cervical and splanchnic sympathetic activity was recorded before and during administration of inhalation anaesthetics, in rabbits ventilated with oxygen and given gallamine. During control periods, when light anaesthesia was maintained with pentobarbitone, sympathetic discharge responded to changes in arterial pressure. Increased arterial Pco₂ exaggerated the amplitude of the respiratory sympathetic rhythm, and had a more variable effect on the mean impulse discharge rate. Preganglionic activity was increased by 25–50 per cent cyclopropane, which usually raised arterial pressure; by halothane, which caused severe hypotension; and by diethyl ether, which produced smaller circulatory changes. These experiments question the concept of "central vasomotor depression" during inhalation anaesthesia in the rabbit.

Changes in preganglionic sympathetic activity produced by inhalation anaesthetics have not been studied directly apart from a brief communication by Martin and Marrazzi (1942), stating that cyclopropane and chloroform do not affect cervical sympathetic discharge in cats. Deutsch, Linde and Price (1962), however, measured an increased plasma adrenaline level during cyclopropane anaesthesia in the dog, while in the same species Millar and Morris (1960) found no increase in circulating catecholamines when halothane was given. The former result suggests that excitation of the sympathetic nervous system by cyclopropane may account for the arterial hypertension which usually occurs. This view is supported by head perfusion experiments (Price et al., 1963), also in the dog, while similar studies suggest that there is depression of central sympathetic discharge during halothane anaesthesia (Price, Linde and Morse, 1963), which accords with the reduced arterial pressure and the catecholamine measurements.

In an attempt to confirm and extend these findings, we have recorded directly from sympathetic nerves during administration of cyclopropane, halothane and diethyl ether; this paper presents results obtained from preganglionic fibres. A short account of some of the results has already been published (Millar and Biscoe, 1964) and a demonstration of the techniques employed was given to the Physiological Society (Biscoe and Millar, 1964b).

METHODS

Twenty-three rabbits were anaesthetized with intravenous sodium pentobarbitone (Abbott Laboratories, 60 mg/ml). The dose initially required was assessed on the basis of respiratory rate, corneal reflex, pupil dilatation, and response to a painful stimulus; it was usually 40–50 mg/kg. Subsequent injections were made through a femoral vein catheter. Femoral arterial pressure was recorded with a Statham P23A transducer and Sanborn recorder. The gauge and cannula were filled, and periodically flushed, with heparinized saline (5000 units heparin, injection BP, Boots Pure Drug Co. Ltd., in 100 ml of 0.9 per cent sodium chloride solution). The trachea was...
cannulated low in the neck, and intermittent positive pressure respiration with 100 per cent oxygen was usually begun immediately.

Intravenous drug administration.

During the period of preparation the animal was given intravenous doses of 6 to 12 mg of sodium pentobarbitone at intervals of approximately 45 minutes. The amounts required for light anaesthesia were assessed prior to the injection of gallamine, and were given subsequently throughout the remainder of the experiment except during administration of the inhalation anaesthetics. These were given as the effects of the barbiturate anaesthesia wore off; further injections of pentobarbitone were administered after recovery from each inhalation anaesthetic.

Gallamine triethiodide (May & Baker Ltd., powder dissolved in 0.9 per cent sodium chloride solution, or supplied as injection BP) was injected intravenously in doses of 4 mg at intervals of 45–60 minutes while the actions of the inhalation anaesthetics were being studied. The first injection was given toward the end of the preparatory period. The muscle relaxant prevented spontaneous respiratory efforts which could interfere with nerve potential recording, and helped to ensure steady mechanical ventilation of the lungs. In several experiments intravenous injections of 6 per cent dextran in 0.9 per cent sodium chloride solution (Intradex, Glaxo) were given to raise the arterial pressure. Maintenance of the mean pressure at 80–100 mm Hg, together with intermittent positive pressure respiration and 100 per cent oxygen, permitted nerve recordings to be continued for many hours.

The preganglionic cervical sympathetic nerve was approached by reflecting the larynx and pharynx in the midline. This also gave access to the carotid sinus and aortic depressor nerves.

The splanchnic and adrenal nerves were approached from the lateral side retroperitoneally. There were frequently two splanchnic nerves, emerging from below the diaphragm and running towards the coeliac ganglion. Several branches usually passed to the adrenal gland; these were very small and could be identified only by using the operating microscope. Electrical stimulation of the splanchnic nerves, which produced the classical two-phase rise in arterial pressure, confirmed that they were efferent nerves to the adrenal gland; cutting the adrenal nerves abolished the second (humoral) rise in pressure and did not affect the initial (neurogenic) response (Liddell and Sherrington, 1929). In one rabbit there was a well-marked ganglion at the level of the adrenal gland, at a distance of 1–2 cm from the coeliac ganglion.

The sympathetic nerves were covered in warm liquid paraffin, the temperature of which was occasionally monitored with a thermistor probe and maintained at 37–38°C. They were dissected on a stainless steel plate fixed to the steel frame to which the animal was secured. Recordings were made from slips of nerve with bipolar platinum wire electrodes connected to a high input impedance AC pre-amplifier, Tektronix type 122; this was earthed to the steel frame. The action potentials were displayed on an oscilloscope, Tektronix type 502, and photographed on 35-mm film from a similar monitor oscilloscope.

The signal from one vertical oscilloscope amplifier was fed to a pulse height selector. This comprised both discriminator and pulse-shaping sections. Nerve action potentials between selected upper and lower voltage limits were converted into square pulses, which were then counted on a ratemeter. The pulse height selector output was also used to trigger a Venner Electronics Reset Unit (TS 32); this caused the resetting to zero of a time scale which was displayed on the oscilloscope. The output of the pulse height selector could also be viewed directly on the oscilloscope. The ratemeter (Nuclear Enterprises Ltd.) had variable time constants and range scales. A permanent continuous record of its output was obtained on a Texas Instruments Servoriter. The output of the pulse height selector was continuously monitored to ensure that a change in the signal-to-noise ratio did not affect the number of potentials counted during an experimental sequence. This was done in two ways, either by viewing the pulse height selector output signal or by inspection of the resetting step-function time signal (shown in fig. 9, and Biscoe and Millar, 1964a). Either of these signals could be photographed together with the nerve recording, while audio-monitoring was used continuously during recording.

Respiration was sometimes monitored by
means of a thermistor probe in the tracheal cannula. The temperature of the animal was maintained at 36–38 °C with a thermosensitive transistor amplifier controlling the current flowing through a heating blanket (Krnjevic and Mitchell, 1962).

Intravenous injections of adrenaline chloride (BP 1953, 1 in 1000 solution, Evans Medical Ltd.) were given to study the effect of increased arterial pressure on sympathetic discharge.

In four rabbits, 0.5-ml samples of arterial blood were withdrawn and the Po4 was measured by polarography, using a Beckman Physiological Gas Analyzer, Model 160. The arterial Po4 was invariably above 250 mm Hg, and the level was approximately halved when 50 per cent cyclopropane was given; halothane or ether anaesthesia was associated with insignificant changes.

In ten rabbits the end-tidal carbon dioxide concentration was monitored continuously with an infra-red analyzer (Beckman Medical Gas Analyzer, Model LB-1); it was usually in the range 3–4 per cent.

In eleven experiments 2-ml samples of arterial blood were withdrawn at intervals from the femoral artery, for measurement of arterial pH, Pco3, and standard bicarbonate by the method of Siggaard Andersen et al. (1960).

Administration of inhalation anaesthetics.

