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EFFECTS OF END-TIDAL CONCENTRATIONS OF CYCLOPROPANE, HALOTHANE AND DIETHYL ETHER ON PERIPHERAL AUTONOMIC NEUROEFFECTOR SYSTEMS IN THE RAT

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1 The effects of the inhalation anaesthetics, cyclopropane, halothane and diethyl ether were examined on peripheral neuroeffector systems in the pithed and in the conscious rat.

2 In the absence of a suitable means of accurately quantifying doses of inhalation anaesthetics given to small animals, an apparatus was constructed whereby end-tidal gas samples were collected semi-automatically from the mechanically ventilated rat.

3 Cyclopropane (15.3 and 29.3% end-tidal), halothane (0.20, 0.52 and 0.83% end-tidal) and diethyl ether (2% and 4% end-tidal) lowered the arterial pressure of the pithed rat. Heart rate was increased by diethyl ether 4%, decreased by halothane and unchanged by cyclopropane.

4 While each anaesthetic depressed the pressor responses to sympathetic nerve stimulation, cyclopropane increased and halothane and diethyl ether depressed the pressor responses to exogenous noradrenaline.

5 Each anaesthetic reduced the motor responses of the smooth muscle of the colon to parasympathetic stimulation.

6 The significance of the effects on peripheral neuroeffector systems is discussed in relation to the overall circulatory changes produced by these anaesthetics in the whole animal.

Introduction

General anaesthesia is often accompanied by effects on the cardiovascular system which vary with the depth of anaesthesia and the agent used (see reviews by Price, 1960; Dundee, 1966). Arterial pressure is increased by the so called 'sympathomimetic' anaesthetics e.g., cyclopropane (Jones, Guldmann, Linde, Dripps & Price, 1960), is depressed by halothane (Goldberg, 1968) and appears to be relatively unaffected by diethyl ether (Eger, Smith, Cullen, Cullen & Gregory, 1971). These cardiovascular changes may be mediated centrally and/or peripherally (Millar, 1971).

Experimental methods employed hitherto to investigate the peripheral cardiovascular effects of anaesthetics have suffered from certain limitations. Results obtained *in vitro* are often difficult to apply to the *in vivo* situation, while the investigation of peripheral actions, *in vivo*, may be complicated by accompanying central effects. In addition, many *in vivo* studies of anaesthetics, in animals, have been complicated by the enforced use of basal anaesthetics.

In the present investigation, a comparison of the actions of cyclopropane, halothane and diethyl ether was made on peripheral autonomic neuroeffector systems, *in vivo*, in the absence of basal anaesthetics and without concomitant central interference, to permit a more accurate picture of the involvement of peripheral sites in the overall circulatory effects of these anaesthetics to be drawn. Some of these results have already been presented to the British Pharmacological Society (Clanachan, Gillespie, Millar & Muir, 1974).

Methods

Male Sprague-Dawley rats (250–300 g) were used in all experiments.

Conscious rats

Permanent indwelling arterial (carotid) and venous (external jugular) cannulae were inserted for the respective measurement of arterial pressure and the injection of drugs as described by Popovíc & Popovíc (1960). Under aseptic conditions, rats were anaesthetized with halothane in an O_2/N_2O carrier mixture (1:1 v/v) and the polythene cannulae, with attached

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Luer fitting, filled with heparinized (50 iu/ml), saline (0.9% w/v NaCl solution) and sealed with a 3-way tap, before insertion. Both cannulae were brought to the exterior through a small (1 cm) midline incision between the scapulae and attached by ligatures onto surrounding tissue. In this position, the taps could not be disturbed by the animal and appeared to cause little discomfort. Following the insertion of the cannulae, the animals were allowed to recover completely (3 days) and then placed in a perspex cylindrical restraining chamber (25 cm × 5 cm i.d.) which had, at one end, a small mixing compartment to receive administered gases. The chamber allowed restricted movement but prevented the animal from turning around. A small opening on the top of the chamber allowed access to the cannulae. The aortic cannula was untied and connected to an electronic pressure transducer for measurement of arterial pressure. Heart rate was measured via a ratemeter (Devices) triggered from the arterial pressure pulse. The arterial pressure and heart rate were displayed on a Devices chart recorder. An initial period of 30 min served to allow the animal to become acclimatized to the chamber and the control inspired gas (O_2/N_2, 1:1 v/v). The time course of the cardiovascular changes were monitored, continuously as required.

