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EFFECT OF TILTING ON THE PRESSOR RESPONSES TO McN-A-343, A MUSCARINIC SYMPATHETIC GANGLION STIMULANT

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1 In anaesthetized cats and dogs treated with mecamylamine, the pressor response to McN-A-343 was increased when the animals were changed from a supine to a head-up, tilted position. This potentiation was not seen in rats.

2 The potentiation of the McN-A-343 pressor response was not affected by propranolol, destruction of the brain, or removal of the intestines, spleen or adrenal glands. It was promptly abolished by applying pressure to the lower half of the tilted animal. No increase in the pressor response to McN-A-343 occurred when cats were tilted head down. The potentiated response in tilted cats was abolished by atropine.

3 The pressor effects of adrenaline, noradrenaline, tryamine and angiotensin in cats treated with mecamylamine were either reduced or unchanged when the animal was changed from the supine to the tilted position. In one cat not treated with mecamylamine in which orthostatic hypotension occurred, tilting potentiated the pressor responses to dimethyl phenylpiperazinium iodide.

4 In cats anaesthetized with chloralose, the reflex pressor response to bilateral carotid occlusion was reduced by tilting. After mecamylamine treatment the residual atropine-sensitive response to carotid occlusion was potentiated when the animal was placed in the tilted position.

5 These results suggest that muscarinic stimulation of sympathetic ganglia by McN-A-343 raises blood pressure by predominantly reducing venous capacity, in contrast to noradrenaline and angiotension which increase blood pressure mainly by arterial vasoconstriction.

6 It is not clear whether this is a general property of sympathetic ganglionic stimulation or is restricted to stimulation of muscarinic sites.

Introduction

The physiological control mechanisms and the pharmacological reactivity of blood vessels have been investigated for many years but not until the last two decades have methods evolved which allowed simultaneous assessment of changes in resistance and capacitance vessels within selected parts of the vasculature (Haddy & Gilbert, 1956; Mellander, 1960; Browse, Lorenz & Shepherd, 1966; Mellander & Johansson 1968). Mellander (1960) concluded from his experiments on the vasculature of cat skeletal muscle that the capacitance blood vessels were more reactive to sympathetic nerve stimulation than were the corresponding resistance vessels. Although this view was later contested (Browse *et al.*, 1966) it was thought of interest to determine whether or not general activation of sympathetic nerves, by chemical stimulation of ganglia, would cause relatively selective effects on the capacitance blood vessels, observable in the responses of the whole animal.

Tilting an animal in the head-up position causes venous distension and increased venous pooling and so decreases venous return, effects much exaggerated by treatment with ganglion blocking drugs. Animals in the head-up tilt position might be expected, therefore, to be more responsive than when supine to drugs which increase blood pressure predominantly by causing venous constriction. If this is so, then difference in responses to pressor drugs that occur between animals in the supine and tilted positions should depend on the relative constrictor activities of those drugs on resistance and capacitance vessels. We have, therefore, compared the pressor effects of 4-(*m*-chlorophenyl-carbamyloxy)-2-butynyl trimethyl ammonium chloride (McN-A-343) and other hypertensive compounds in supine and head-up tilted animals. McN-A-343 was chosen for practical reasons, since not only did it give more consistent and better sustained responses to intravenous infusion than dimethyl phenylpiperazinium iodide (DMPP), but, as its actions are mediated via muscarinic receptors (Roszkowski, 1961), responses could still be studied after ganglion blockade.

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Methods

Cats (2.0 to 3.0 kg) of either sex were anaesthetized either with chloralose (80 mg/kg i.v.) following induction with halothane, or with pentobarbitone sodium (45 mg/kg i.p.). Male or female dogs (6 to 10 kg) and male rats (250 g) were anaesthetized with pentobarbitone sodium, 30 mg/kg intravenously and 45 to 60 mg/kg intraperitoneally respectively. To maintain stable anaesthesia with pentobarbitone, additional small doses were given intravenously as required throughout the experiment. In some experiments spinal cats and pithed rats were prepared. The animals were placed on operating tables which could be tilted automatically to any pre-arranged angle (measured as the angle of tilt from the horizontal). The tables were designed so that the heart of the animal remained at the same height from the floor in both the supine and tilted positions, and pressure transducers were positioned so that their zero reference points were always at heart level. Body temperature was maintained at 37°C with both table and overhead heating controlled from a rectal thermistor. The trachea was routinely cannulated or intubated and blood pressure was recorded from a carotid, femoral or brachial artery. Intravenous injections or infusions were made into a femoral, jugular or cephalic vein. In some experiments venous pooling in the tilted position was reversed by applying a positive pressure to the lower half of the animal with either an inflatable plastic bag (g-suit) attached around the rib cage at the level of the sternum or by immersion in water to the level of the diaphragm. In eight cats both carotid arteries were exposed and occluded, using protected bulldog clamps, for 30 s periods every 20 min with the animals in the supine and tilted position.