A 2-litre rubber bag and a Heidbrink-type expiratory valve were placed between the inlet of a Palmer (non-rebreathing) respiratory pump and a Boyle anaesthetic apparatus. Flow rates of oxygen and cyclopropane were measured with Rotameters. Diethyl ether (May & Baker Ltd.) vapour was delivered from a Copper Kettle (Morris, 1952). Halothane BP (Fluothane, ICI Ltd.) was administered by directing the oxygen flow through a calibrated vaporizer (Flutec Mark 2, Cyprane Ltd.), accurate to within 0.1 vol per cent at dial settings of 2 and 3 per cent halothane and gas flow rates of 4 litres per minute. The expiratory valve was left in the open position to allow partial escape of the gas flows required for accurate vaporization of halothane; otherwise, pressure effects might have affected the concentrations of halothane delivered (Hill and Lowe, 1962).

In two experiments the expired halothane concentration was measured with an ultraviolet halothane meter (Hook & Tucker, Ltd.).

The three inhalation anaesthetics were usually studied in the order corresponding to their speeds of uptake and elimination: cyclopropane, halothane, ether. Sufficient time was allowed between each administration to permit maximum recovery of arterial pressure and sympathetic activity toward control levels. This occurred rapidly after cyclopropane, but in all cases the administration of another inhalation anaesthetic was delayed at least until the recovery period exceeded that of exposure to the preceding agent, and usually the delay was one and a half to two times the duration of the previous administration. The times of administration presented here include a lag of about 1 minute due to the gas volume contained in the inspiratory delivery tube between the animal and the respiration pump.

RESULTS

During control periods, when the level of basal anaesthesia with pentobarbitone was evenly maintained, the integrated sympathetic discharge from multifibre strands usually remained constant for 30 minutes or longer, and activity could be monitored for many hours.

The effects of sodium pentobarbitone, when given in doses of 6–12 mg intravenously, were inconsistent but produced only small alterations in arterial pressure and sympathetic discharge rate. Eight experiments were examined in detail. In four of these arterial pressure was unchanged after injection of 6 mg doses; in three of the four rabbits showing transient hypotension in response to 6 or 12 mg pentobarbitone, recovery was complete within 3 minutes. Sympathetic discharge rate was unaltered in two, increased in two, and reduced in four of these eight experiments; on five of the six occasions in which sympathetic activity was modified there was a return to the pre-injection level within 90 sec. Changes in arterial pressure, in one experiment, and in preganglionic discharge rate, in another, had not recovered until 4 minutes after the injection of sodium pentobarbitone.

The effects of gallamine triethiodide on sympathetic activity appeared to be negligible. In eight of fifteen injections in twelve animals there
was a mean fall in the discharge frequency of 3 per cent, with complete recovery in 1 min; in the other seven examples there was no change. A small fall in arterial pressure, lasting for less than 30 sec, occurred in only two animals. In the only other rabbit to show any response, there was a brief rise in arterial pressure lasting for 90 sec. The injection of gallamine was associated with a fall in heart rate of 10–20 beats/min, lasting less than 30 sec; this represented a small change, since the control heart rates were usually about 300 beats/min.

Figure 1 illustrates a typically transient reduction in mean arterial pressure and heart rate, following injection of a mixture of 12 mg sodium pentobarbitone and 4 mg gallamine. This also caused a brief increase in the mean cervical sympathetic discharge rate and a temporary loss of the respiratory modulations.

Cervical sympathetic fibres showed a respiratory rhythm during positive pressure ventilation of the lungs; towards the end of expiration and at the start of inspiration there was a burst of activity; an example is shown in figure 2. This rhythm was disrupted briefly by administration of pentobarbitone (fig. 1).

Further records are shown in figure 3, in which positive pressure inflation of the lungs is indicated by changes in end-tidal $P_{CO_2}$ (expiration upwards). In the example A, the rate of impulse discharge reached a peak during both inspiration and expiration. Figure 3B shows the effect on the discharge of stopping mechanical ventilation; the peaks of activity continued with the same period but were no longer coupled as in figure 3A. The coupling persisted after the vagi had been cut (fig. 4A) but was less constant when the rate of respiration was slowed (fig. 4B). Inspection of these records shows that the coupling did not have a constant relation either to the end-tidal $P_{CO_2}$ or to the arterial pressure wave.

The nature of the rhythmic activity shown in figures 3 and 4 is further clarified by reference to the findings in another rabbit in which the vagi, carotid sinus, and aortic nerves had been cut. Figure 5a shows, above, the end-tidal $P_{CO_2}$ during positive pressure ventilation (expiration upwards) and below, the integrated sympathetic discharge with a rhythm which is faster than the ventilation rate. Figure 5b is a film record taken later in the same experiment and shows sympathetic action potentials occurring rhythmically in bursts. The end-tidal $P_{CO_2}$ trace is irregular because the animal was breathing against the pump as the effect of gallamine wore off. When the pump was stopped the animal breathed spontaneously, shown in the $P_{CO_2}$ trace, and the bursts of action potentials were in time with this spontaneous respiration. This clearly suggests a central origin for certain types of sympathetic respiratory rhythm (Adrian, Bronk and Phillips, 1932) which can occur even when the end-tidal $P_{CO_2}$ is as low as about 20 mm Hg (fig. 5). A further example of this rhythm is shown in figure 16, from another experiment wherein the vagi and baroreceptor nerves had been cut.

A cardiac rhythm (grouped impulses in time with the arterial pulse wave) was seen occasionally in the cervical sympathetic nerve, three examples being obtained. In one rabbit in which the carotid and aortic sinus nerves were divided in stages the rhythm persisted until the last (aortic) baroreceptor nerve was cut.

Sympathetic responses to an increase in inspired $P_{CO_2}$.

Records were obtained from the cervical sympathetic nerve in three, and from the adrenal nerve in two, rabbits. In every experiment an exaggeration of the respiratory modulation of sympathetic activity was produced by carbon dioxide; when the inspired carbon dioxide concentration was increased by 5–10 per cent, the amplitude of the sympathetic rhythm was approximately doubled. Figure 6 shows a series of action potential records from the preganglionic cervical nerve. In sequence a the animal was breathing 100 per cent oxygen; mean arterial pressure was 66 mm Hg. Measurements of the amplitude of the variation in sympathetic discharge, from the ratemeter record, showed a fluctuation of 26/sec about a mean rate of 90/sec. After 6 min of 3 per cent carbon dioxide the sympathetic rate was 84 and the variation 38/sec (fig. 6c). Sequence d, taken during ventilation with 8 per cent carbon dioxide, shows more marked synchronization of the action potential bursts; the
Records from above down: heart rate counted for 5 sec periods (■); mean arterial pressure (mm Hg); preganglionic cervical sympathetic nerve, integrated discharge rate in impulses/sec (time constant, 1 sec). At the arrow sodium pentobarbitone 12 mg and gallamine triethiodide 4 mg were injected intravenously.

Film record. Upper trace: action potentials recorded from the preganglionic cervical sympathetic nerve; impulse discharge is mainly during expiration. Lower trace: arterial pressure (mm Hg).
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variation was now 40/sec and the mean rate had returned to the control level, 90/sec. When the inspired carbon dioxide was raised to 10 per cent for 6 min, there was no further change in mean sympathetic discharge rate or rhythm, although there was greater synchronization of the bursts (fig. 6c). Until this point, mean arterial pressure during administration of carbon dioxide had remained at 77 mm Hg, but the level increased to 90 mm Hg when 20 per cent carbon dioxide was given (fig. 6f). At this concentration, cervical sympathetic discharge showed a marked increase, to 127/sec, the amplitude of the rhythm remaining at about 38/sec, but becoming more regular.

The experiment just described illustrates that at carbon dioxide concentrations below about 10 per cent, the effect on the mean preganglionic sympathetic discharge rate may be relatively small although there is a pronounced increase in the amplitude of the rhythmic oscillation associated with pulmonary ventilation.