Pithed rat preparation

Rats were anaesthetized with halothane (4%) in an O_2/N_2 carrier mixture (1:1 v/v), pithed, (Gillespie & Muir, 1967) and immediately ventilated at 60/min with the carrier gas. Tidal volume was adjusted to 1.5 ml/100 g body wt. to maintain $Paco_2$ at approximately physiological values (40 mmHg). One carotid artery and one ipsilateral external jugular vein were cannulated for the respective measurement of arterial pressure and the administration of drugs. Body temperature was maintained at 37°C ± 1°C by a tungsten lamp and monitored by a rectal thermometer.

The spinal nerve roots were stimulated via a movable pithing electrode (Gillespie, MacLaren & Pollock, 1970) by square wave pulses (1 ms) at the frequencies and time periods indicated in the text. The voltage used was supramaximal for the response being observed. A length of silver wire (approximately 5 cm) was inserted subcutaneously, parallel to the spine in the lumbar region to serve as the indifferent electrode. Stimuli were delivered from an isolated stimulator (Devices) triggered from a pulse generator (Devices). The duration of stimulation was controlled by a Digitimer. Muscle twitching was prevented by the administration of pancuronium bromide (2 mg/kg) into the external jugular vein. The effects of anaesthetics on the rise in arterial pressure elicited by stimulation of the pre-ganglionic sympathetic outflows from L1-L2 or by exogenously administered noradrenaline (i.v.) were measured. The adrenal glands were not affected as indicated by the absence of any change in heart rate. The effects of the anaesthetics on peripheral parasympathetic neuroeffector junctions were also investigated. To do this, the colon was chosen and responses from it were recorded following electrical stimulation of the preganglionic parasympathetic outflow at L5-L6 (10 Hz, 30 s) by the pithing rod (Gillespie *et al.*, 1970). These responses were measured as changes in the intraluminal pressure of a saline-filled balloon inserted through the anus to a distance of 6 cm into the rectum and colon. The colon was first emptied by a saline enema and the balloon connected to a pressure transducer to which a resting pressure of approximately 10 mmHg had been applied.

Collection of end-tidal samples

End-tidal sampling was effected by the automatic withdrawal of gas, from the tracheal cannula, during expiration, by a constant output extractor pump. The volume of the sample was controlled by the duration of operation of the extractor pump (Figure 1). The onset of the sampling period was regulated by selecting the appropriate delay, from the start of inspiration, which produced the peak positive pressure in the trachea as detected by a sample diaphragm pressure switch (Type DW20, Max Bicher, Schaffhausen Switzerland) connected to the tracheal cannula. The pressure switch provided a start signal to a Digitimer which produced an output signal which operated a solid state relay. This relay controlled the start and duration of operation of the extractor pump. The time between the start signal to and the output signal from the Digitimer could be delayed to enable gas samples to be obtained at the end of expiration. To confirm that end-tidal samples were in fact being withdrawn, the delay was adjusted until the partial pressure of CO_2 ($PACO_2$) in the sample was maximum when measured by an infra-red analyser. This was done routinely. Gas samples (approximately 0.3 ml) were withdrawn for a fixed (200 ms) period into an all glass collection syringe (Figure 1, B,) the plunger of which was attached to that of a second identical syringe A. The nylon tubing between B and the tracheal cannula was short (1 cm) to minimize anaesthetic loss. The collection of gas during 30 respiratory cycles was required to provide a sufficient volume (approximately 9 ml) for gas analysis. Before sampling was started, syringe B was empty and syringe A full of air. During the period of operation of the pump, a sample of gas was withdrawn from syringe A causing the plungers to move along the barrel into A and out along the barrel of B. This caused a gas sample, of similar volume to that withdrawn from B, to be withdrawn from the tracheal cannula and to be