Substances used were: adrenaline (BDH); noradrenaline (BDH); tyramine hydrochloride (BDH; angiotensin II (Hypertensin-Ciba); mecamylamine hydrochloride (M.S.D.); dimethyl phenylpiperazinium iodide (DMPP) (Flucka AG); atropine sulphate (BDH) and McN-A-343, as the chloride. For injection, drugs were dissolved or diluted in 0.9 w/v aqueous NaCl, (saline).

Results

Effect of tilting on the resting blood pressure of anaesthetized cats

Tilting cats to 80° from the horizontal in the head-up position for periods of 5 min at intervals of 25 min caused immediate but short-lived falls in blood pressure (Figure 1). Recovery was rapid and was complete within 2 min, after which blood pressure sometimes rose to above pretilt values. Returning the cats to the supine position caused a small rise in blood pressure which rapidly returned to normal.

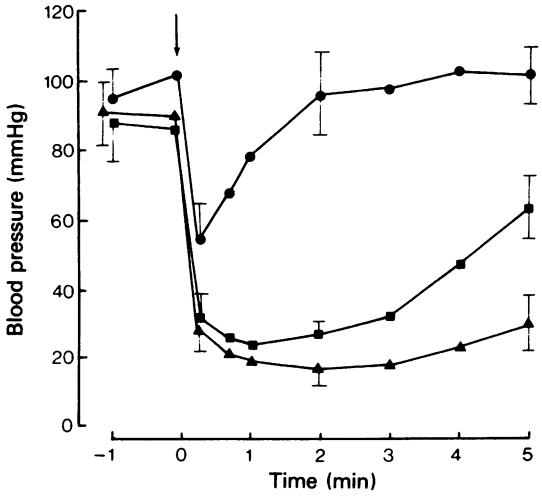

Figure 1 The falls in blood pressure in a group of 5 cats anaesthetized with pentobarbitone when tilted (at arrow) for 5 min from the horizontal to 80° from the horizontal: before mecamylamine (●) after 5 mg/kg mecamylamine (■): after mecamylamine and 1 mg/kg atropine (▲). Values are means; vertical lines show 95% confidence limits.

A variable degree of tachycardia occurred when tilted, which persisted for the duration of the tilted period. Increasing the depth of anaesthesia, especially with pentobarbitone, led to more marked and prolonged orthostatic hypotension. Tilting caused a larger and more sustained fall in blood pressure after treatment with (2.5 or 5 mg/kg i.v.) mecamylamine. However, there was still slow partial recovery (60%) during the last 2 min of the tilt period, which was abolished by atropine (0.5 or 1.0 mg/kg i.v.) (Figure 1). On returning mecamylamine-treated cats to the supine position, blood pressure rose to well above pre-tilt levels before declining during the next 5 to 10 min to control values.

Atropine alone usually had no effect on the reflex blood pressure response to tilting, but in one cat an intravenous dose of 0.5 mg/kg caused marked orthostatic hypotension which was reversed by applying pressure to the lower part of the body (Figure 2).

Responses to McN-A-343 or noradrenaline in supine and tilted cats

Intravenous infusions of McN-A-343 (20 $\mu g\ kg^{-1}\ min^{-1}$) or noradrenaline (0.4 $\mu g\ kg^{-1}\ min^{-1}$) into supine, chloralose-anaesthetized cats for periods of 5 min evoked peak increases in arterial mean blood pressure of 49 ± 4.9 and 47 ± 1.8 mmHg (mean ±

