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THE EFFECTS OF INTRAVENOUS ANAESTHETICS ON THE CARDIOVASCULAR SYSTEM OF THE RABBIT

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1 A pithed rabbit preparation is described that allows selective stimulation of the vertebral outflows.

2 The responses to stimulation of sympathetic vasopressor fibres were blocked by hexamethonium and phentolamine but potentiated by cocaine, whereas the responses to stimulation of cardio-accelerator fibres were blocked by propranolol.

3 Ketamine, althesin and pentobarbitone enhanced the effects of noradrenaline and attenuated the effects of sympathetic nerve stimulation. Thiopentone enhanced the effects of both noradrenaline and sympathetic nerve stimulation.

4 In pithed rabbits a transient, dose-related cardiovascular depression was produced by each agent irrespective of whether vasomotor tone was present whereas in decerebrate rabbits the corresponding cardiovascular depression was longer lasting.

5 It is concluded that the cardiovascular depression produced by intravenous anaesthetics in intact rabbits is due to a combination of central and peripheral effects.

Introduction

Anaesthetic agents can affect the cardiovascular system by eliciting effects at several sites simultaneously to produce a net effect which is often difficult to interpret in the intact animal (Price, 1960). These may include the inhibition of reflexes as well as direct central or peripheral actions.

In a recent study with several intravenous anaesthetics (McGrath, Mackenzie & Millar, 1975a; Mackenzie, McGrath, Tetrault & Millar, 1976) in decerebrate or pentobarbitone-anaesthetized rabbits the effects on the cardiovascular system could be correlated with changes in central sympathetic activity. However, the relative contributions of central and peripheral actions to the net effects could not be distinguished. We have, therefore, compared the effects of the intravenous agents thiopentone, althesin and ketamine on the cardiovascular system of the pithed rabbit with those on the decerebrate rabbit in order to identify the peripheral components of their actions and as a corollary to define more closely the peripheral consequences of their central actions.

In this study the pithing rod was introduced via a trephine hole in the skull instead of via the orbit of the eye. The latter mode of entry is not possible in the rabbit due to the anatomy of the skull. The technique of Gillespie MacLaren & Pollock (1970) for pithed rats and cats was also extended by making the additional measurements of cardiac output and left ventricular pressure.

The pithed rabbit preparation was first examined with respect to the effects of stimulation of the autonomic outflow at different levels and to the influence of specific antagonists on these responses.

Secondly the effects of the intravenous anaesthetics althesin, thiopentone, pentobarbitone and ketamine were tested on the cardiovascular responses of the pithed rabbit to noradrenaline and to sympathetic nerve stimulation. It was of interest to compare the purely peripheral effects of these agents since in clinical use (Domino, Chodoff & Corssen, 1965; Clarke, Montgomery, Dundee & Bovill, 1971; Coleman, Downing, Leary, Moyes & Styles, 1972) and in the conscious rabbit (McGrath *et al.*, 1975a; Mackenzie *et al.*, 1976) they produce contrasting effects, althesin behaving rather like the barbiturates in depressing the cardiovascular system, while ketamine elevates both blood pressure and heart rate.

Finally, the sympathetic outflow in the pithed rabbit was continuously stimulated in order to elevate artificially the peripheral resistance to the level found

in decerebrate rabbits and a comparison was made of the cardiovascular actions of the intravenous anaesthetics on the two preparations.

A preliminary report of some of these results has been published (McGrath & Mackenzie, 1976).

Methods

Adult male New Zealand white rabbits (3.0–3.5 kg) were anaesthetized with 3.0% halothane in 100% O_2. The trachea was intubated and anaesthesia continued with 2.5% halothane. The left carotid artery was cannulated with a pair of concentric cannulae, each connected to a pressure transducer. The inner cannula was introduced until its tip lay in the left ventricle as measured by the change in the pressure pulse, and the outer one left with its tip in the carotid artery approximately 10 mm from the aorta. A thermistor probe was introduced into the right carotid artery until its tip lay in midstream in the aorta and a cannula was introduced into the right jugular vein for administration of drugs and of cold saline (0.9% w/v NaCl solution) for measurement of cardiac output by the cold dilution method (Fegler, 1954).

The rabbit was then turned over into the prone position, its head held rigid in a metal head holder and a 13 mm trephine hole drilled in the parietal area of its skull. This hole was subsequently enlarged with bone nibblers so that both sides of the parietal skull were removed. After increasing the halothane concentration to 3%, mid-collicular decerebration was performed by suction. With both carotid arteries effectively occluded and the arterial pressure lowered due to halothane, bleeding was minimal. Halothane administration was then terminated, gallamine (1 mg/kg i.v.) given (to prevent muscle twitching due to stimulation of ventral root motor fibres in the subsequent experiment) and mechanical ventilation (Harvard Instruments Ventilator, Model 613) with 100% O_2 employed to maintain the end tidal CO_2 at 4% (Beckman LB2 Medical Gas Analyser).

From this point the animals were treated in one of three ways.

(1) *Pithed rabbit*

The rabbit was fully pithed via the trephine hole. The pithing rod consisted of a stainless steel rod (2 mm in diameter) which was covered with a teflon sheath (o.d. 3.6 mm) except for 12 mm at its tip.

The autonomic outflows were stimulated using as electrodes the unshielded tip of the pithing rod and an indifferent electrode of silver wire placed subcutaneously dorsal and parallel to the cervical vertebrae (stimulation parameters: Devices Isolated Output Stage, 1 ms pulses, supramaximal voltage (nominal 70–100 V), frequencies indicated in text). The position of the electrode tip was gauged by its distance from the tentorium cerebelli, visible through the trephine hole. This position relative to the vertebrae was then checked by X-ray at the end of the experiment.

Where appropriate, continuous stimulation at T8 for 7–8 min produced a maintained elevation of arterial pressure. Test drugs were administered when the elevated arterial pressure had reached a plateau for at least 2 minutes. In each experiment an initial control period of such stimulation was carried out to verify that the pressor response would be maintained in the absence of drugs.

(2) *Decerebrate rabbits subsequently pithed*

One group of six rabbits were allowed 1 h to recover from the anaesthetic following decerebration before pithing in order that various cardiovascular parameters could be measured before and after pithing in the same rabbits (see Table 3).

(3) *Decerebrate rabbits*

In this group the rabbits were allowed to recover from the anaesthetic and pithing was omitted. The earlier placement of carotid cannulae was also omitted, arterial pressure being recorded from a cannula advanced into the abdominal aorta via the femoral artery.

Arterial pressure, left ventricular pressure, the differential of left ventricular pressure (dP/dt), the heart rate extracted from left ventricular pressure, and end tidal CO_2 were all displayed on a Devices M19 6-channel pen recorder.

Throughout each experiment arterial blood samples were taken at least every 60 min for analysis of P_{O_2}, P_{CO_2} and pH (IL Models 213 and 227). Base excess was calculated and, where necessary, the appropriate amount of sodium bicarbonate was given to correct acidosis.

Rectal temperature was maintained at 38.0 ± 0.5°C with a homoeothermic blanket (C.F. Palmer).

Drugs were administered as a bolus injection via the femoral vein in the case of decerebrate and the jugular vein in the case of pithed rabbits. Preliminary experiments indicated that the choice of vein made no material difference to the responses under observation so the jugular vein was left intact in the decerebrate rabbits.