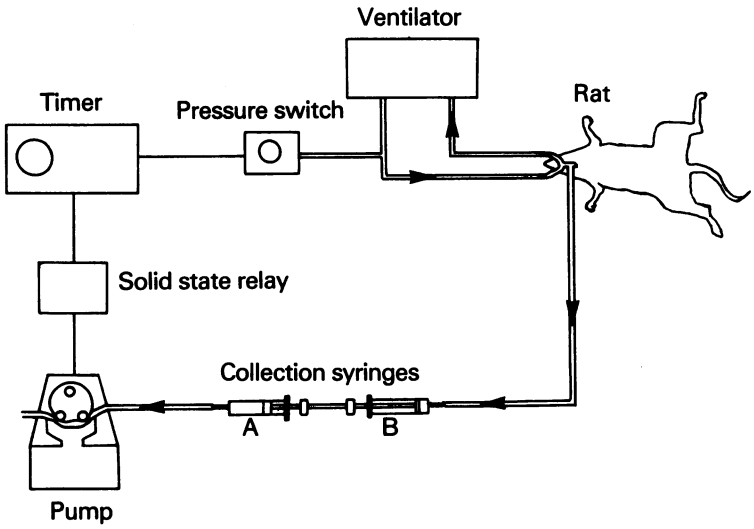

Figure 1 Diagram of the semi-automated end-tidal gas sample collector which was designed and constructed for use with the mechanically-ventilated rat. Not drawn to scale. (For method of operation—see text.)

passed directly into syringe B. The two syringe-system allowed gas samples to be passed from the tracheal cannula directly into the collection syringe (B) without being subject to dilution in the dead space of the rubber tubing in the sampling pump.

Analysis of P_aCO_2 *and* P_ACO_2 *tension*

The partial pressures of CO_2 in arterial blood (P_aCO_2) and end-tidal gas (P_ACO_2) were measured immediately following extraction by the use of a blood gas analyser. The analyser was calibrated before each determination using standard, concentrations of gases (British Oxygen). Arterial blood samples (0.2 ml) were obtained manually with an all glass syringe inserted into a side arm in the arterial cannula. The mean P_aCO_2–P_ACO_2 difference (2.4 ± 0.7 mmHg, $n = 20$) was well within the range (0–5 mmHg) obtained in larger animals by established methods (see Severinghaus, 1960).

Administration of inhalation anaesthetics

Diethyl ether, halothane and pure cyclopropane gas were administered from an anaesthetic machine in an O_2/N_2 carrier mixture (1:1 v/v). The N_2 in the carrier gas was displaced so that the inspired O_2 concentration remained constant (50%). Different concentrations of halothane and diethyl ether were prepared by directing the carrier gas (4 l/min) through calibrated vaporizers.

Analysis of inhalation anaesthetics

Anaesthetics were analyzed by a flame ionization gas chromatographic method modified from that of Rutledge, Seifen, Alper & Flacke (1963). Calibration curves were constructed, daily, using accurate standard concentrations of gases.

Drugs

The following drugs were used: cyclopropane (British Oxygen), diethyl ether (BDH), halothane (ICI), noradrenaline bitartarate (Koch-Light) and pancuronium bromide (Organon). Doses of the last two substances in the text refer to the salt.

Results

End-tidal anaesthetic concentrations in the pithed rat

The uptake of cyclopropane and halothane, as measured by the increase in end-tidal concentration, was examined at three, constant, inspired concentrations. End-tidal samples were withdrawn from 30 consecutive breaths following the elapse of 30s, 3.5 min, 6.5 min, 9.5 min, 14.5 min and finally following a maximum of 19.5 min of anaesthetic administration.

The pattern of the uptake of cyclopropane and halothane was similar (Figure 2). All values are given $\pm$ s.e. mean. End-tidal concentrations of both

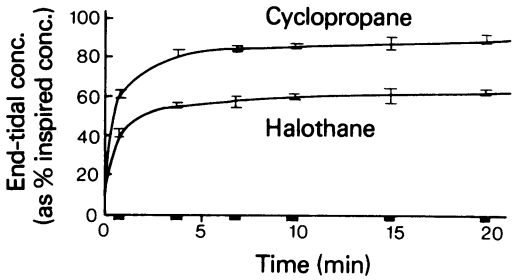

Figure 2 End-tidal concentrations ($n = 5$) expressed as a % of the corresponding inspired concentration (ordinate scale), with time during administration of cyclopropane (16.8% insp.) and halothane (0.8% insp.) in the pithed rat. End-tidal samples were collected during the 30s time periods indicated by the horizontal bars. The end-tidal concentration with time differed for each anaesthetic, the end-tidal concentration of cyclopropane had reached 90.9% at a time (20 min) when that of halothane had reached 63.8% of the inspired concentration. Vertical lines show s.e. means.