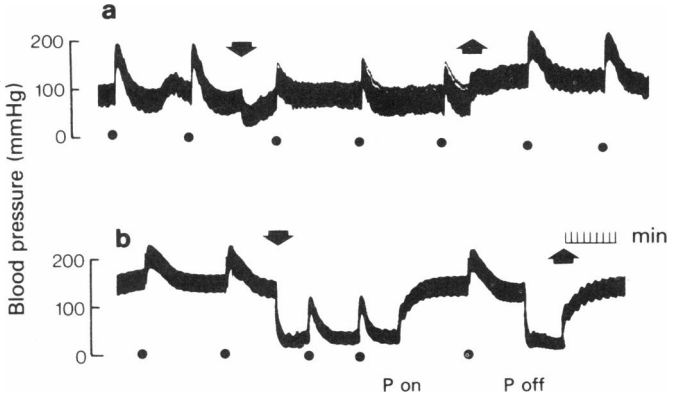

Figure 2 Blood pressure responses of a cat anaesthetized with chloralose to noradrenaline (●) and to tilting (at arrows) before (a) and after (b) atropine (0.5 mg/kg). Positive pressure (P) applied to the lower part of the body when tilted reversed the orthostatic hypotension. The cat was tilted, head up, to 80° from the horizontal.

s.e., $n = 17$) respectively. Repeating the McN-A-343 and noradrenaline infusions after placing the cats in the 80° head-up tilted position caused significantly smaller pressor responses (32 ± 3.9 and 14 ± 1.6 mmHg, respectively) to both drugs (Figure 3).

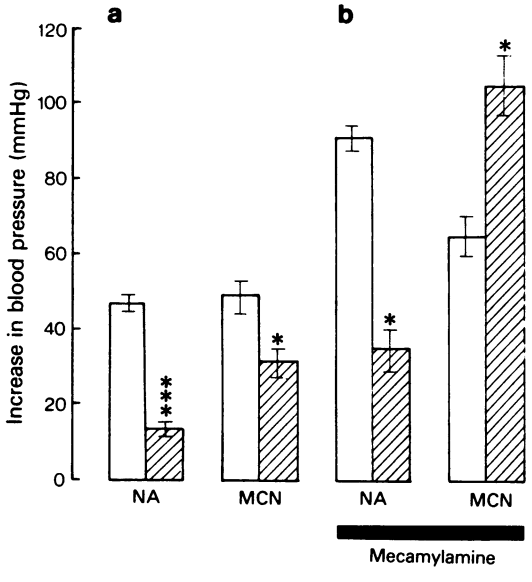

Figure 3 Pressor responses (mean; vertical lines show s.e.) to 5 min infusions of noradrenaline (NA) or McN-A-343 (MCN) of a group of 7 cats anaesthetized with chloralose, either horizontal (open columns) or tilted, head up, to 80° from the horizontal (hatched columns) before (a) and after 5 mg/kg of mecamylamine (b). Between (a) and (b) the doses of noradrenaline and McN-A-343 were reduced from 0.4 to 0.2 μg kg^{-1} min^{-1} and from 20 to 10 μg kg^{-1} min^{-1} respectively. * $P < 0.05$; *** $P < 0.01$ (Analysis of variance).

The supine pressor responses to McN-A-343 and noradrenaline were potentiated after mecamylamine 5 mg/kg i.v. As in untreated cats, tilting caused a reduction of the noradrenaline (0.2 μg kg^{-1} min^{-1}) pressor response (35 ± 5.5 mmHg compared to 92.0 ± 4.0 mmHg). In contrast, pressor responses to McN-A-343 (10 μg kg^{-1} min^{-1}) were significantly increased (105 ± 7 mmHg compared with 65.0 ± 5.9 mmHg) (Figure 3).

The effects of tilting on the pressor responses to McN-A-343 and noradrenaline were essentially similar if the drugs were given by a bolus intravenous injection rather than by slow infusion. In chloralose-anaesthetized cats, noradrenaline pressor responses were significantly smaller when the cats were tilted than when supine, while the McN-A-343 pressor responses were slightly but not significantly increased (Table 1). After mecamylamine treatment the noradrenaline pressor responses were again reduced when the animal was placed in the tilted position but the McN-A-343 pressor responses were now significantly increased (Table 1).