In contrast, figure 7 illustrates another experiment wherein the mean rate of discharge did increase in the cervical sympathetic nerve when carbon dioxide was administered. The films of action potentials were taken simultaneously with the corresponding ratemeter records. Sequences a and b show, respectively, the control responses and those after 5 min of 5 per cent carbon dioxide. The amplitude of the rhythm had slightly increased in b, but there was also a rise in the mean discharge rate. After 5 min of 8 per cent carbon dioxide, the rhythm was greatly increased, with a further small rise in mean rate (fig. 7c). Sequences d and e show later stages of the same process, at carbon dioxide concentrations of 10 and 20 per cent; the most striking effect was again the increase in amplitude of the respiratory rhythm.

![Fig. 3](https://academic.oup.com/bja/article-abstract/37/11/804/242406)

From above down: end-tidal Pco₂ (mm Hg); arterial pressure (mm Hg); preganglionic cervical sympathetic nerve, integrated discharge rate in impulses/sec (time constant, 0.33 sec); film record of the action potentials taken simultaneously. A: the sympathetic discharge shows synchronized bursts which are coupled, during both inspiration and expiration. B: the effect on this rhythm of stopping mechanical ventilation, at the horizontal mark.
The final sequence, illustrated in figure 7e, shows the ratemeter record on returning to administration of 100 per cent oxygen. A fall in the mean sympathetic discharge rate occurred to below the control level, with a reduction in the amplitude of the rhythmic oscillations, both effects being observed within 1 minute. After a further 4 min the respiratory fluctuations were still more marked than before carbon dioxide administration, and did not return to the previous level until another 2 min had passed, indicated by the gap in the trace. The mean impulse discharge rate remained lowered, however.

A change from ventilation with 100 per cent oxygen to room air, or vice versa, caused no detectable alteration in the mean level of sympathetic activity in several experiments.

Haemorrhage.

During splanchnic nerve recording, in two experiments, arterial hypotension was induced by haemorrhage, after allowing time for elimination of previously administered inhalation anaesthetics. Activity in the sympathetic strands under study was shown to be inhibited by intravenous adrenaline. Preganglionic sympathetic discharge was increased as arterial pressure was reduced but this was not associated with effects on the amplitude of the respiratory oscillations in sympathetic discharge. Changes in the mean splanchnic discharge rate in one experiment are plotted against mean arterial pressure in figure 8. The numbers adjacent to the points refer to the order in which the measurements were made as blood was removed or replaced. The points are grouped around the line drawn by eye and suggest a positive inverse correlation.

Vasomotor fibres.

Since recordings were made from the cut end of cervical and splanchnic sympathetic nerves, it was not possible to be certain of the destination
of fibres whose discharge rates were being measured, or of their relation to peripheral vascular control. The following criteria suggested, however, that their responses were similar to those of vasomotor fibres.

Firstly, there was a reflex response to arterial pressure changes. This was shown by partial or complete inhibition of preganglionic discharge when a rise in arterial pressure was produced by intravenous adrenaline (5–10 μg), this test being applied one or more times during every experiment (fig. 9a); again, by fleeting sympathetic inhibition when a small volume of saline or dextran in saline was injected rapidly intravenously; also, by the increase in sympathetic activity which occasionally accompanied the brief hypotension caused by intravenous pentobarbitone; and by the inverse linear relation between discharge frequency and arterial pressure demonstrated above for haemorrhage.

Secondly, electrical stimulation of the depressor (aortic baroreceptor) nerve in the rabbit evoked simultaneous reductions in arterial pressure and preganglionic sympathetic discharge, the two effects being well correlated quantitatively in several experiments (Biscoe and Millar, 1966a).

Thirdly, stimulation of the rabbit during light anaesthesia (for example, by touching the wound edges) commonly produced an abrupt and parallel fall in both sympathetic discharge and arterial pressure.

Lastly, the characteristics of the sympathetic discharge observed during the control periods in the present experiments are similar to those observed by previous workers (Adrian, Bronk and Phillips, 1932; Iggo and Vogt, 1960) who have assumed a close interrelation between cervical sympathetic responses and those of arterial pressure.

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**Fig. 5**

(a) shows: above, end-tidal Pco₂ (mm Hg); below, integrated preganglionic cervical sympathetic discharge rate in impulses/sec, time constant 0.33 sec.

(b) is a film record showing, above, action potentials recorded in the same experiment as in (a) and, below, the end-tidal Pco₂ in mm Hg. During the period marked “pump off”, mechanical ventilation of the lungs was stopped.
The effectiveness of baroreceptor denervation, when undertaken, was confirmed by showing a negligible reduction or no change in preganglionic discharge in response to intravenous adrenaline 5–10 μg.

Patterns of activity observed in the splanchnic and adrenal nerves.

In the adrenal and other branches of the splanchnic nerve, four types of impulse discharge could be distinguished:

1. Spontaneous activity which showed a respiratory rhythm and which could be partially or completely inhibited by the rise in arterial pressure produced by intravenous adrenaline. This response was similar to that of cervical sympathetic strands (fig. 9a). Sixteen groups of fibres showing these characteristics were identified in sixteen nerve strands.

2. An irregular spontaneous discharge apparently without relation to respiration or arterial pulse. The fibres exhibiting this activity were excited by the rise in arterial pressure induced by adrenaline, and were present in five of the sixteen strands (fig. 9b).

![Fig. 6](https://academic.oup.com/bja/article-abstract/37/11/804/242406)

Action potentials recorded from the cervical sympathetic preganglionic nerve, illustrating the effect on the discharge rate of increasing the inspired $\text{Pco}_2$. The inspired carbon dioxide concentration in oxygen is indicated to the left of the figure. In (a) the rabbit breathed 100 per cent oxygen; the time during which the indicated carbon dioxide concentrations were administered was 6 min in each case.
(3) Spontaneous activity showing a fairly regular discharge which could be increased by a rise in arterial pressure, and which was inhibited during inspiration. This was observed in two groups of fibres in sixteen strands.

(4) Brief high-frequency bursts of action potentials, unaffected by a rise in arterial pressure, were seen in three of the sixteen strands (fig. 9c, d).

**Fig. 7**

Records from the cervical sympathetic preganglionic nerve to show the effect on the activity of increasing the inspired carbon dioxide concentration. To the left are ratemeter recordings calibrated in impulses/sec (time constant, 1 sec). To the right are film records taken during the corresponding ratemeter records. In each case the gas mixtures were given for 5 min before the records were taken: (a) the inspired gas was 100 per cent oxygen; (b) 5 per cent carbon dioxide in oxygen; (c) 8 per cent carbon dioxide in oxygen; (d) 10 per cent carbon dioxide in oxygen; (e) 20 per cent carbon dioxide in oxygen, and the changes in sympathetic discharge on returning to 100 per cent oxygen. Note the different time scales for the film strips and the ratemeter.
Acid-base changes.

Measurements of the effects of the inhalation anaesthetics on preganglionic sympathetic discharge were made only during pulmonary ventilation with high oxygen concentrations. In addition to maintaining a viable preparation for many hours, it was considered that good oxygenation would limit the extent to which metabolic acidosis develops during long experiments on the rabbit. Nevertheless, a degree of pulmonary over-ventilation was usually required in order to maintain arterial pH at near normal levels. This was preferred to underventilation, since in previous studies progressive increases in plasma catecholamine concentrations were measured as pH was reduced by carbon dioxide ventilation or acid infusions (Morris and Millar, 1962a, b). Measurement of arterial pH, Pco₂, and standard bicarbonate were made at intervals in eleven rabbits during investigation of the effects of the anaesthetics on cervical sympathetic activity. The means of the lowest and the highest acid-base values from these experiments were respectively: for arterial pH, 7.35 (SD ± 0.07) and 7.44 (SD ± 0.06); for arterial Pco₂, 27 mm Hg (SD ± 4.6) and 32 mm Hg (SD ± 4.6); and for standard bicarbonate 18.0 mM/l. (SD ± 2.8) and 21.3 mM/l. (SD ± 2.8).