The doses of althesin, ketamine and thipentone used in this study were selected as those having slightly sub-anaesthetic, low-anaesthetic and moderate anaesthetic effects in rabbits and falling within the range used in previous studies on the baroreceptor reflex (McGrath, Mackenzie & Millar, 1975b; Mackenzie *et al.*, 1976). The dose of pentobarbitone used was that which maintained anaesthesia in these latter studies where the rabbits were not decerebrate.

At least 40 min was left between consecutive

injections of the agents to allow full recovery. In the case of pentobarbitone this was extended to at least 70 minutes.

Statistical analysis was performed using Student's *t* test.

Drugs

The following drugs were used: althesin (Glaxo Laboratories: preparation composed of alphaxalone 0.9% and alphadolone acetate 0.3% w/v in a solvent of polyoxyethylated castor oil 20% in saline; doses are stated in ml/kg), cocaine hydrochloride, hexamethonium bromide (Sigma), halothane (Fluothane, ICI), gallamine triethiodide (Flaxedil, May & Baker), isoprenaline sulphate (Boots), ketamine hydrochloride (Parke-Davis), (−)-noradrenaline bitartrate (Sigma), pentobarbitone sodium (Nembutal, Abbott), phentolamine mesylate (Rogitine, CIBA), (±)-propranolol hydrochloride (Sigma) and thiopentone sodium (Intraval Sodium, May & Baker).

Results

Characteristics of the pithed rabbit preparation

Maintenance of the preparation. Following pithing, the arterial pressure rose to a mean value in excess of 150 mmHg as a result of damage discharge from the sympathetic outflow, but then fell steadily over a period of 5–10 min to a resting level of 54.0 ± 2.4 mmHg systolic, 27.4 ± 1.7 mmHg diastolic.

The resting levels of arterial pressure, heart rate and cardiac output (Table 2) were maintained consistently throughout an experimental period of approximately 6 h at which time the experiments were terminated by stopping the respirator.

With the respirator set to give an end tidal CO_2 of approximately 4% (rate 25–30 per min, stroke volume approximately 50 ml), it was not normally necessary to adjust this further. The tendency towards acidosis varied between animals, but on average 0.125 mEq kg^{-1} h^{-1} of sodium bicarbonate was given.

Responses to stimulation of the autonomic outflow at different levels. Since the dimensions of the vertebrae were similar throughout the group of rabbits used, the distance of the tip of the pithing rod electrode from the tentorium cerebelli was a reliable guide to the electrode's anatomical position. Table 1 relates the anatomical position of the electrode to this distance.

Figure 1 (a, b and c) shows the responses produced by stimulating the autonomic outflows with a fixed train of stimuli at successive 20 mm intervals along the vertebral canal in a rabbit. In the upper lumbar region small rises in arterial pressure were produced which increased in size as the electrode was moved rostrally into the thoracic region, reaching a maximum at T4-5 (14 cm from reference point). The heart rate began to increase at T7 (16 cm from the reference point). Rostral movement to T3 (12 cm from reference point) produced further increase in the heart rate. At T3, although the arterial pressure response was less than at T4-5, the pulse pressure increased, indicating a pressure rise due to an increase in cardiac output rather than an increase in peripheral resistance (Figure 1d).

In addition, at the position where an increase in heart rate occurred, a proportional increase in arterial pulse pressure was found. It was thus concluded that with the electrode in the region sacral to T7, pressor responses that were produced were due solely to stimulation of vasopressor fibres, at T3 they were mainly due to stimulation of sympathetic fibres to the heart, and at intermediate positions they were due to both. In subsequent experiments, therefore, 2 positions were selected as suitable for observing the effects of blocking drugs, T8 (17 cm) and T3 (12 cm) as the optimum examples for vasopressor and cardio-accelerator stimulation respectively.

Effect of frequency of stimulation on autonomic responses. The effects of stimulation of the autonomic outflow at T8 at different frequencies are shown in Figure 1. Frequencies from 1 Hz to 20 Hz produced frequency-related rises in arterial pressure without an increase in heart rate. At frequencies up to and including 10 Hz the responses were well maintained over the 2 min stimulation period, while at 20 Hz the response declined slowly after reaching its peak. The increase in arterial pressure at 5 Hz could be maintained at a plateau level for up to 12 min of continuous stimulation. There was also a frequency-related increase in positive left ventricular dP/dt_{max} and in left ventricular end-diastolic pressure

Table 1 Relationship between the length of the pithing rod electrode sacral to the tentorium cerebelli and the position of the unshielded electrode at the tip of the pithing rod

Length of rod (cm)	28	26	24	22	20	18	17	16	14	12
Vertebral outflow adjacent to the electrode	L3	L2	L1	T11	T10	T9	T8	T7	T5,4	T3

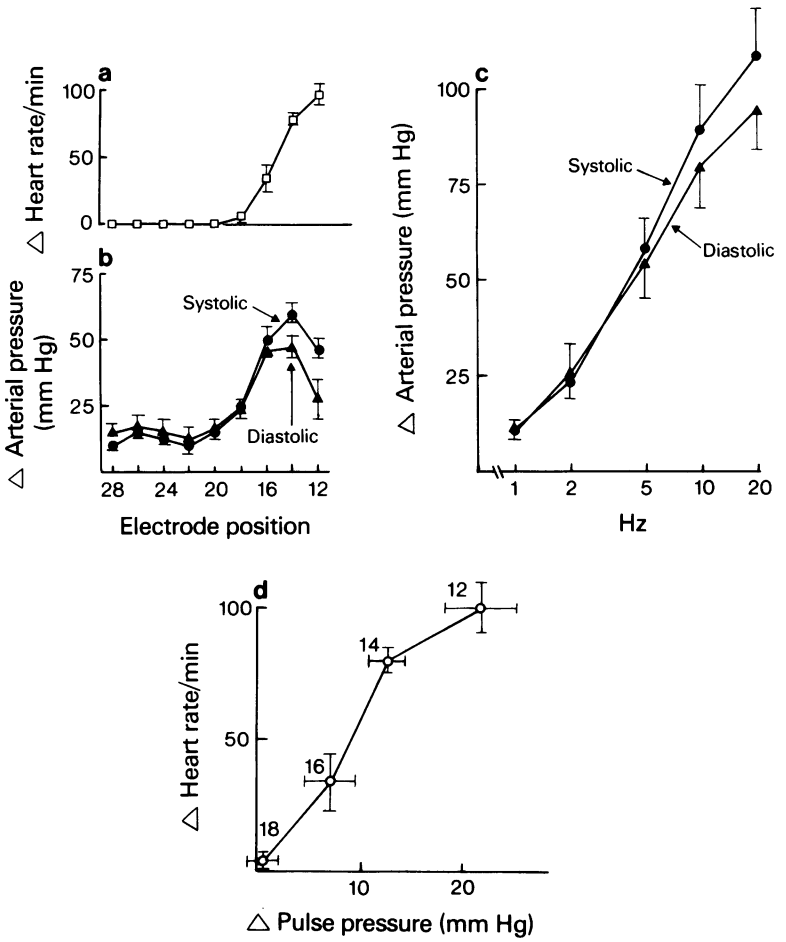

Figure 1 The increase in (a) heart rate and (b) arterial pressure (systolic; diastolic) resulting from electrical stimulation of the sympathetic outflow with the electrode at various positions along the vertebral canal relative to the reference point (see Table 1). Stimulation parameters 10 Hz, 20 s period. Points represent mean for 6 rabbits. Vertical lines show s.e. mean. Note that although an elevation of arterial pressure is elicited by stimulation at positions between L3 and T7 (28–20 cm), there is no effect on heart rate. (c) The effect of stimulation of the sympathetic outflow at T8 (17 cm) at various frequencies on the stystolic (●) and diastolic (▲) blood pressure. Responses are the maximum increases obtained during continuous stimulation at each frequency. Points represent mean for the same 6 rabbits as in (a) and (b). Vertical lines show s.e. mean. (d) Relationship between the change in heart rate and the change in arterial pulse pressure. Results are the mean for the same six rabbits as in (a) and (b). Horizontal and vertical lines show s.e. mean. Vertebral position of the electrode is indicated on the graph.