Pressor responses to McN-A-343 in supine and in tilted mecamylamine-treated cats were abolished by atropine (50 μg/kg i.v.). A continuous infusion of propranolol (50 μg kg^{-1} min^{-1}) had no effect on the potentiation of the McN-A-343 pressor response on changing from the horizontal to the tilted position, although the tachycardia in response to tilting, noradrenaline or McN-A-343 was abolished. Removal of the intestines, spleen or adrenal glands also had no effect on the potentiation of the McN-A-343 pressor responses (Table 2). In spinal cats, pressor responses to McN-A-343 were still significantly greater in tilted animals but the degree of potentiation was less than in mecamylamine-treated cats (Table 2). However, spinal cats would only tolerate a tilt of about 30 to 40° from the horizontal, compared with the usual 80°

Table 1 Effect of tilting cats anaesthetized with chloralose on pressor responses to noradrenaline (NA) or McN-A-343 (McN) before and after treatment with mecamylamine (5 mg/kg). (The cats were tilted, head-up, to 80° from the horizontal)

Drug (μg/kg i.v.)	*Treatment*	*Increase in mean blood pressure* (mmHg) *Supine*	*Tilted*
NA (1–1.5)	None	61.3 ± 2.5	41.4 ± 3.5*
McN (50–100)	None	51.7 ± 2.9	63.4 ± 4.2
NA (0.5–2.0)	Mecamylamine	75.7 ± 5.3	57.8 ± 6.7*
McN (20–50)	Mecamylamine	52.5 ± 7.6	110.1 ± 7.7***

Mean values ± s.e. are shown of 14–31 observations made in groups of 7 cats.
* $P < 0.01$, *** $P < 0.001$ (Analysis of variance).

The postural hypotension and the potentiation of the McN-A-343 pressor responses were promptly abolished when the venous pooling caused by tilting was counteracted by applying a positive pressure to the lower half of the body (Figure 4). Inflation of the g-suit to 30 to 40 mmHg itself raised blood pressure in mecamylamine-treated cats, the mean response from 3 cats of 51 ± 11.3 mmHg in the tilted position being significantly ($P < 0.05$) greater than when the cats were supine (17 ± 3.4 mmHg).

Effect of head-down tilt

Tilting mecamylamine-treated cats to about 60° with the head down increased systemic blood pressure. In a group of 9 cats the mean response to 15 periods of tilting was an increase of 49 mmHg. Pressor responses to either infusion or injections of McN-A-343 or noradrenaline were unchanged by tilting the cat from the supine to the head-down position.

Effect of tilting dogs and rats

In anaesthetized dogs treated with mecamylamine, the increases in blood pressure after McN-A-343 were significantly greater with the animals in the head-up tilted position than when horizontal and responses to noradrenaline were smaller (Table 3). Changing the position of rats, either pithed or anaesthetized with pentobarbitone and treated with mecamylamine, had no effect on responses to noradrenaline or McN-A-343 (Table 3).

Effects of tilting cats on other hypertensive compounds

The effects of tilting on the pressor responses to adrenaline, angiotensin and tyramine were investigated in cats anaesthetized with pentobarbitone and pretreated with mecamylamine. Responses to all three drugs were no greater in tilted than in supine cats,

Table 2 Pressor responses of mecamylamine-treated, anaesthetized cats to McN-A-343 in the supine and head-up tilted positions after various treatments

Treatment	*Increase in mean blood pressure* (mmHg) *Supine*	*Tilted*
Untreated ($n = 7$)	52.5 ± 7.6	110.1 ± 7.7
Propranolol 50 μg kg^{-1} min^{-1} i.v.	63.6 ± 6.6	134.6 ± 11.9
Intestines removed ($n = 5$)	31.8 ± 3.7	88.9 ± 13.5
Splenectomised ($n = 3$)	22.9 ± 1.1	70.8 ± 2.2
Adrenalectomised ($n = 2$)	88.5	159.5
Spinal ($n = 7$)	53.2 ± 4.0	79.8 ± 7.9†

Values are mean blood pressure increases ± s.e. mean in the number of animals shown in parentheses. †Tilted to 40°; other animals to 80°.