EFFECTS OF CYCLOPROPANE, HALOTHANE AND ETHER

In assessing the actions of the inhalation anaesthetics, control levels based on the mean preganglionic sympathetic discharge rate and arterial pressure both before and after anaesthetic administration would have been influenced by the frequent failure of arterial pressure to return to exactly the same level after discontinuing each anaesthetic; sometimes, also, 5 to 20 ml dextran in saline was required to restore the pressure to near the initial level. The effects of the anaesthetics were assessed, therefore, by comparison only with the impulse discharge rate and arterial pressure level which preceded administration.

It is possible that gradual deterioration of the animals during the progress of an experiment may have influenced measurements made during the latter part; this could have affected certain responses, though no difference in the qualitative effects observed could be detected when the order of administration of agents was altered. Never-
theless, in apparently healthy rabbits the responses observed in consecutive administrations of one anaesthetic were seldom identical quantitatively. In order to minimize effects attributable to repeated administrations, mean values and statistical inferences usually refer only to one (almost invariably the first) administration of each of the three anaesthetics in any animal.

**PREGANGLIONIC CERVICAL SYMPATHETIC**

**Cyclopropane.**

Nine rabbits were ventilated with 50 per cent cyclopropane in oxygen. In eight of these animals, arterial pressure increased progressively after 2 to 3 min, to a maximum level averaging 21 per cent above control after 4 to 8 minutes (SE±4.1; 0.01>P>0.001). In each case there was an associated rise in preganglionic cervical sympathetic discharge rate, to a mean of 80 per cent above the pre-anaesthetic level at the times corresponding to the peak rise in arterial pressure. This increase was highly significant (SE±18; 0.01>P>0.001). In the single rabbit which did not show an increase in arterial pressure above control, the sympathetic discharge rate was increased by 50 per cent after 4 min of cyclopropane.

The maximum increase in sympathetic activity evoked by cyclopropane, which was by a mean of 93 per cent above the control level (SE±5.3; 0.001>P), coincided with the peak rise in arterial pressure in three of the eight tests; in four instances the effects were separated by 2 min, and in one case by 4 min. At the time of peak sympathetic discharge rate, the average increase in arterial pressure in all nine tests was by 10 per cent above control.

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**FIG. 9**

Action potentials from the splanchnic nerve (a, b, and c) and adrenal nerve (d), showing the types of activity which may be found in different strands.

(a) Upper trace shows grouped discharge in time with respiration. Lower trace shows the mean arterial pressure in mm Hg. At the first arrow 5 μg adrenaline chloride were injected intravenously, at the second arrow the drug was washed in with 0.9 per cent NaCl solution.

(b) Upper trace, action potentials. Lower trace, arterial pressure (mm Hg). At the first arrow 7.5 μg adrenaline chloride were injected intravenously, and washed in at the second arrow.

(c) Upper trace, action potentials; lower trace, resetting time scale described under "Methods".

(d) Upper trace, action potentials recorded from the adrenal branch of the splanchnic nerve and having the same characteristics as those in (c); lower trace, resetting time scale.
cent above control, which was insignificant (SE ± 4.7; 0.1 > P > 0.05).

Arterial pressure showed variable effects within the first 2–3 min of administration of 50 per cent cyclopropane. In one of the nine rabbits studied, there was no change from the control level. In another three animals, arterial pressure had already started to rise. A brief period of hypotension, most pronounced 2 min after induction, occurred in four other experiments, in three of which cervical sympathetic discharge had increased above the control level. One of these three is illustrated in figure 10A, where the mean arterial pressure fell as preganglionic sympathetic activity increased. After 2 min the arterial pressure also started to rise. The one experiment in which there was an initial fall both in sympathetic rate and arterial pressure is illustrated in figure 11A. In this case the pressure reached its lowest point about 30 sec before the sympathetic discharge rate, and then began to rise slowly. By contrast, cervical sympathetic activity showed a slower fall but recovered more rapidly. Both arterial pressure and sympathetic rate eventually exceeded their control levels.

Figure 10A also shows the characteristic, and associated, increases in preganglionic discharge and arterial pressure within the first 8 min of cyclopropane administration. After reaching a peak the pressure usually declined towards control levels as the 50 per cent concentration was maintained. In figure 10A this effect was very

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**FIG. 10**

The upper graphs (●) are plots of the impulse discharge rate in the cervical sympathetic preganglionic nerve (impulses/sec) against time (min). The lower graphs, (○) represent mean arterial pressure (mm Hg) taken at the same time as the upper graphs and on the same time scale in min; 50 per cent cyclopropane was given between the arrows.

A: response with all other nerves intact.
B: response with the vagus, sinus, and aortic nerves cut bilaterally.
marked; after 10 min the pressure was below control while the sympathetic rate, after showing a transient fall, remained elevated. This maintained increase in sympathetic discharge was the usual response, and in only one experiment did the rate fall transiently below the control level during continuous administration of 50 per cent cyclopropane. This is shown in figure 12. Arterial pressure and sympathetic rate were both at a maximum at 4 min; subsequently the pressure fell and remained at a low level, more than 50 per cent below control, until the anaesthetic was discontinued at 30 min. In contrast, the sympathetic activity, though also showing a fall in rate below control at 10 min, later recovered to a new level maintained 11 per cent above control throughout the remainder of the administration. Both pressure and sympathetic rate recovered to near control levels when cyclopropane was discontinued.

Filmed records of action potentials illustrating the effects of cyclopropane are shown in figure 13 a–d. The first trace shows the discharge before administration, and figure 13b,c that after 6 min and 14½ min of 50 per cent cyclopropane. There was a progressive increase in activity and a loss of the synchronized bursts shown in the first

**FIG. 11**

(A) Preganglionic cervical sympathetic discharge frequency: ●, in impulses/sec; ○, systolic arterial pressure (mm Hg); □, diastolic arterial pressure (mm Hg); abscissa, time (min). At the arrow the administration of 50 per cent cyclopropane was started.

(B) Recording from the splanchnic nerve. The upper record is traced from the ratemeter output (impulses/sec). The lower records as in (A). Time is in min. At the arrow 50 per cent cyclopropane was given.
FIG. 12
Preganglionic cervical sympathetic nerve responses. Upper graph (●) impulses/sec; lower
graph (O) mean arterial pressure (mm Hg); both are plotted against the same time scale in
min; 50 per cent cyclopropane was administered between the arrows.

FIG. 13
Action potential records from preganglionic cervical sympathetic nerve strands. (a) 100 per
cent oxygen; (b) after 6 min 50 per cent cyclopropane in oxygen; (c) after 14½ min 50 per
cent cyclopropane in oxygen; (d) 15 min off cyclopropane. Records (e)–(i) from a second
experiment: (e) 100 per cent oxygen; (f) after 4 min of 3 per cent halothane in oxygen;
(g) after 13½ min 3 per cent halothane in oxygen; (h) after 14 min off halothane; (i) 14½ min
off halothane.
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Upper graph (●) preganglionic cervical sympathetic discharge rate (impulses/sec); lower graph (O) systolic and (□) diastolic arterial pressure (AP). Same time scale. 25 per cent cyclopropane was administered between the arrows.

Following induction with 50 per cent cyclopropane, this concentration was continued beyond the time of maximum increase in arterial pressure in seven of the nine rabbits studied; in the other two animals the anaesthetic concentration was reduced to 25 per cent. The sympathetic discharge rate continued to increase in seven animals, while the rate declined in two to levels below those corresponding to the maximum rise in arterial pressure. After administration of 50 per cent cyclopropane throughout, or of this concentration followed by 25 per cent cyclopropane, for a period of 14–30 min in four animals, arterial pressure was finally reduced on average by 25 per cent whereas the sympathetic rate was 46 per cent above the control level.