anaesthetics increased rapidly from zero in the first few (2–4) min of adminstration and then more slowly (4–10 minutes). During the next 15 min there was no further significant increase in end-tidal concentration. When expressed as a % of the corresponding inspired concentration, the end-tidal concentration of cyclopropane, when in equilibrium with inspired air was seen to have achieved a higher level than that of halothane and had reached 90.9 ± 1.2% ($n = 5$) of the inspired concentration in 19.5 minutes. The end-tidal halothane concentration, in the same period, had reached only 63.8 ± 1.6% ($n = 5$) of the inspired concentration (Figure 2).

Effects of inhalation anaesthetics on the arterial pressure and heart rate

(a) *The conscious rat.* As end-tidal gas samples could not be obtained from the spontaneously breathing intact rat, the doses of the inhalation anaesthetics refer to the inspired concentrations. Arterial pressure and heart rate were measured following up to 20 min periods of anaesthesia and expressed as a mean % ± s.e. mean of the anaesthetic-free control value in the same animal. The control resting values for arterial pressure and heart rate, measured after a 20 min period of acclimatization in the restraining chamber were 136 ± 7 mmHg systolic, 106 ± 5 mmHg diastolic and 346 ± 7 beats/min respectively, $n = 16$. Cyclopropane (16.8%) increased both systolic (to 150 ± 6% of control, $n = 4$) and diastolic (to 142 ± 5% of control, $n = 4$) pressure but not heart

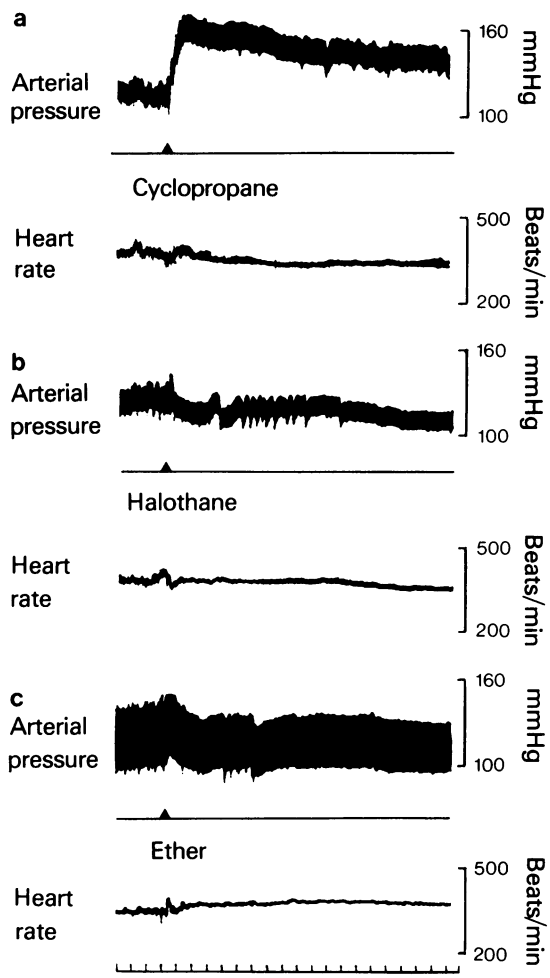

Figure 3 Effect of (a) cyclopropane, (b) halothane and (c) diethyl ether (Ether) on the arterial pressure (mmHg) and heart rate (beats/min) when administered to the conscious rat. Cyclopropane (16.8% insp.) produced an initial rapid increase in arterial pressure after which there was a slow gradual decline towards control. In contrast, halothane (0.8% insp.) and diethyl ether (5% insp.) produced a gradual fall in arterial pressure. Heart rate was not significantly changed.

rate following 1–2 min of administration (Figure 3a) after which period both systolic and diastolic pressures slowly decreased.