(2.4 ± 0.3 mmHg, $n=5$) which indicates that in this situation the non-innervated heart was responding to the increased peripheral resistance by increasing its force of contraction.

The maximum increases in systolic and diastolic arterial pressure to continuous stimulation at different frequencies from 6 experiments are shown in Figure 1c. In view of the responses shown in Figure 1c, a standard stimulation period of 10 Hz for 20 s was selected as capable of producing a submaximal response which could be either increased or decreased by the action of drugs.

Continuous stimulation of the sympathetic outflow. Stimulation at T8 (5 Hz) for a period of up to 12 min produced a maintained elevation of arterial pressure due to an increased peripheral resistance. Left ventricular dP/dt_{max} and cardiac output were also increased, whereas heart rate was unaffected (Table 2).

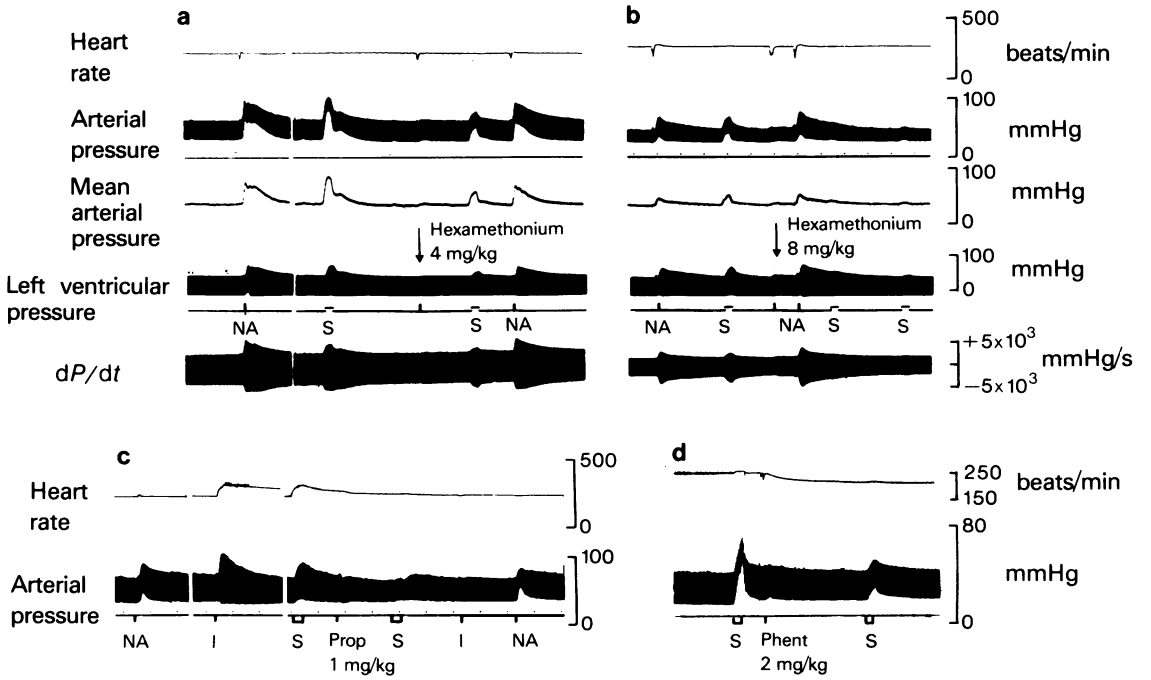

Figure 2 The effects of antagonist drugs on cardiovascular responses in the pithed rabbit. The effects of 2 doses of hexamethonium, in (a) 4 mg/kg, and (b) 8 mg/kg, on the responses to electrical stimulation of sympathetic outflow at T8 (S, 10 Hz, 20 s) and to noradrenaline (NA, 0.3 μg/kg). Note that although the response to electrical stimulation is greatly reduced, the response to noradrenaline is unaffected. (c) Effects of propranolol (Prop, 1 mg/kg) on responses to stimulation of the sympathetic outflow (S, T3, 10 Hz, 20 s), noradrenaline (NA, 0.5 μg) and isoprenaline (I, 1 μg). (d) Effects of phentolamine (Phent, 2 mg/kg) on the response to stimulation of the sympathetic outflow (S, T8, 10 Hz, 20 s). Note that β-adrenoceptor antagonism by propranolol abolishes the increase in heart rate produced by isoprenaline and electrical stimulation. The vasopressor component of electrical stimulation is greatly reduced by the α-adrenoceptor antagonist phentolamine. Time marker in minutes.

Table 2 Absolute levels of cardiovascular parameters in pithed rabbits

	Control	*Continuous stimulation*	n	P*
Cardiac output (ml/min)	327 ± 22	408 ± 22	15	< 0.001
Stroke volume (ml)	1.48 ± 0.10	1.86 ± 0.11	15	< 0.05
Heart rate (beats/min)	215 ± 5	221 ± 6	22	< 0.5
Peripheral resistance (mmHg ml^{-1} min)	0.152 ± 0.012	0.228 ± 0.022	15	< 0.001
dP/dt +ve *max* (mmHg/s)	1080 ± 77	1750 ± 144	18	< 0.001
Mean arterial pressure (mm Hg)	39.4 ± 1.9	75.1 ± 4.6	22	< 0.001

Control—resting levels. Stimulation—plateau levels in the same rabbits 3 min after commencing continuous stimulation (T8, 5 Hz). Each parameter is expressed as a mean ± s.e. mean.
* *P* values indicate the significance levels of the difference between the 'control' and 'continuous stimulation' group for each parameter calculated by paired *t* test.