In two experiments, following a first administration of the higher concentration, 25 per cent cyclopropane was given subsequently for periods of 28 and 30 min respectively. Sustained increases in systolic and diastolic pressures and cervical sympathetic discharge were then measured throughout the entire period, as shown for a 30-min exposure in figure 14.

An early but brief rise in arterial pressure occurred within 1 to 3 min of discontinuing cyclopropane. At this time sympathetic discharge was unchanged or already beginning to decline. This effect was noted in seven of the eight rabbits anaesthetized with 50 per cent cyclopropane for periods of 8 to 12 min during cervical sympathetic recording; in the other animal, studied for 30 min, arterial pressure responses were obscured by cardiac arrhythmias (which ceased within 30 sec of stopping cyclopropane). The changes in one experiment are shown in figure 15; in this case sympathetic discharge fell as cyclopropane was discontinued, an effect perhaps attributable, reflexly, to the rise in arterial pressure. The maximum change noted, and occurring as in all the other experiments without an associated increase in preganglionic discharge, was a rise in mean arterial pressure from 59 mm Hg after 8 min of 50 per cent cyclopropane,
Recordings above of mean arterial pressure (mm Hg); below, integrated impulse discharge rate in the preganglionic cervical sympathetic nerve (impulses/sec, time constant 3.3 sec). At the arrow, when 50 per cent cyclopropane was discontinued, 100 per cent oxygen was given.

Vagi, sinus and aortic nerves cut. Film records of action potentials from the preganglionic cervical sympathetic nerve. (a) 100 per cent oxygen; (b) after 10 min 50 per cent cyclopropane in oxygen; (c) 14 min off cyclopropane; (d) after 10 min of 10 per cent ether.
to 118 mm Hg 3 min later. After the early rise in arterial pressure the level fell and later increased gradually, with a reduction in preganglionic discharge, as the anaesthetic was eliminated.

Effects of cyclopropane after cutting the carotid sinus, aortic, and vagus nerves in another group of rabbits. In the eight animals studied, the average initial arterial pressure level, 114 mm Hg, was higher than that in the animals with intact nerves. In one animal, the pressure increased to reach a maximum 28 per cent above the control level after 6 min of 50 per cent cyclopropane (fig. 10b), while another rabbit showed a small transient rise in arterial pressure only on a second administration (excluded from the statistical analysis below). Otherwise, although cervical sympathetic discharge was increased by cyclopropane in all the denervated animals, arterial pressure was reduced by an average of 20 per cent (SE±8.4; 0.05>P>0.02). The maximum rises in sympathetic activity, which occurred 4 to 8 min after induction, were significant (mean increase 55 per cent, SE±22; 0.05>P>0.02). The response to 50 per cent cyclopropane in a denervated animal is shown in the filmed records of figure 16 a–c. In b, after 10 min the rate of the counted impulses was increased from 48/sec to 57/sec; there was also fragmentation of the sympathetic rhythm of central origin.

Halothane.

Three per cent halothane was administered to seven rabbits, the other three animals studied being given a concentration of 1.5 or 2.0 per cent. Since arterial pressure was consistently lowered by concentrations above 1.5 per cent, the effects in all ten animals have been considered together. Changes in cervical sympathetic activity have been related arbitrarily, to two levels of arterial pressure during halothane anaesthesia, corresponding as nearly as possible to 30 and 60 per cent reductions from the control value. For each pressure level, eight measurements were available from the ten rabbits. Cervical sympathetic activity was increased by a mean of 43 per cent (SE±13; 0.02>P>0.01) above control at an average

![Graph](https://academic.oup.com/bja/article-abstract/37/11/804/242406)

**Fig. 17**

Preganglionic cervical sympathetic nerve responses. Upper graph (●) discharge rate in impulses/sec; lower graph (O) mean arterial pressure (mm Hg). The time scale in min is the same for each graph. Between the arrows 3 per cent halothane was given.
arterial pressure of 64 mm Hg reached after 2 to 12 min of halothane anaesthesia. At a mean pressure of 37 mm Hg, attained after 6 to 24 min, the impulse discharge rate was 45 per cent above control (SE±16; 0.05>P>0.02). The results in one experiment are shown in figure 17, where the time course of a 26-min exposure to 3 per cent halothane is plotted for sympathetic rate and mean arterial pressure. The pressure fell progressively for 16 min and eventually approached a steady low level. By contrast, sympathetic activity increased to reach a peak at 9 min; at 16-20 min there was a decline, followed by subsequent recovery. When halothane was discontinued, a precipitous fall in sympathetic rate occurred, and there was a rise in arterial pressure followed by a more gradual recovery to control levels. The photographic records of figure 13c-i, show the increase in sympathetic activity during halothane anaesthesia in another experiment. The control rate (c) was 70/sec and there was a synchronized respiratory rhythm. After 4 min (f) the discharge rate reached a maximum of 120/sec, which subsequently fell slightly to 111/sec after 13½ min. In addition to this considerable increase, the rhythmical characteristics of the sympathetic discharge were partly abolished, but returned, quite suddenly, between 14 and 14½ min after discontinuing halothane (compare fig. 13h and i).

While arterial pressure became progressively lower as anaesthesia with halothane was continued, sometimes reaching 20 mm Hg with the 3 per cent inspired concentration, the result shown in figure 17 illustrates the typical finding that in the rabbit these low arterial pressure levels were not associated with reductions in the cervical sympathetic discharge rate.

Similarly, although administration of 1.5 and 2.0 per cent halothane was associated with greater variability of sympathetic activity, the mean impulse discharge rate generally remained slightly or moderately above control levels.

In two rabbits, the arterial pressure and sympathetic responses to halothane were studied over 30-min periods during which the expired halothane concentration was held constant at approximately 1 vol per cent. This required adjustment of the inspired concentration to match the uptake of halothane, which became progressively less as anaesthesia continued. In one animal there were two 4-minute periods, 9-13 min and again 20-24 min after starting administration, when the inspired concentration was at 2.0 per cent and the mixed expired concentration remained steady between 0.95 and 1.14 vol per cent. Since pulmonary ventilation was unaltered, it may be assumed that the uptake of halothane by the animal stayed almost constant during these periods. In this experiment, arterial pressure was lowered from a control level of 107 mm Hg to 43 mm Hg after 12 min and to 41 mm Hg after 22 min of halothane; the associated increases in preganglionic sympathetic discharge were by 12 per cent and by 16 per cent respectively. The results in the other experiment were similar.

Thus, while most of the measurements reported here were associated with a fixed inspired concentration of halothane, there was no evidence that preganglionic sympathetic discharge was reduced by halothane when the uptake of the anaesthetic was maintained at a more constant level.

Effects of halothane after cutting the carotid sinus, aortic, and vagus nerves in another group of rabbits. Before halothane administration, the average control arterial pressure in six denervated animals was 118 mm Hg. Six measurements of sympathetic discharge were available during halothane anaesthesia, at arterial pressures approximately 30 and 60 per cent below the control level. At a 30 per cent reduction in arterial pressure, sympathetic activity showed variable increases above control in every animal, although the mean rise, by 20 per cent, was insignificantly different from zero (SE±9.6; 0.1>P>0.05). At an arterial pressure level 60 per cent below control, sympathetic discharge was increased by 22 per cent, this being a significant change (SE±8.2; 0.05>P>0.02).

Diethyl Ether.