Halothane (0.80%) produced a gradual fall in blood pressure which after 20 min had been significantly reduced to 85.2 ± 2.7% (systolic) and 90.8 ± 2.8% (diastolic) $n = 4$, of control values. Heart rate remained unaltered (Figure 3b). Diethyl ether (5%)

also produced a gradual fall in systolic and diastolic pressures (Figure 3c) which, after 20 min were significantly reduced to 91.4 ± 2.8% and 91.9 ± 1.3%, $n = 4$, of controls respectively. Heart rate was not significantly altered.

(b) *Pithed rat.* To determine changes produced by the inhalation anaesthetics on cardiovascular neuroeffector systems, changes in arterial pressure and heart rate were measured (a) in the absence of all neural tone in the pithed, anaesthetic-free animal (b) in the presence of a constant artificial sympathetic tone induced by electrical stimulation of the nerve roots in the spinal canal. (c) following noradrenaline (i.v.). All values are given ± s.e. mean. Resting mean arterial pressure (MAP) and heart rate remained stable for long periods (approximately 8 h); the control (pre-anaesthetic) values were 56 ± 1 mmHg and 300 ± 2 beats/min, $n = 120$, respectively. Cyclopropane, halothane and diethyl ether each depressed the MAP (Table 1) and the pressor responses to preganglionic sympathetic nerve stimulation (10 Hz, 10 s every 5 min at L1-L2) (Figure, 4a). Heart rate was less noticeably affected; it was depressed at higher concentrations of halothane (0.52% and 0.83%) and increased by diethyl ether (4%) but unchanged by cyclopropane in any of the concentrations investigated. The effect of the anaesthetics on the pressor response to exogenous noradrenaline was variable (Figure 4b). Both halothane and diethyl ether were depressant but noticeably less effective than against the pressor response to preganglionic sympathetic nerve stimulation. Cyclopropane (6.2% and 15.3% but not at 23.3%) enhanced the response to exogenous noradrenaline but inhibited (at 15.3% and 23.3%) responses to preganglionic sympathetic nerve stimulation.

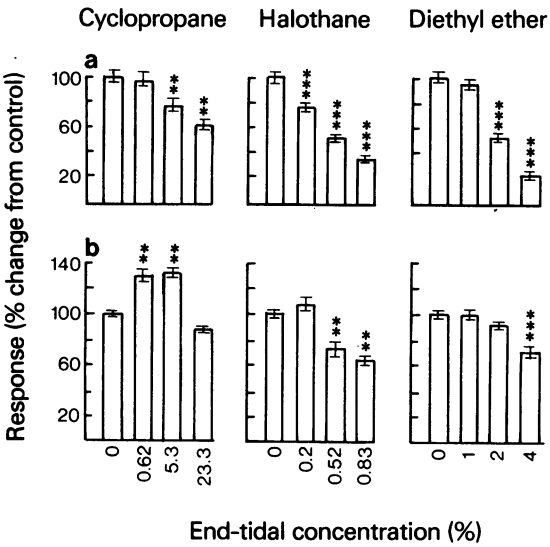

Figure 4 The effect of different end-tidal concentrations of anaesthetics (abscissae) on the increase in mean arterial pressure produced by (a) preganglionic sympathetic nerve stimulation or (b) exogenous noradrenaline (0.4 μg/kg) in the pithed rat. Stimulation (10 Hz, 10 s, 1 ms) at L1-L2 produced reproducible pressor increases of 37 ± 3 mmHg, $n = 56$. This was taken as control 100% in (a). Noradrenaline produced a mean arterial pressure increase of 65 ± 3 mmHg, $n = 56$, which was taken as the control 100% in (b). Values are given as mean ± s.e. mean, $n = 4$. Asterisks represent the levels of probability *(P)* as follows: *$0.05 > P > 0.01$; **$0.01 > P > 0.001$; ***$P < 0.001$.