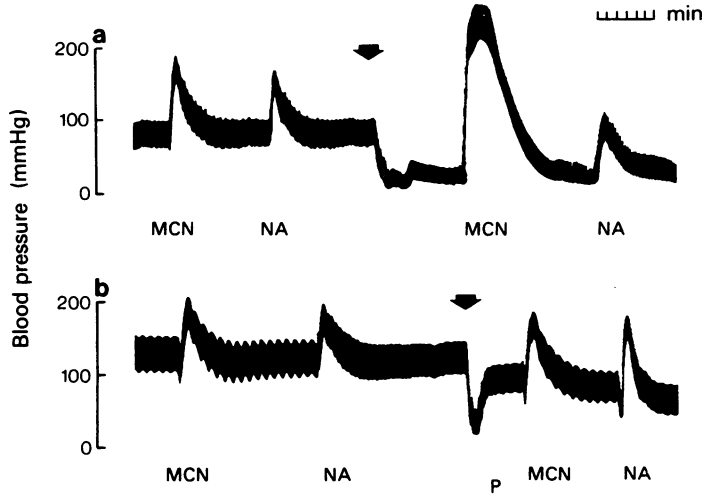

Figure 4 Blood pressure response of a cat anaesthetized with chloralose and treated with mecamylamine (5 mg/kg) to noradrenaline (NA) and McN-A-343 (MCN) supine and tilted to 80° (arrow). Note the marked potentiation in McN-A-343 response when tilted (a) and the absence of potentiation when the orthostatic hypotension was reversed (b) by applying a positive pressure to the lower part of the body (P).

Table 3 Effect of tilting on the pressor responses to noradrenaline (NA) and McN-A-343 (McN) in dogs and rats

Animal	*Treatment*	*Drug* (μg/kg i.v.)	*Increase in blood pressure* (mmHg) *Supine*	*Tilted*
Dogs (9)	Mecamylamine	NA (0.5–1.0)	54.8 ± 3.8	45.3 ± 4.0
	Mecamylamine	McN (10–50)	54.8 ± 4.2	91.8 ± 4.0***
Rats (6)	Mecamylamine	NA (0.5)	41.7 ± 1.8	39.5 ± 3.1
	Mecamylamine	McN (100)	48.7 ± 2.0	47.8 ± 2.3
Rats (5)	Pithed	NA (0.5)	39.0 ± 2.0	24.0 ± 3.6
	Pithed	McN (100)	33.3 ± 2.0	29.6 ± 2.0

Mean values ± s.e. mean are shown of observations made in the number of animals given in parentheses.
*** $P < 0.001$ (Student's *t*-test).

Table 4 Effect of tilting on the pressor response of cats anaesthetized with pentobarbitone to intravenous pressor drugs

Drugs	*Pretreatment*	*Increase in mean blood pressure* (mmHg) *Supine*	*Tilted*
McN-A-343 (10–30 μg)	Mecamylamine	26.2 ± 3.0	91.6 ± 8.8***
Adrenaline (1–2 μg)	Mecamylamine	62.0 ± 2.4	63.3 ± 3.6
Noradrenaline (0.25–0.5 μg)	Mecamylamine	70.0 ± 1.7	61.4 ± 3.0
Angiotensin (0.1–0.2 μg)	Mecamylamine	70.7 ± 6.9	54.4 ± 6.3
Noradrenaline (1–2 μg)	Mecamylamine	89.0 ± 6.4	86.6 ± 8.9
Tyramine (50–100 μg)	Mecamylamine	62.8 ± 1.8	47.2 ± 2.3*
Noradrenaline (0.25–0.5 μg)	Mecamylamine	80.8 ± 2.4	69.8 ± 3.1**
DMPP (50–100 μg)	None	68.1 ± 2.0	73.8 ± 4.4
Noradrenaline (0.2–2 μg)	None	58.5 ± 1.7	39.9 ± 2.4***

Mean values ± s.e. are shown of 11–20 observations made in groups of 5–8 cats.
* $P = 0.05$; ** $P < 0.01$, *** $P < 0.001$ (Student's *t* test).

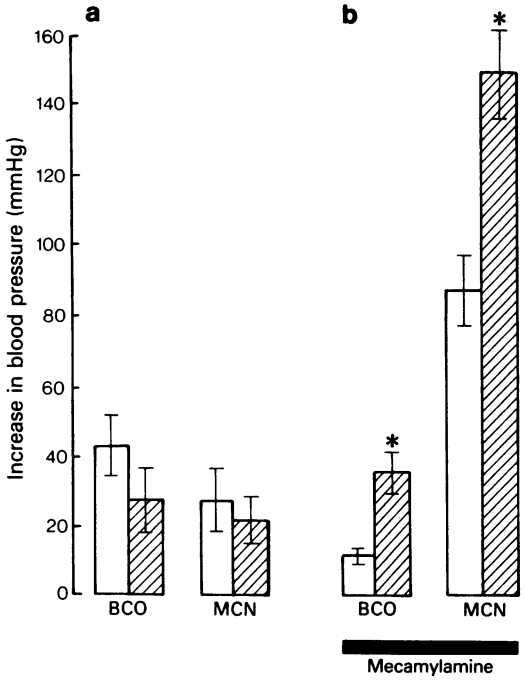

Figure 5 Mean pressor response (vertical lines show s.e. mean) of a group of chloralose-anaesthetized cats to bilateral carotid occlusion (BCO) or McN-A-343 (MCN), supine (open columns) and tilted (hatched columns) before and after mecamylamine (5 mg/kg). *$P < 0.05$ (Analysis of variance).

although responses to McN-A-343 were still significantly increased.