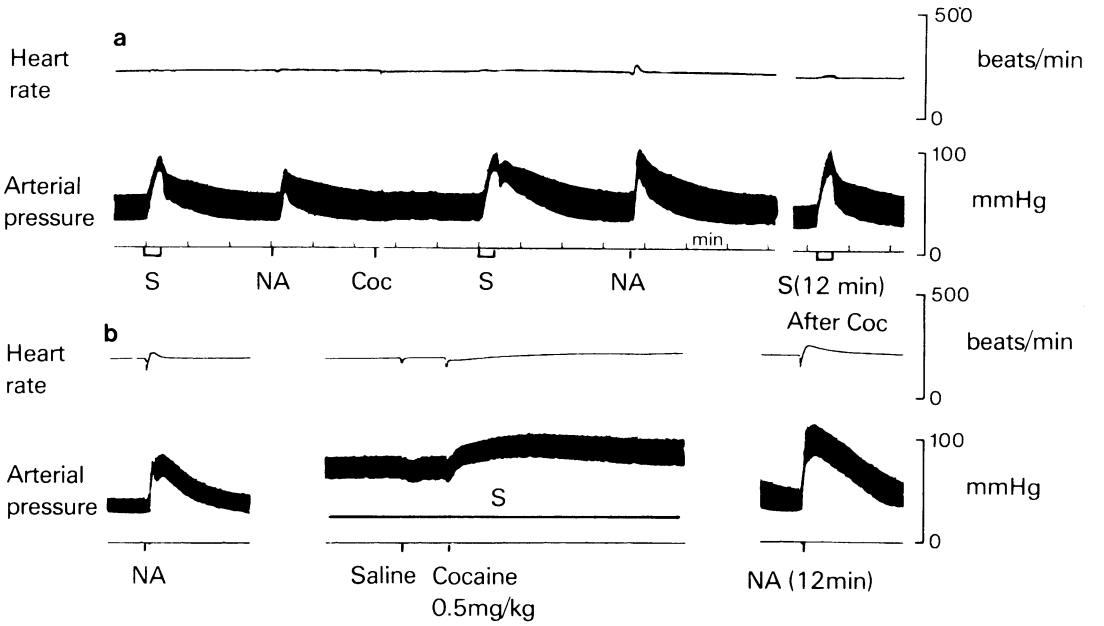

Figure 3 The potentiation by cocaine (Coc, 0.5 μg/kg) of the responses due (a) to stimulation of the sympathetic outflow (S, T8, 10 Hz, 20 s), and noradrenaline (NA, 0.3 μg/kg), and (b) to continuous stimulation at bar (T8, 5 Hz) in a subsequent experiment. Note that whilst cocaine potentiates the effects of continuous stimulation, it does not affect the resting arterial pressure in the absence of such stimulation.

Effects of blocking drugs. The arterial pressure response to stimulation at T8 was inhibited by hexamethonium (4 mg/kg and 8 mg/kg) whereas the response to an intravenous dose of noradrenaline (0.3 μg/kg), producing a similar pressor response, was not (Figure 2a, b). It was necessary to employ the rather high dose of hexamethonium (8 mg/kg) to abolish the pressor response to sympathetic stimulation (Figure 2b), and an even higher dose (16 mg/kg) to abolish the response to stimulation at T3 of the cardio-accelerator nerves. The blockade was nevertheless specific in that the responses to the respective agonists, noradrenaline and isoprenaline, were unaffected by these doses.

Isoprenaline (1 μg) produced a rise in heart rate and systolic arterial pressure similar to that obtained by stimulation at T3. The heart rate responses to isoprenaline and to sympathetic nerve stimulation were abolished by propranolol (1 mg/kg). Noradrenaline (0.3 μg/kg) produced a small transient rise in heart rate as well as a vasopressor response. Propranolol (1 mg/kg) abolished this latter heart rate response but not the corresponding vasopressor response (Figure 2c).

Phentolamine (2 mg/kg) antagonized the arterial pressor response to stimulation at T8 (Figure 2d) and the arterial pressor response to noradrenaline (0.3 μg/kg).

Effects of cocaine. Cocaine (0.5 mg/kg) did not itself alter arterial pressure or heart rate but increased the arterial pressure responses produced by stimulation at T8 and by noradrenaline (0.3 μg/kg) and the heart rate response produced by noradrenaline (0.3 μg/kg) (Figure 3a). In another experiment, cocaine (0.5 mg/kg) was given during a period of continuous stimulation at 5 Hz (T6–7) (Figure 3b, centre panel). In this latter situation, cocaine elevated arterial pressure. After stopping electrical stimulation, the arterial pressure returned to control level and the responses of both arterial pressure and heart rate to noradrenaline (0.3 μg/kg) were potentiated (Figure 3b).

Effects of intravenous anaesthetics in the pithed rabbit

Effects on responses to trains of vasopressor stimulation or to noradrenaline

Althesin and ketamine. The effects of 3 doses of each of the intravenous anaesthetics were tested against the pressor responses to an intravenous injection of noradrenaline (0.3 μg/kg) or to stimulation of the sympathetic outflows at T8 (10 Hz for 20 seconds).

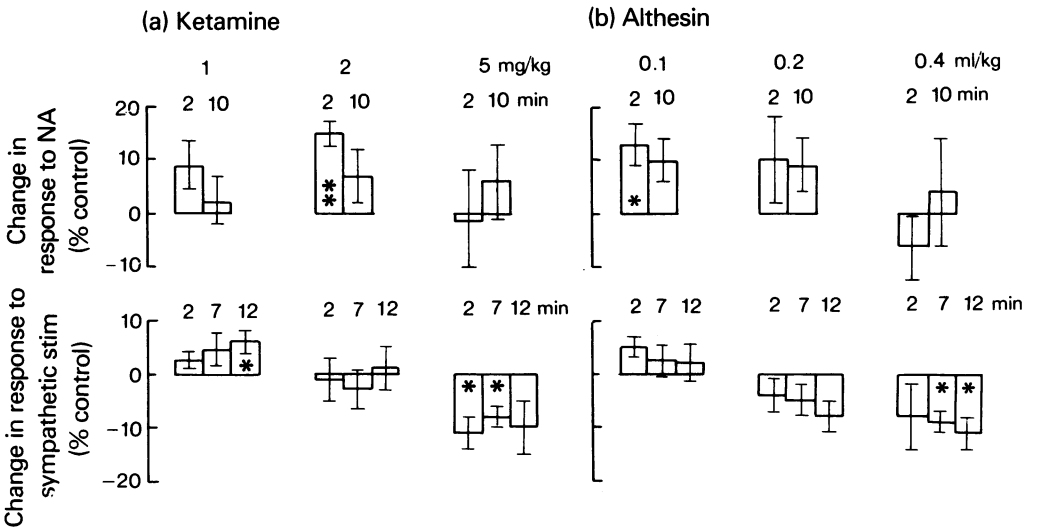

Figure 4 The effects of (a) ketamine and (b) althesin on the responses of the mean arterial pressure of the pithed rabbit to noradrenaline (NA, 1 μg) or to sympathetic nerve stimulation (T8, 10 Hz, 20 seconds). Responses at the times after injection indicated above the columns were expressed as a percentage of pre-drug control responses. The columns represent the mean change from control, vertical lines show s.e. mean ($n=5$). The doses of anaesthetic tested were, from left to right, (a) ketamine, 1, 2 and 5 mg/kg, (b) althesin 0.1, 0.2 and 0.4 ml/kg.
Asterisks denote significance of statistical comparison with controls by Student's t test. * $0.05>P>0.01$; ** $0.01>P$.

The effects of the two agents were similar. Both slightly potentiated pressor responses to noradrenaline at the lower doses but failed to do so at the highest doses. Both also produced a small potentiation of the response to sympathetic nerve stimulation at the lowest dose and depressed these responses at the highest dose with the effect of the intermediate dose taking an intermediate position (Figure 4).

Pentobarbitone and thiopentone. In 4 out of 5 rabbits, pentobarbitone (5 mg/kg) enhanced the effects of noradrenaline and attenuated the effects of sympathetic nerve stimulation in a similar manner to the higher doses of ketamine and althesin. This effect was not, however, statistically significant (Figure 5b). The solvent in which pentobarbitone was dissolved was given in the same volume dosage to three rabbits but had no effect on any of the responses monitored.