Nine to 14 per cent ether in oxygen was given to seven rabbits. After 4 min, cervical sympathetic discharge was increased by an average of 29 per cent above control; this was a highly significant change (SE±7.4; 0.01>P>0.001). At this time, mean arterial pressure was reduced by 11 per cent (SE±3.1; 0.05>P>0.02). After 10 min of ether, the rises in sympathetic discharge rate were greater, reaching a mean of
71 per cent above control, but due to the wide range of increases (by 7 to 224 per cent) this effect was not statistically significant (SE±30; 0.1>P>0.05); at this time, arterial pressure was reduced on average by 28 per cent, a highly significant change from the control level (SE±6.9; 0.01>P>0.001). Figure 18a illustrates the time course of the changes in sympathetic rate and mean arterial pressure in response to 12.5 per cent ether. There was a progressive increase in the discharge rate, until after 10 min a new level was maintained. The arterial pressure showed initial variation, followed by a progressive decline reversed only by discontinuing the administration.

Effects of ether after cutting carotid sinus, aortic and vagus nerves in another group of rabbits. Seven to 15 per cent ether was administered to six denervated rabbits. After 8 min, cervical sympathetic activity was increased by 36 per cent, which was a significant change from control (SE±12; 0.05>P>0.02). At this time, arterial pressure was reduced by a mean of 22 per cent, which was also significant (SE±7.7; 0.05>P>0.02). The records in figure 16c and d show some effects of ether administration after the baroreceptor nerves and vagi had been cut. The sympathetic rhythm seen in figure 16c, which was presumably of central origin, increased in frequency after 10 min of 12 per cent ether, while the mean discharge rate rose from 57/sec to 62/sec (d). A similar increase in frequency of the rhythm was seen in other experiments during ether administration. Figure 18b also shows a response to ether in a denervated rabbit anesthetized for 11 min. There was a steady rise in sympathetic rate throughout, while the arterial pressure, after a rapid fall, recovered to a higher level which was still below control. This pattern of partial recovery of arterial pressure was seen on two other occasions when the carotid sinus, aortic, and vagus nerves had been divided.
SPLANCHNIC NERVE

Nine strands were dissected from the splanchnic nerve in six rabbits. Variable responses to the anaesthetics of the atypical fibre groups, mentioned previously, were usually concealed in the total integrated discharge rates, but were identified on film.

Changes in the activity of rhythmically discharging fibres which were unaffected by adrenaline were not studied during administration of the inhalation anaesthetics, although their activity was seen to persist.

Those units whose discharge frequency was reduced by intravenous adrenaline showed similar responses to cyclopropane, halothane, and ether, as those previously described for cervical sympathetic nerve strands. The results presented below refer to one administration of each anaesthetic in individual animals.

Cyclopropane.

In four rabbits, four splanchnic sympathetic strands showing uniform inhibition by intravenous adrenaline were studied during ventilation with 50 per cent cyclopropane for periods of 8 to 14 min. Arterial pressure increased to reach a maximum averaging 44 per cent above control levels after 6 to 10 min, this being associated with a mean increase in the sympathetic discharge rate of 124 per cent (SE±34; 0.05>P>0.02). The results in one of these experiments are illustrated in figure 19b. In this case the major rise in sympathetic activity was delayed, uncharacteristically, for 8 min. The arterial pressure had already risen, and increased more steeply as the sympathetic rate increased. The photographic records of figure 20 illustrate several features of cyclopropane excitation. In a, there was synchronization of the activity of a single unit, which became more marked in b after 2 min of 50 per cent cyclopropane, when the rate of firing was increased from 35 to 48 per 20-sec period. After 6 min (c), the rhythm began to fragment, and the discharge rate increased further, to a maxi-

![Graphs](https://academic.oup.com/bja/article-abstract/37/11/804/242406)
PREGANGLIONIC SYMPATHETIC ACTIVITY AND ANAESTHETICS

maximum of 55 per 20-sec period. At d, 15 min after the start of anaesthesia, the rate was reduced to 41 in a 20-sec period, and the activity within bursts was irregular. In addition a second downward-going spike was recruited. Record e shows the discharge 12 min after discontinuing cyclopropane, when the frequency was now 19 per 20-sec period.

Figure 20f–h shows the effect of 50 per cent cyclopropane on a splanchnic nerve strand in another experiment. The rate of firing of all the spikes was increased after 8 min, and there was recruitment of a small upward-going potential towards the centre of the record. Figure 21a–c is unusual, and shows depression by cyclopropane of an upward-going spike (compare b, after 7 min 50 per cent cyclopropane, with a and c). The other potentials show marked excitation. In one animal a splanchnic cardiac rhythm became audible during cyclopropane administration.

Halothane.

Five splanchnic sympathetic strands were studied in five rabbits anaesthetized with 3 per cent halothane. At arterial pressure levels 30 per cent below control (reached after 2 to 14 min of anesthesia), changes in sympathetic discharge were variable; the average increase, by 20 per cent, was insignificantly different from zero (SE ± 17; 0.4 > P > 0.3). A 60 per cent reduction in arterial pressure was reached after 6 to 24 min, when the discharge frequency was 76 per cent above control. This increase was significant (SE ± 26; 0.05 > P > 0.02). A representative experiment is illustrated in figure 22b; the sympathetic rate was at first reduced with the arterial pressure, but at 4 min the activity recovered and remained above control, with some variation until the halothane was discontinued. Figure 21d–g are film records taken during this experiment. Figure 21e shows a marked increase in sympathetic discharge corresponding to the first peak on the graph in figure 22b; after 12–13 min of halothane (fig. 21f) there was a fall towards control levels; and the last sequence (g) shows the subsequent fall in activity below control when the halothane was stopped.

In one animal from this group the arterial pressure responses to 3 per cent halothane were unusual; after an early small reduction in pressure (associated with a rise in sympathetic discharge), the pressure increased to above con-

![Image of action potential records from the splanchnic nerve](https://academic.oup.com/bja/article-abstract/37/11/804/242406/fig-20)

**Fig. 20**

Action potential records from the splanchnic nerve. (a) 100 per cent oxygen; (b) after 2 min, (c) after 6 min, and (d) after 15 min 50 per cent cyclopropane in oxygen; (e) 12 min off cyclopropane; (f) from another rabbit given 100 per cent oxygen; (g) after 8 min 50 per cent cyclopropane in oxygen; (h) 15 min off cyclopropane.
control levels between 6 and 12 min; at the latter time splanchnic sympathetic discharge had increased by 91 per cent. Thereafter arterial pressure fell to reach a level 66 per cent below control after 28 min of 3 per cent halothane; at this time sympathetic activity was increased by 100 per cent. Subsequently, recovery of both arterial pressure and sympathetic discharge occurred to control levels.

**Diethyl Ether.**

Four splanchnic sympathetic strands were studied in four rabbits during administration of diethyl ether in concentrations of 8 to 10 per cent. The impulse discharge rate was increased, after periods of 16 to 20 min, to an average of 77 per cent above control, this being significant (SE±24; 0.05>P>0.02). Arterial pressure was progressively reduced to a level 22 per cent below control, at these times. In figure 23B ether is shown to cause a progressive rise in sympathetic rate and an associated fall in arterial pressure.

**ADRENAL NERVE**

In three experiments the response of the adrenal branch of the splanchnic nerve was studied during anaesthesia with cyclopropane. In two of these experiments, one of which is shown in figure 19A, increases in sympathetic activity (mean, 110 per cent) occurred over approximately the same periods as the rises in arterial pressure (mean, 72 per cent) produced by 50 per cent cyclopropane. In the third study the responses were unlike those of other sympathetic nerves; the rise in arterial pressure induced by cyclopropane reached a maximum 50 per cent above control after 4 min, but at this time adrenal nervous activity was reduced by 33 per cent; subsequently arterial pressure fell to 80 per cent of control after 10 min, when the impulse discharge rate was 27 per cent above control level. These unusual effects may have resulted from persisting activity of central baroreceptor pathways during cyclopropane anaesthesia.