Table 1 Effect of different end-tidal concentrations (ETC) of anaesthetics on the resting mean arterial pressure (MAP) and heart rate (HR) of the pithed rat

	ETC	*MAP (% change from control)*	P	*HR (% change from control)*	P
Cyclopropane	6.2	−2 ± 3	NS	+5 ± 4	NS
($n = 4$)	15.3	−10 ± 2	< 0.01	−2 ± 3	NS
	23.3	−12 ± 1	< 0.001	−3 ± 4	NS
Halothane	0.20	−21 ± 7	< 0.05	+2 ± 3	NS
($n = 4$)	0.52	−18 ± 3	< 0.001	−4 ± 1	<0.05
	0.83	−21 ± 3	< 0.001	−9 ± 2	<0.01
Diethyl ether	1	−2 ± 3	NS	−3 ± 2	NS
($n = 6$)	2	−7 ± 2	< 0.05	+3 ± 4	NS
	4	−19 ± 3	< 0.001	+10 ± 4	<0.05

Values are expressed as the mean % change ± s.e. mean from the pre-anaesthetic control. NS indicates no statistical significance.

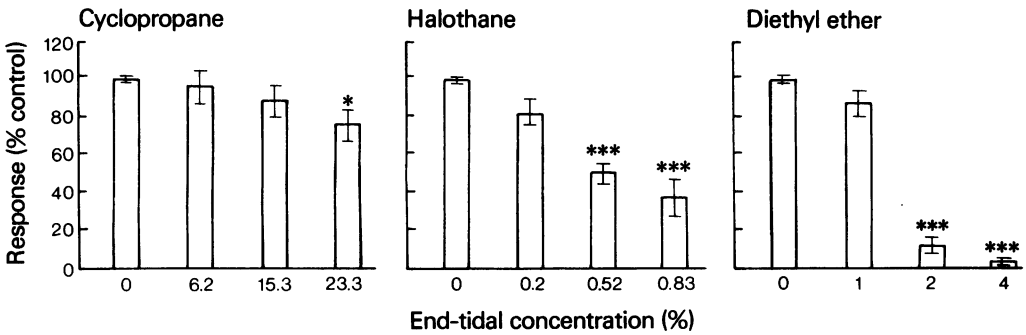

Figure 5 The effect of different end-tidal concentrations of cyclopropane, halothane and diethyl ether on the response of the colon (expressed as a % of the anaesthetic-free control) to preganglionic parasympathetic stimulation in the pithed rat.

Effect of the inhalation anaesthetics on the response of the colon to electrical stimulation of the parasympathetic outflow

Responses from smooth muscle of the colon were chosen as representative of parasympathetically-innervated tissue because the responses could be relatively easily measured in the presence of known end-tidal anaesthetic concentrations following a (20 min) period of administration (Figure 5). In control rats, electrical stimulation (10 Hz, 30 s) of the parasympathetic outflow (L5-L6) produced reproducible increases in intracolonic pressure of 29.4 ± 1 mmHg, $n = 56$. Cyclopropane (23.3%), halothane (0.52% and 0.83%) and diethyl ether (2% and 4%) each depressed these responses significantly in a dose-dependent manner.

Discussion

A comparison of the cardiovascular responses of the pithed with those of the intact animal, showed that while heart rate was not greatly affected by any of the anaesthetics in the intact rat, halothane depressed and diethyl ether increased heart rate, significantly at the higher concentrations, in the pithed animal. In both pithed and intact preparations, halothane and diethyl ether depressed arterial pressure; cyclopropane also lowered blood pressure in the pithed animal but exerted a pressor effect in the intact rat.

In the pithed rat, in the absence of central circulatory control mechanisms, the decrease in arterial pressure could only arise from effects on cardiovascular end organs, i.e. the heart and peripheral vasculature. However, it is unlikely that a decrease in peripheral resistance could have been important for two reasons. First, the peripheral vasculature in the pithed animal is presumably already maximally dilated due to the loss of centrally mediated tone following pithing. Secondly neither adrenalectomy nor sympathectomy decreases arterial pressure further in the pithed rat (Simpson, 1975) and it is unlikely that any significant vasomotor tone is contributed by circulating catecholamines released, for example, following pithing. The decrease therefore probably arose from a negative inotropic action on cardiac muscle, rather than from a decrease in peripheral resistance, resulting in a decline in cardiac output and arterial pressure. A number of anaesthetics including those in the present study are believed to reduce the force of cardiac contraction by a direct action on heart muscle (see Price & Helrich, 1955; Flacke & Alper, 1962). Interestingly, in view of their ability to sensitize the myocardium to the arrythmogenic actions of catecholamines (see Katz & Epstein, 1968), noradrenaline in doses up to 4 μg/kg intravenously produced no cardiac arrythmias in the pithed rat during halothane or cyclopropane administration.