Thiopentone enhanced the effects of both noradrenaline (significantly at 4 mg/kg) and sympathetic nerve stimulation (significantly at 2 mg/kg). The highest dose of thiopentone (8 mg/kg) had no significant effect (Figure 5a).

Direct effects on the cardiovascular system. The effects of intravenous anaesthetics were assessed in pithed rabbits first in the absence of any nerve stimulation and then during continuous stimulation of the lower thoracic vertebral outflows.

In the absence of sympathetic nerve stimulation each of the intravenous agents tested produced an immediate but short-lived depression of the cardiovascular system which was maximal within 30 s post-injection with full recovery occurring within 2–3 min (Figures 6a, 7a, 8a, 9a).

With each agent this cardiovascular depression was dose-related and the degrees of depression produced by the small, intermediate and large doses were comparable between agents.

In each case the heart rate, left ventricular systolic pressure and myocardial contractility (dP/dt_{max}) fell on a similar time course to the fall in arterial pressure (Figures 6a, 7a, 8a, 9a).

During continuous nerve stimulation the four intravenous anaesthetic agents tested produced cardiovascular depression on a similar time scale to that found in its absence. The extent of depression of arterial and ventricular pressure and of dP/dt was larger in absolute terms than in the absence of stimulation (Figure 10) and in the case of all but althesin was greater even when expressed as a percentage of pre-injection levels (Figures 6b, 7b, 8b, 9b). The falls in heart rate were similar to those found in the absence of sympathetic stimulation (Figures 6b,

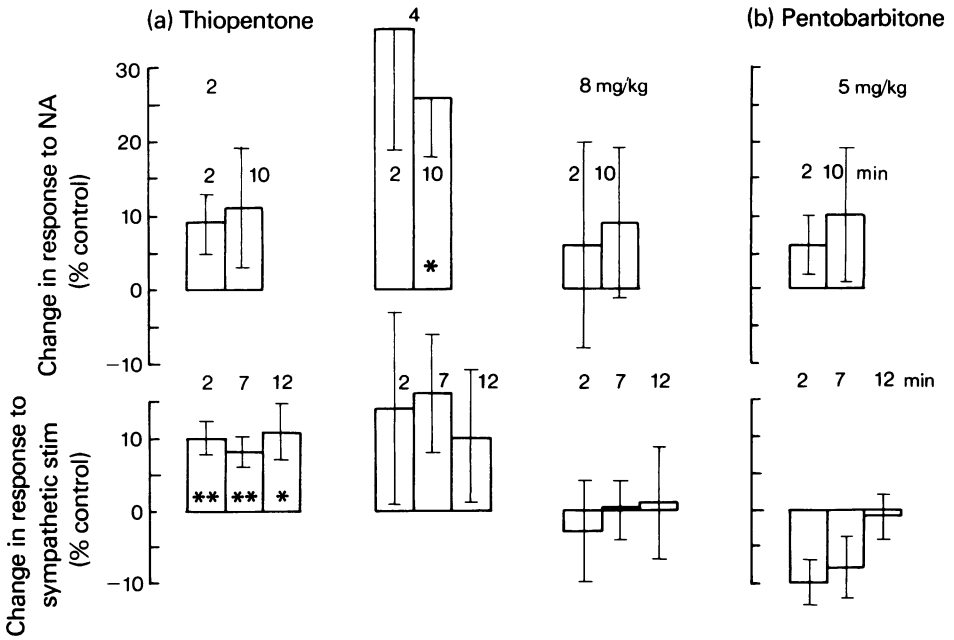

Figure 5 The effects of (a) thiopentone and (b) pentobarbitone on the responses of the mean arterial pressure of the pithed rabbit to noradrenaline (NA, 1 μg) or to sympathetic nerve stimulation (T8, 10 Hz, 20 seconds). Responses at the times after injection indicated above the columns were expressed as a percentage of pre-drug control responses. The columns represent the mean change from control; vertical lines show s.e. mean ($n=5$). The doses of anaesthetic tested were, from left to right, (a) thiopentone 2, 4 and 8 mg/kg, (b) pentobarbitone 5 mg/kg.
Asterisks denote significance of statistical comparison with controls by Student's t test. * $0.05>P>0.01$; ** $0.01>P$.

Table 3 Comparison of several cardiovascular parameters in a group of rabbits (a) when decerebrate, (b) following pithing, (c) following pithing and during continuous sympathetic vasopressor nerve stimulation (T8, 5 Hz)

	(a) Pre-pithed	*(b) Pithed*	*(c) Continuous stimulation*
Cardiac output (ml/min)	491 ± 66	301 ± 30	387 ± 29
Stroke volume (ml)	1.59 ± 0.18	1.48 ± 0.19	1.90 ± 0.10
Heart rate (beats/min)	307 ± 15	208 ± 11	208 ± 10
Peripheral resistance (mmHg ml^{-1} min)	0.299 ± 0.024	0.151 ± 0.029	0.259 ± 0.05
Diastolic arterial pressure (mmHg)	86.1 ± 6.1	28.3 ± 3.1	59.0 ± 7.3
Systolic arterial pressure (mmHg)	121.2 ± 5.2	58.2 ± 4.5	89.0 ± 7.3
Mean arterial pressure (mmHg)	103.4 ± 5.7	40 ± 3.6	71.3 ± 9.7
Left ventricular end diastolic pressure (mmHg)	10.2 ± 2.5	−1 ± 2	2.2 ± 1.8
dP/dt +ve *max* mmHg/s	3720 ± 420	1296 ± 91	1930 ± 163

Values are means ± s.e. mean ($n=6$).

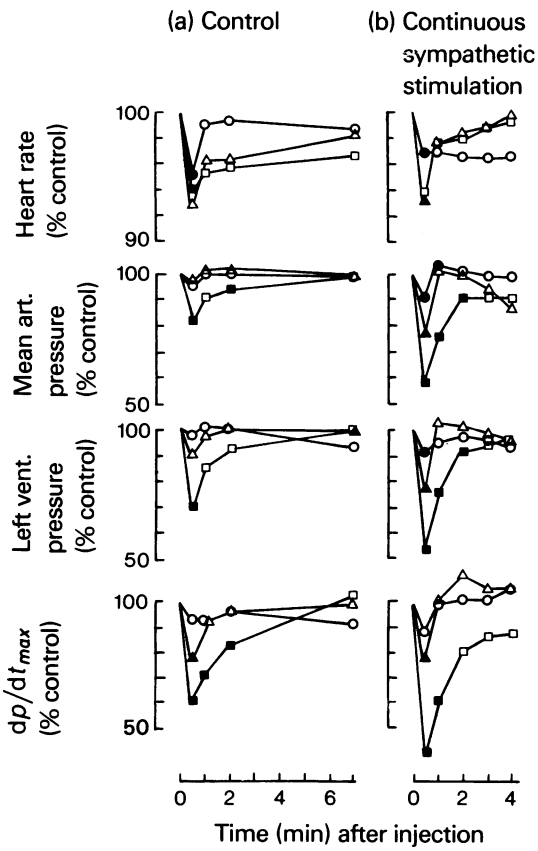

Figure 6 The effects of thiopentone on the cardiovascular system of the pithed rabbit. (a) In the absence of sympathetic nerve stimulation; (b) in the presence of continuous stimulation of the sympathetic outflow at T8 (5 Hz). Thiopentone doses: (○) 2 mg/kg, (△) 4 mg/kg; (□) 8 mg/kg. Each parameter is expressed as a percentage of pre-injection levels. The first point on each graph represents the maximum effect, which occurred between 15 and 30 s after injection. Filled symbols indicate points that are significantly different from pre-injection control levels, i.e. $P<0.05$, $n=5$.