Adrenal nervous activity was studied in two rabbits during ventilation with 3 per cent halothane. Thirty and 50 per cent reductions in arterial pressure were associated with mean increases in the discharge rate of 69 and 77 per cent respectively. In the example illustrated in figure 22A there was a rise in sympathetic activity of over 100 per cent at 8 min; recovery from halothane was very rapid.

Ether, administered to two rabbits for periods of 12 and 14 min, raised arterial pressure at these times by 6 and 4 per cent respectively, while the

![Action potential records from the splanchnic nerve.](https://academic.oup.com/bja/article-abstract/37/11/804/242406)

**FIG. 21**

Action potential records from the splanchnic nerve. (a) 100 per cent oxygen; (b) after 7 min 50 per cent cyclopropane in oxygen; (c) 6 min off cyclopropane; (d)–(g) a second strand from the same nerve; (d) 100 per cent oxygen; arterial pressure below; (e) after 64 min and (f) after 12½ min 3 per cent halothane; (g) 20 min off halothane.
corresponding increases in adrenal impulse discharge rate were by 204 and 14 per cent. The former dramatic increase in sympathetic rate is plotted in figure 23A, which shows the associated small change in mean arterial pressure.

Changes in heart rate. These were assessed by counting the number of beats in 5-second periods. In the rabbit, all three inhalation anaesthetics usually produced increases in heart rate of about 10-20 per cent; in one only of the nine animals given halothane was there a fall in heart rate which persisted throughout a 12-min administration.

DISCUSSION

Many original observations of Adrian, Bronk and Phillips (1932) on the activity recorded from the cervical sympathetic nerves of the rabbit have been confirmed in the present experiments, and the usefulness of a pulse-height selector and rate-meter has been established for assessing changes in the activity of multifibre sympathetic strands.

The identification of the destination of the sympathetic fibres under study was an obvious problem, but we have presented data relevant to the effects of the inhalation anaesthetics on those units whose activity was closely related to alterations in arterial pressure. All nerve strands dissected from the cervical sympathetic of the rabbit appeared to reflect the interrelation of arterial pressure and sympathetic discharge in a reproducible and consistent manner. On the other hand, while many sympathetic fibres in the splanchnic nerve responded similarly, there was far less uniformity. No information was obtained regarding the functions of the atypical splanchnic and adrenal units.

Our experiments confirm the previous comment of Iggo and Vogt (1960), that rhythms in preganglionic sympathetic activity may have several origins, involving both central and peripheral mechanisms. We have found (Biscoe and Millar, unpublished) that single baroreceptor units show a rhythm in time with the respiratory variations in arterial pressure, in artificially ventilated rabbits, while chemoreceptor fibres in the cat also show a respiratory rhythm (Biscoe and Purves, 1965). Systemic baroreceptor and chemo-

**FIG. 22**

Graphs, above (●) nerve impulses/sec and below (O) mean arterial pressure (mm Hg). Same time scale for each vertically aligned pair; 3 per cent halothane was given between the arrows. A, from the adrenal nerve; B, from the splanchnic nerve, in another experiment.
receptor stimuli, separately or together, appear to be mainly responsible for sympathetic rhythms of peripheral origin. Bursts of sympathetic activity, synchronized with inspiration, were occasionally observed in the present experiments in rabbits; but an expiratory rhythm was more usual, as described for this species by Adrian, Bronk and Phillips (1932). The cat is said to show a predominant inspiratory synchronization (Iggo and Vogt, 1960), but variations in pulmonary ventilation may account for some of these apparent species differences.

Continuous monitoring of the rhythmical sympathetic discharge clarified the effects of increasing the inspired carbon dioxide concentration. Thus, while there was always a striking increase in the amplitude of the sympathetic rhythm, the mean rate of discharge either remained unchanged or increased. It may, therefore, be questioned whether an increase in the rate of change of sympathetic efferent discharge may be a more effective stimulus to liberation of sympathetic transmitter at effector organs than is a rise in the mean frequency of firing. It is at any rate curious that consistent increases in the mean sympathetic discharge rate did not accompany administration of carbon dioxide concentrations up to 10 per cent, since these have been shown to increase plasma noradrenaline levels in the dog (Morris and Millar, 1962a).

We have found that 6–12 mg sodium pentobarbitone, given at intervals of about 45 min, suffices to maintain light but adequate anaesthesia in the rabbit, without influencing preganglionic sympathetic discharge other than temporarily. This was fortunate, and unexpected in view of known depressant actions of pentobarbitone on nervous transmission (Brooks and Eccles, 1947; Eccles, 1946; Eccles, Schmidt and Willis, 1963; Pradham and Galambos, 1963; Schmidt, 1963; Thesleff, 1956). Elmes and Jefferson (1942), however, measured a fall in the adrenaline content of the innervated, compared to the denervated, adrenal gland when pento-

Fig. 23
Graphs, above (●) nerve impulses/sec and below (○) mean arterial pressure (mm Hg). Same time scale for each vertically aligned pair; 8 per cent ether was given between the arrows. A, from the adrenal nerve; B, from the splanchnic nerve, in the same experiment.
barbitone preceded by morphine was given to cats. This result is difficult to interpret, but does show, in accord with the present experiments, that excitation of the sympathetic nervous system can occur in the presence of pentobarbitone.

The rises in arterial pressure produced by cyclopropane suggest a similar action in the rabbit to those previously described in the dog (Deutsch, Linde, and Price, 1962), and man (Jones et al., 1960). The rise in arterial pressure was shown to be consistently associated with proportionately greater increases in preganglionic discharge, which reached a peak usually closely related in time to that of arterial pressure. This association, although suggestive, does not of course prove a specific correlation between these effects, since there may be coincident direct actions of cyclopropane on sympathetic ganglia, heart, or blood vessels. There is evidence, for example, that the contraction of strips of rabbit aorta in response to noradrenaline is augmented by cyclopropane (Price and Price, 1962), while the increased excitability of the myocardium during cyclopropane anaesthesia, shown by the common occurrence of ventricular arrhythmias, is well known in all species studied. The present data do not demonstrate the respective contributions of increased preganglionic discharge and of peripheral effects to the rises in arterial pressure evoked by cyclopropane. Previous evidence of sympathetic excitation during cyclopropane anaesthesia has been derived from depletion of the adrenaline content of the adrenal gland in the cat (Elmes and Jefferson, 1942), and from the measurement of increases in plasma catecholamine concentrations in the dog (Deutsch, Linde and Price, 1962) and in man (Price et al., 1959; Millar and Morris, 1961).

Since, as occurs in other species, there was eventually a decline of arterial pressure but not of preganglionic discharge to below control levels, it may be deduced that after about 6 to 10 min of 50 per cent cyclopropane in the rabbit the increase in sympathetic activity is usually overcome by depressant effects exerted distally (at sympathetic ganglia, heart, blood vessels). This was demonstrated by the transient rise in arterial pressure frequently observed in the early moments after discontinuing cyclopropane; since this was not accompanied by an increase in preganglionic discharge, it indicates an action dependent on elimination of cyclopropane from effector organs (and possibly sympathetic ganglia) rather than from the central nervous system. Similarly, transient hypertension was also noted when high arterial carbon dioxide tensions were rapidly reduced, in a previous study (Millar, 1960).