The overall peripheral cardiovascular responses to these anaesthetics can probably be regarded as the resultant of their effects on the pressor responses to preganglionic sympathetic stimulation and circulating noradrenaline. The reduction in the pressor response to preganglionic sympathetic stimulation in the pithed rat indicates that cyclopropane, halothane and diethyl ether, even in low concentrations antagonize efferent sympathetic tone which would, in the intact animal, decrease peripheral resistance and contribute to a fall in arterial pressure. Since the response of the colon to preganglionic parasympathetic stimulation was also inhibited, approximately to the same extent, this effect is relatively non-specific. With regard to the site of this inhibition, in the case of halothane and diethyl ether, the pressor responses to exogenous noradrenaline were also depressed. This

indicates a reduction in the sensitivity of the vasculature to noradrenaline. However, as the responses to preganglionic stimulation were inhibited to a greater extent than those to noradrenaline, transmission at the ganglion synapse (cf. Larrabee & Posternak, 1952; Christ, 1977) and/or the nerve ending are probably the more important sites. In intact animals in the presence of efferent sympathetic activity and circulating catecholamines, this peripheral depressant action of halothane could be responsible therefore for the decrease in arterial pressure observed with low concentrations (0.5% end-tidal). At higher concentrations, the peripheral depressant property and the decrease in efferent sympathetic discharge (Millar, Warden, Cooperman & Price, 1970) probably both contribute to the profound hypotension (30 to 40 mmHg) associated with such concentrations. The maintenance of arterial pressure at normal values during diethyl ether anaesthesia in intact animals, in spite of its peripheral depressant properties, is probably to be accounted for by the centrally mediated increase in sympathoadrenal activity (Price, Linde, Jones, Black & Price, 1959; Millar & Biscoe, 1965; 1966) which presumably overcomes the peripheral depression.

The site of inhibition of efferent tone produced by cyclopropane is more likely to be the ganglion itself or the postganglionic nerve ending than the effector membrane since the pressor responses to exogenous noradrenaline were potentiated rather than reduced by the anaesthetic especially at low concentrations (Figure 4b). On the other hand cyclopropane, in a preparation sensitive to vasopressor agents (Gillespie & Muir, 1967), by itself produced no rise in arterial pressure in the pithed rat. There is little likelihood, therefore, that the directly mediated contraction evident in some vascular beds (McArdle & Black, 1963) is sufficient to account for the increase in arterial pressure *in vivo* seen with cyclopropane. The present results suggest that in the intact animal, in the presence of efferent sympathetic activity and circulating catecholamines, the increase in arterial pressure seen with low concentrations is most likely to arise from an enhancement of circulating catecholamines. This view may provide a basis for the pressor effect of cyclopropane seen in unpremedicated subjects during induction (Eger *et al.*, 1971) when anaesthetic concentrations would be low. It is more difficult to assess the possible contribution of the peripheral effects of cyclopropane when used in intermediate concentrations (15.3% end-tidal). Here the peripheral component appeared to comprise the resultant of two opposing actions, a potentiation of the pressor response to noradrenaline and a reduction of responses to preganglionic sympathetic stimulation. At higher concentrations (23.3% end-tidal), although the peripheral action of cyclopropane was depressant (since the pressor responses to sympathetic stimulation were reduced and those to NA were unaffected) and, therefore, might be expected to lead to a reduction in the arterial pressure in the intact animal, the arterial pressure is, in fact, elevated (Figure 3; Eger *et al.*, 1971). The arterial pressure may be elevated at these higher concentrations in the intact animal by the centrally mediated increase in efferent sympathetic discharge (Millar & Biscoe, 1965; 1966) which overcomes the peripheral depressant action of the anaesthetic.

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