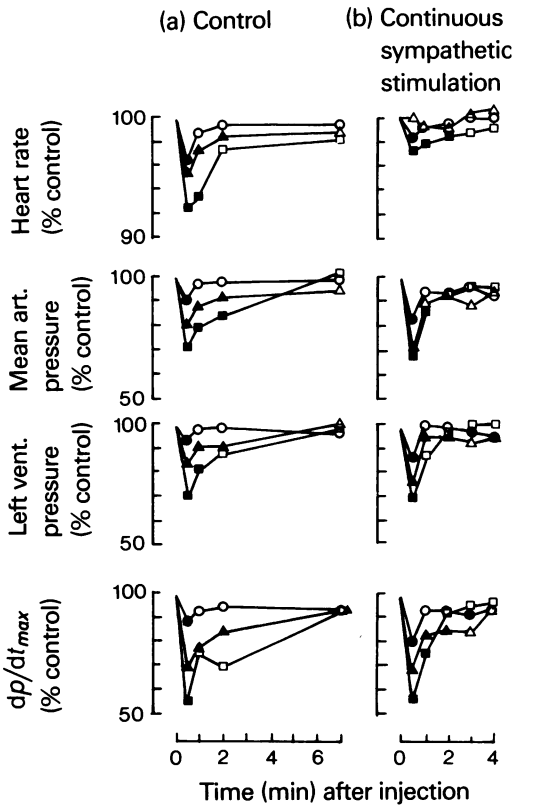

Figure 7 The effects of althesin on the cardiovascular system of the pithed rabbit. (a) In the absence of sympathetic nerve stimulation; (b) in the presence of continuous stimulation of the sympathetic outflow at T8 (5 Hz). Althesin doses: (○) 0.1 ml/kg, (△) 0.2 ml/kg, (□) 0.4 ml/kg. Each parameter is expressed as a percentage of pre-injection levels. The first point on each graph represents the maximum effect, which occurred between 15 and 30 s after injection. Filled symbols indicate points that are significantly different from pre-injection control levels, i.e. $P<0.05$, $n=5$.

8b, 9b, 11) with again the exception of althesin which produced smaller falls in heart rate in the presence of sympathetic vasopressor stimulation (Figures 7b and 11).

Comparison of pithed and decerebrate rabbits

Table 3 compares the resting values of various cardiovascular parameters in decerebrate rabbits before and after pithing. The peripheral resistance of the decerebrate rabbits was comparable with those in the pithed rabbits when the sympathetic outflows of the latter were continuously stimulated. The arterial pressure, heart rate, dP/dt and cardiac output were however greater in the decerebrate preparation.

When intravenous anaesthetics were administered several differences emerged between the rabbit preparations. The most striking difference was on arterial pressure. In the decerebrate rabbits the fall in arterial pressure was greater in magnitude and duration than that obtained in the pithed rabbits. In the pithed rabbits whose sympathetic nerves were continuously stimulated, and whose initial arterial pressures were relatively close to those in the decerebrate rabbits,

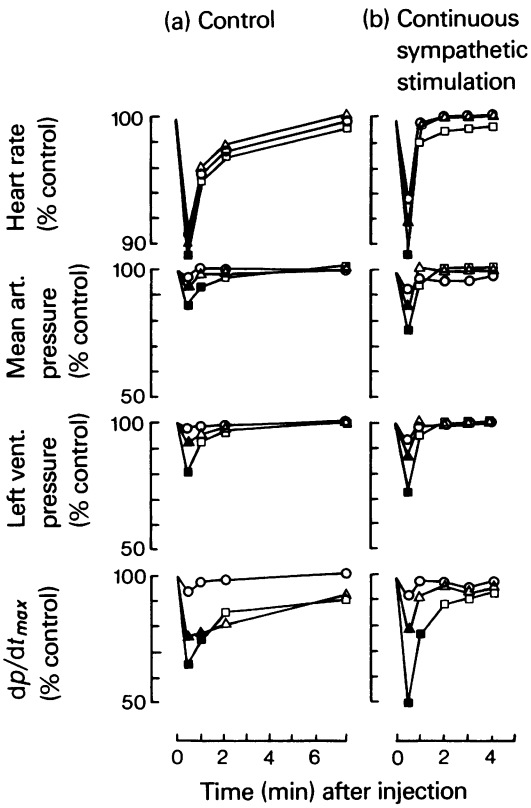

Figure 8 The effects of ketamine on the cardiovascular system of the pithed rabbit. (a) In the absence of sympathetic nerve stimulation; (b) in the presence of continuous stimulation of the sympathetic outflow at T8 (5 Hz). Ketamine doses: (○) 0.1 mg/kg, (△) 0.2 mg/kg, (□) 0.5 mg/kg. Each parameter is expressed as a percentage of pre-injection levels. The first point on each graph represents the maximum effect, which occurred between 15 and 30 s after injection. Filled symbols indicate points that are significantly different from pre-injection control levels, i.e. $P < 0.05$, $n = 5$.

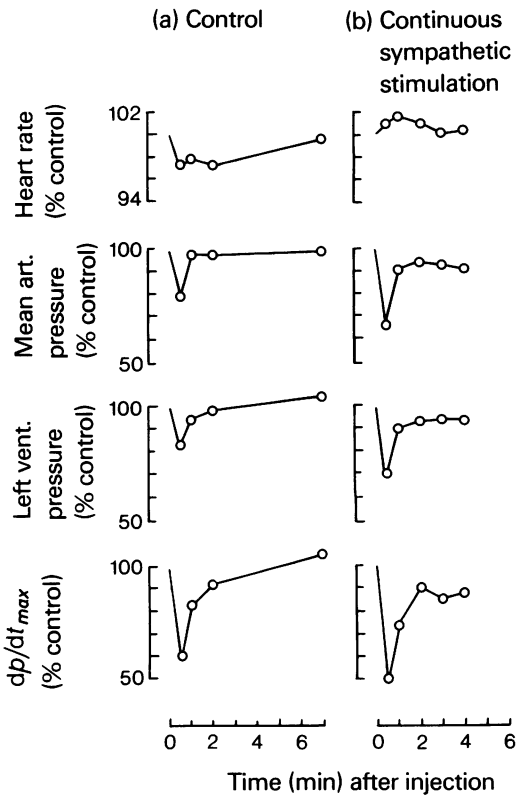

Figure 9 The effects of pentobarbitone (5 mg/kg) on the cardiovascular system of the pithed rabbit. (a) In the absence of sympathetic nerve stimulation; (b) in the presence of continuous stimulation of the sympathetic outflow at T8 (5 Hz). Each parameter is expressed as a percentage of pre-injection levels. The first point on each graph represents the maximum effect, which occurred between 15 and 30 s after injection.

recovery was complete within 2–3 min whereas in the decerebrate rabbits depression was still present at this time.

The falls in heart rate produced by the intravenous agents followed a similar time scale on decerebrate and pithed rabbits except in the case of ketamine which produced no significant changes in the decerebrate preparation (Figure 11).