While these results provide direct evidence that cyclopropane raises the mean level of preganglionic sympathetic discharge, they do not reveal the mechanism. At least two possibilities exist: first, direct excitation of sympathetic pathways in the spinal cord, medulla, or hypothalamus; second, depression of mechanisms normally causing inhibition of preganglionic activity. It has been reported, from studies in the dog, that the characteristic circulatory actions of cyclopropane still occur following classical decerebration, and it has been reasoned that cyclopropane diminishes baroreceptor responses by a central mechanism, this being responsible for central sympathetic excitation (Price et al., 1963). In associated experiments it has been confirmed that this anaesthetic exerts an early and potent inhibitory action on central baroreceptor pathways (Biscoe and Millar, 1966a); but the present studies show clearly that a marked increase in sympathetic discharge still occurs during administration of cyclopropane to baroreceptor-denervated rabbits. Since in the absence of cyclopropane these animals showed only slight or no sympathetic inhibition in response to intravenous adrenaline, the possible role of remaining baroreceptor afferents, as might exist in the splanchnic nerve (Gammon and Bronk, 1935), is speculative.

Thus, while a factor in the excitant effect of cyclopropane may be the removal of baroreceptor inhibition from sympathetic neurones, there remains a marked effect not accounted for on this basis alone.

Many reports have attempted to explain the hypotensive effect of halothane. A central action was suggested in pharmacological studies (Burn et al., 1957; Paton, 1959), and as a result of complex head perfusion experiments in the dog it has been affirmed that most or all of the circulatory effects depend upon depression of central sympathetic discharge (Price, Linde and Morse, 1963). Unless there is a species difference, the
present results do not support this; concentrations of halothane which produced arterial pressures as low as 20–30 mm Hg were still associated with an increased preganglionic sympathetic discharge. The reason for this might lie either in direct central excitation of sympathetic neurones, in a reflex increase in sympathetic discharge secondary to a reduced arterial pressure, or to a combination of these factors.

Reflex increases in sympathetic discharge demand the integrity of the central conducting pathways between systemic baroreceptor nerve endings and preganglionic neurones. Evidence has been presented elsewhere (Biscoe and Millar, 1966a) that while halothane causes a significant inhibition of depressor reflexes, it is still possible to reduce arterial pressure further by baroreceptor nerve stimulation even in the presence of profound hypotension caused by this anaesthetic. On this basis, therefore, increased preganglionic discharge during halothane anaesthesia might be in part reflexly induced. However, significant increases in cervical sympathetic activity were also recorded in baroreceptor-denervated animals in the present experiments.

In contrast to the effects of cyclopropane, measurement of plasma catecholamine concentrations during controlled halothane anaesthesia have failed to demonstrate any except slight, variable, and statistically insignificant rises (Price et al., 1959; Millar and Morris, 1961), although sympathetic responses to hypercarbia and haemorrhage appeared to be unaffected (Millar and Morris, 1960). This is curious, particularly in view of the large increases in adrenal nervous discharge measured in the present experiments. Several explanations may be suggested: for example, that the presence of a particular "background" anaesthetic may influence the responses to halothane; that sympathetic activity is not increased during halothane anaesthesia in species other than the rabbit; that concurrent effects distal to preganglionic fibres prevent the release of increased amounts of transmitter substance at postganglionic nerve-endings, that transmitter release is poorly correlated with changes in the mean integrated rate of preganglionic discharge, or that methods of assaying plasma catecholamine levels have been unable to detect increases below a certain gross order of magnitude.

Another consideration remains, which would be applicable to any inhalation anaesthetic studied in the manner described; this arises from the transient arterial hypotension, and fall in preganglionic sympathetic discharge, which occur readily when, for example, the incised skin edge is touched in rabbits which appear to be otherwise adequately anaesthetized (whether respiration is spontaneous or controlled). This response (which is infrequent in species such as the dog and cat) suggests that during experimental procedures in the rabbit afferent stimuli resulting from the experimental procedures could produce continuous sympathetic inhibition. Administration of inhalation anaesthetics in amounts sufficient to prevent central effects of such stimuli might then be responsible for a rise in sympathetic activity which is non-specific for individual anaesthetics and based on an analgesic action. The importance of this seems questionable since in a few experiments (Millar and Biscoe, unpublished) deepening of the "background" anaesthetic with 80 per cent nitrous oxide or 1.5 per cent trichloroethylene in oxygen produced only small changes in preganglionic activity.

Effects of halothane distal to preganglionic neurones are discussed further in later papers (Biscoe and Millar, 1966b; Millar and Biscoe, 1966). The circulatory actions of halothane in the rabbit, unlike those of cyclopropane, appear to depend on depressant effects exerted from an early stage at sites more peripheral than preganglionic lateral horn cells.

In the case of both cyclopropane and halothane, parallel reductions in arterial pressure and preganglionic sympathetic discharge occurred occasionally, but only within the first 2-3 min of administration. Baroreceptor sensitization (Biscoe and Millar, 1964a), which could initiate such effects, is therefore unlikely to be a major factor in halothane hypotension, but may be responsible for transient reductions in arterial pressure during induction with halothane, or with cyclopropane (Price and Widdicombe, 1962).

Sympathetic excitation during ether anaesthesia has been recognized for many years. For example, in 1912 Elliott showed that ether depleted the adrenaline content of the cat's adrenal gland, and that this effect was abolished by denervation; similar results were reported by other workers.
(Elmes and Jefferson, 1942). A reduction in the noradrenaline content of the hypothalamus and mid-brain of the dog, following ether anaesthesia, was demonstrated by Vogt (1954). Further evidence derives from studies in which ether was administered to intact and sympathectomized dogs (McAllister and Root, 1941; Brewster, Isaacs and Wainø-Andersen, 1953). Increased plasma adrenaline and noradrenaline levels have been measured during ether anaesthesia in the dog and man (Millar and Morris, 1961; Price et al., 1959).

The present experiments confirm that ether increases preganglionic sympathetic discharge, but the site of action remains unidentified. The occurrence of sympathetic excitation in baroreceptor-denervated animals largely precludes an action based solely on pharmacological blockade of central baroreceptor pathways. Reflex effects arising from peripheral receptors, for example in the respiratory tract, cannot be discarded since ether has been shown to sensitize systemic baroreceptors (Robertson, Swan and Whitteridge, 1956), pulmonary stretch receptors (Whitteridge and Bulbring, 1944), and muscle spindle nerve endings (Matthews, 1933). Involvement of the spinal cord was implied by Bhatia and Burn (1933), who demonstrated sympathetic stimulation during ether anaesthesia in spinal cats.

These studies have shown that in association with the typical hypotensive action of halothane, and in the case of relative overdose either with a rapidly acting gas such as cyclopropane or a more slowly acting vapour such as diethyl ether, preganglionic sympathetic activity continued at a discharge rate above that existing before administration of the anaesthetic. It is frequently stated that general anaesthetics cause central vasomotor depression, but this may require a more precise explanation in view of the lack of any such effect in the experiments described, even in the presence of severe hypotension.

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L’ACTION SYMPATHIQUE PREGANGLIONNAIRE ET LES EFFETS DE L’ANESTHESIE

SOMMAIRE

L’activité sympathique préganglionnaire cervicale et splanchnique a été enregistrée avant et pendant l’inhalation d’anesthésiques chez des lapins sous oxygène et recevant de la gallamine. Dans les périodes de contrôle quand on maintenait une légère anesthésie par le pentobarbitone, des décharges sympathiques ont répondu aux changements de tension artérielle. Une augmentation de la Pco₂ a entraîné une augmentation de l’amplitude du rythme respiratoire sympathique, et a eu un effet plus variable sur le taux moyen des influx. L’activité préganglionnaire a été augmentée de 25-50 pour cent avec le cyclopropane, qui a d’habitude augmenté la tension artérielle; avec l’halothane qui détermine une grave hypotension; avec le diéthyl-éther qui produit de moindres changements circulatoires. Ces expériences mettent en doute le concept de la “dépression vasomotrice centrale” au cours de l’anesthésie par inhalation chez le lapin.

PRAGANGLIONÄRE SYMPATHISCHE AKTIVITÄT UND DIE AUSWIRKUNGEN AUF DIE ANÄSTHESIE

ZUSAMMENFASSUNG