Discussion

The pithed rabbit provides a preparation on which to examine the peripheral cardiovascular effects of autonomic nerve stimulation or drugs and has been employed here to assess the effects of intravenous anaesthetics on peripheral sympathetic nerve responses.

Stimulation of the vertebral outflows with the pithing rod allows selective stimulation of the cardiac sympathetic nerves at T3 or the vasopressor sympathetic nerves at T8. One major difference between the rabbit and the rat or cat (Gillespie *et al.*, 1970) is that no large adrenal pressor or cardio-accelerator response was encountered despite exploration throughout the thoracolumbar region. No explanation of this discrepancy is immediately apparent. The adrenals of the rabbit contain an extremely high proportion of adrenaline (West, 1955) but adrenaline given intravenously in low doses produced both pressor and cardio-accelerator effects

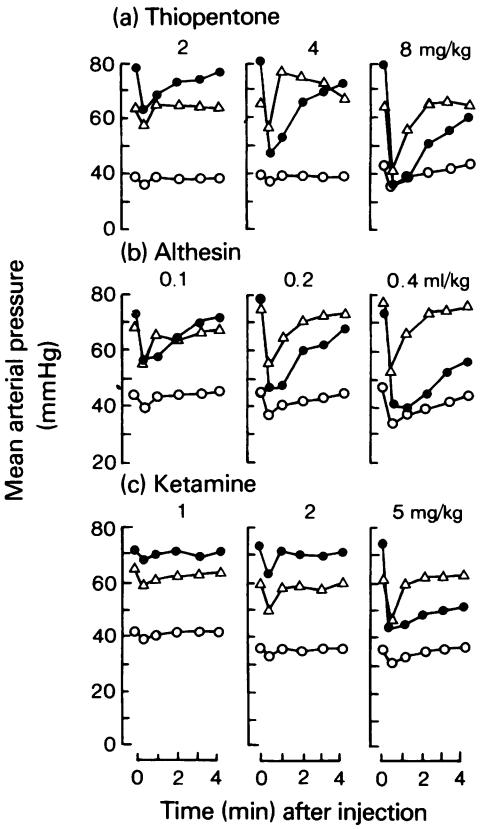

Figure 10 Comparison of the effects of (a) thiopentone (b) althesin and (c) ketamine on the mean arterial pressure of the pithed or decerebrate rabbit. (●) Decerebrate rabbits, (○) pithed rabbits, (△) same pithed rabbits but during continuous stimulation of the sympathetic outflow at T8 (5 Hz); $n=5$ throughout. Standard error bars have been omitted for clarity but s.e. mean in each case was similar to that indicated in Table 1.

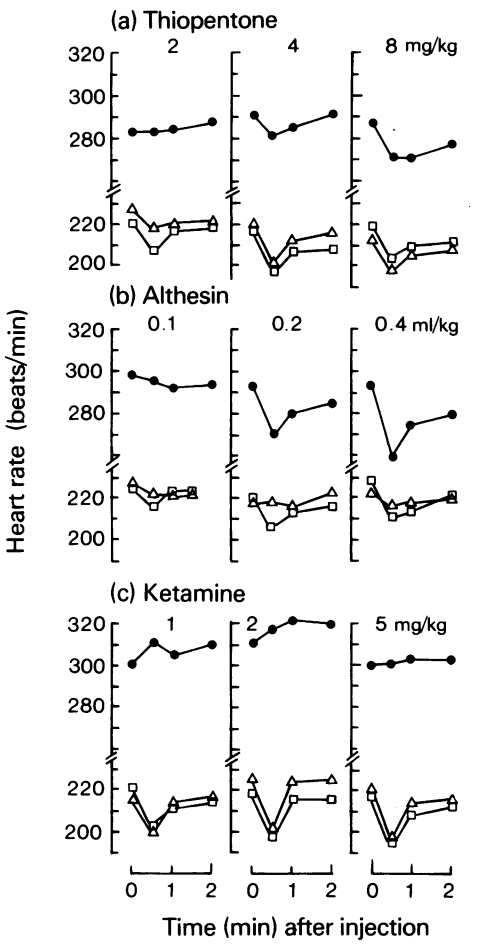

Figure 11 Comparison of the effects of (a) thiopentone, (b) althesin and (c) ketamine on the heart rate of the pithed or decerebrate rabbit. (●) Decerebrate rabbits, (□) pithed rabbits, (△) same pithed rabbits but during continuous stimulation of the sympathetic outflow at T8 (5 Hz); $n=5$ throughout. Standard error bars have been omitted for clarity but s.e. mean in each case was similar to that indicated in Table 1.

(authors' unpublished observations) suggesting that the absence of the adrenal response in the preparation is due to failure to stimulate release of catecholamines from the adrenals rather than the absence of response to released catecholamines. However, the absence of the adrenal response is of advantage as it enables the production of a maintained sympathetic vasopressor response.

When the thoraco-lumbar sympathetic outflow of the pithed rat was stimulated continuously, the pressor response was not well maintained due to the effects of adrenal catecholamines on the heart (Gillespie & Muir, 1967a, b). With the pithed rabbit, stimulation at T8 produced no change in heart rate but a maintained rise in arterial pressure which was due solely to the direct vasopressor effect of the sympathetic nerves. This further contrasts with the pithed rat where it was not possible to produce a marked elevation of blood pressure without cardiac stimulation (Gillespie *et al.*, 1970).

With continuous stimulation at T8 the resulting increase in peripheral resistance increased the afterload on the heart and thus increased the work of the heart as expected from Starling's Law and reflected by a maintained increase in left ventricular dP/dt_{max} (Linden & Snow, 1974). With continuous stimulation, the cardiovascular system reached a new equilibrium position within a few minutes, whereby the heart rate

remained as before, the arterial pressure was elevated and the heart contracted more forcibly to maintain the cardiac output. At this point the peripheral resistance was comparable to that in the decerebrate rabbit but the heart rate and myocardial contractility were lower, presumably due to the effects of cardiac sympathetic tone in the decerebrate preparations. This resulted in a lower cardiac output in the pithed preparation although the stroke volume was in fact greater than in the decerebrate preparation (see Table 3).

A further contrast between the preparations which is relevant to the effects of drugs is that the regional distribution of the peripheral resistance will be different. In the pithed rabbit the only nerves contributing will be those emanating from the lower thoracic region and these will be active only at the stimulator frequency of 5 Hz, whereas in the decerebrate rabbit vasoconstriction will be more generalized and the frequency of nerve traffic variable. In this context it is worth noting that continuous stimulation of the thoracic outflows produced not only an increase in peripheral resistance but also an increase in cardiac output. A possible explanation for this is that such stimulation will not distinguish between sympathetic fibres to arterioles and those to veins. Whereas arteriolar constriction will increase peripheral resistance, an increase in venomotor tone will produce an increase in venous return and lead to an increase in cardiac output. At the stimulation frequency of 5 Hz used here, the relative effect on capacitance vessels compared with resistance vessels will be particularly marked since the former are relatively more sensitive to such low frequencies of stimulation (Mellander, 1960).

As with the pithed rat and cat (Gillespie *et al.*, 1970), the nature of the nerves stimulated by the pithing rod electrode could be verified by the use of specific blocking drugs. All responses to stimulation with the pithing rod electrode were abolished by hexamethonium, whereas the corresponding responses to the agonist drugs noradrenaline and isoprenaline were unaffected, verifying that stimulation was of the preganglionic vertebral outflows. The dose of hexamethonium required to abolish the responses from different organs varied considerably as was found previously in the pithed rat (Gillespie & McGrath, 1973). The vasopressor responses to stimulation at T8 and to noradrenaline were inhibited by the α-adrenoceptor antagonist phentolamine, whereas the cardio-accelerator responses to stimulation at T3 and to noradrenaline or isoprenaline were inhibited by the β-adrenoceptor antagonist propranolol.

The responses to stimulation of adrenergic nerves or to injected noradrenaline could be potentiated by cocaine. Cocaine has been shown to potentiate responses to noradrenaline in the pithed rat by blocking the uptake of noradrenaline into adrenergic nerve terminals (Muscholl, 1961; Simpson, 1975). Blockade of noradrenaline uptake is also likely to be the mechanism in the rabbit since both α- and β-adrenoceptor effects were potentiated and cocaine, at the dose used, had no effects on arterial pressure or heart rate on its own. It was interesting to note that during continuous stimulation of the vasopressor nerves at T8, cocaine did elevate the arterial pressure. This example illustrates the type of peripheral response which can be detected by this preparation but which might be absent in the intact animal due to the buffering effect of the baroreceptor reflexes, and indicates that either inhibition or potentiation of nerve responses can be demonstrated.

The results indicate that the intravenous anaesthetic agents tested have both central and peripheral actions, each of which, at anaesthetic doses, can affect the cardiovascular system.

In the pithed rabbit the effects on peripheral cardiovascular responses were dose-related. At low doses there was some evidence of potentiation of the responses to noradrenaline while at the higher doses depression of sympathetic nerve responses was found.

Evidence from *in vitro* preparations has demonstrated that ketamine can potentiate adrenergic responses by blockade of neuronal noradrenaline uptake (Nedergaard, 1973; Montel, Starke, Gorlitz & Schumann, 1973). However, with intravenous administration of ketamine to the pithed rat it was shown that the cardiovascular effects depended on a balance between the potentiating effect of noradrenaline uptake blockade and the depressant effects on synaptic transmission. Thus doses of ketamine which potentiated responses to injected noradrenaline depressed responses to sympathetic nerve stimulation at both the ganglion synapse and at the post-ganglionic nerve-muscle junction (Clanachan & McGrath, 1976).

Similar factors appear to have operated in the present study with sympathetic nerve responses being depressed at anaesthetic doses by ketamine, althesin and pentobarbitone.

From the resting pithed rabbit it was clear that an immediate peripheral cardiovascular depression followed injection of the anaesthetic agents tested. Heart rate and left ventricular dP/dt both fell on a time scale at least as fast as the fall in arterial pressure, indicating that a major part of the depression was exerted on the heart. A direct depression of the myocardium by several intravenous anaesthetics including ketamine and barbiturates is well documented (Dowdy & Kaya, 1968; Fischer, 1973; Schwartz & Horwitz, 1975). With the technique employed it was not possible to rule out completely some peripheral vasodilatation. The reason for this was that since the effects were so transient, cardiac output and hence peripheral resistance could only be accurately measured 1 min after injection by which time recovery of the arterial pressure was almost complete and no significant changes in peripheral resistance were detected.

With continuous sympathetic stimulation, any effects of the agents on the peripheral sympathetic pathway might be expected to appear. In fact no statistically significant difference stood out when compared with the effects in the resting pithed rabbit. The effects of vasopressor nerve stimulation might, however, have been expected to be potentiated by the lower doses of thiopentone and depressed by the highest doses of althesin and ketamine since these latter effects were found with short periods of vasopressor nerve stimulation.

This may indicate that the responses to nerves in continuous operation are relatively resistant to modification by drugs when compared with the responses to bursts of activity from inactive nerves and suggests caution when interpreting the effects of drugs in the latter situation.

When the effects of these agents were tested on decerebrate rabbits, the depressor effects were larger and longer lasting. This was expected from previous studies where sympathetic nerve activity was monito ed in decerebrate or pentobarbitone anaesthetized rabbits and was seen to fall amost in parallel with the arterial pressure (McGrath *et al.*, 1975a; Mackenzie *et al.*, 1976). Taken together with these latter studies, the present results indicate that the depressor effect in the decerebrate rabbit of thiopentone, althesin and ketamine consists of 2 phases viz.

(1) An initial fall in arterial pressure due to the immediate post-injection depression of the heart and which is virtually over within 1 min, (2) a reduction in central sympathetic discharge which is a few seconds slower to reach its peak than (1), presumably due to the extra time required for the agent to reach the central nervous system, and which lasts for several minutes.

The corresponding effects on the heart rate are more difficult to interpret due to the interaction between the sympathetic and parasympathetic activity in the case of the decerebrate rabbits. However, the effects on the heart rate of pithed and decerebrate rabbits were similar, indicating no dramatic effects other than that of the initial myocardial depression. The one exception to this was with ketamine where the heart rate of the decerebrate preparations was not significantly affected but that of the pithed rabbits was. This may point to an interaction between the two branches of the autonomic nervous system following ketamine which could result from a selective inhibition of the parasympathetic component of the baroreceptor reflex (McGrath *et al.*, 1975a).

The similarity in the peripheral effects of althesin and ketamine is interesting in view of their known contrasting effects on the blood pressure of both man and several animal species (Domino *et al.*, 1965; McCarthy, Chen, Kaump & Ensor, 1965; Clarke *et al.*, 19 1). In the conscious rabbit, at the highest doses employed in the present study and at the same time after injection of the agent, ketamine increased (McGrath *et al.*, 1975a) and althesin decreased (Mackenzie *et al.*, 1976) arterial blood pressure. However, in the decerebrate rabbit both agents produced a parallel reduction in arterial blood pressure and sympathetic nerve activity (McGrath *et al.*, 1975b; Mackenzie *et al.*, 1976). Taken together these latter studies suggested that ketamine and althesin have similar effects on the medullary control of blood pressure, causing a reduction in the central sympathetic output, but that in the intact conscious animal some further effect of ketamine mediated via the central nervous system leads to a net pressor response.

In contrast to the other agents used, thiopentone has been shown to produce a direct constriction of arterial tissue (Burn & Hobbs, 1959; Price & Price, 1962; Altura & Altura, 1975). As this effect was potentiated by cocaine and abolished by an α-adrenoceptor antagonist or by reserpine-treatment (Burn & Hobbs, 1959), it has been suggested that thiopentone produces noradrenaline release. Since thiopentone does not elevate efferent sympathetic activity (Mackenzie *et al.*, 1976), it is likely that the increased peripheral resistance, which has been shown to result from administration of thiopentone (Etsten & Li, 1955; Fieldman, Ridley & Wood, 1955), arises from a peripheral effect. The present study confirms that thiopentone, at anaesthetic doses, can produce potentiation of sympathetic vasopressor responses which is of a purely peripheral origin. However, under the conditions employed here, there was no evidence for a sympathomimetic effect of thiopentone itself.

In conclusion a comparison of pithed and decerebrate preparations can be employed to locate the different sites at which relatively non-specific pharmacological agents such as anaesthetics may exert their effects. It must be borne in mind, however, that much more subtle and complex effects may manifest themselves in the conscious animal or patient (Price, 1960; McGrath *et al.*, 1975b).

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