Mean pressor responses to DMPP were the same in supine and tilted untreated cats, although pressor responses to noradrenaline were reduced by tilting (Table 4). However, in one of the eight experiments, when the cat was tilted blood pressure fell from 123 mmHg to 72 mmHg and the hypotension persisted for the duration of the tilt. This animal's responses to noradrenaline were unchanged by tilting but those to DMPP increased from 49 mmHg, supine to 78 mmHg, tilted.

Effect of tilting on the carotid occlusion reflex

In chloralose-anaesthetized cats the pressor responses to both McN-A-343 and bilateral carotid occlusion (BCO) were reduced when the animal was changed from the supine to the tilted position (Figure 4). After mecamylamine the BCO pressor effects were reduced but not abolished and the McN-A-343 pressor responses were potentiated. When these animals were tilted the pressor responses to both BCO and to McN-A-343 were potentiated (Figure 5). This potentiation of the mecamylamine-resistant component of the BCO responses when the cats were tilted was abolished by atropine (1 mg/kg).

Discussion

It has been known since the discovery of ganglion blocking drugs that increases in blood pressure in response to sympathetic stimulation such as asphyxia, elevation of intracranial pressure or hypothalamic stimulation were not completely abolished by ganglion blockade (Freyberger, Gruhzit, Rennick & Moe, 1950; Freyburger, Gruhzit & Moe 1950; Hilton & Steinberg, 1966; Brown , 1969). Similarly in our experiments the reflex increases in arterial blood pressure in response to carotid occlusion or to tilting were not completely blocked by large doses of mecamylamine. Atropine readily abolished the residual responses, indicating the involvement in these reflex responses of muscarinic receptors. These receptors are presumably present in sympathetic vasomotor ganglia, like those already found in ganglia to the heart and nictitating membrane (Trendelenburg, 1966; Volle, 1966; Flacke & Fleish, 1970) and in the adrenal gland (Lee & Trendelenberg, 1966; Kayaalp & McIsaac, 1969). Whether the pathways involving these muscarinic ganglion receptors are important in normal ganglionic transmission or only when transmission is impaired cannot be determined from our experiments. Atropine caused orthostatic hypotension in only one of our cat experiments and has no effect in dogs (Constantine, McShane & Wang, 1971), although in man, postural dependent hypotension has been reported (Kalser, Frye & Gordon, 1954).

Changing the position of the cat from the horizontal to the head-up tilted position revealed differences between the pressor responses to noradrenaline and to McN-A-343. Before ganglion blockade, responses to noradrenaline were smaller with the cat in the tilted position than when horizontal, and responses to McN-A-343 were also less, although the reduction was less marked than with noradrenaline. When the cats were tilted after ganglion blockade and the pressor drugs given during the resulting hypotensive phase, the responses to noradrenaline were further reduced but the responses to McN-A-343 were now very much larger than when given to cats in the horizontal position. Both the increase in blood pressure and the absolute maximum blood pressure were increased, indicating a true potentiation. The potentiated pressor response was readily blocked by atropine, indicating that only muscarinic receptors were involved in the increased response. The effect of tilting on McN-A-343 responses was not dependent on the anaesthetic and potentiation occurred in both chloralose and pentobarbitone anaesthetized cats.

Preganglionic stimulation of the cat superior cervi-

cal ganglion makes the ganglion more responsive to McN-A-343, even after ganglion blockade (Trendelenburg & Jones, 1963). Tilting causes reflex vasoconstriction and hence increases preganglionic nerve activity to vasomotor ganglia. However, this mechanism is unlikely to contribute to the potentiation of McN-A-343 pressor responses since potentiation still occurred in spinal cats which must have very low or no preganglionic nerve activity. The smaller degree of potentiation that was seen in the experiments with spinal cats may be explained by the low angle of tilt that was used, since the normal 80° tilt was too steep to be tolerated.

In anaesthetized cats, propranolol had no effect on the degree of potentiation so that sympathetic stimulation of the heart is not the cause of this phenomenon. Removal of the intestines, spleen or adrenal glands from anaesthetized cats was without effect on the potentiation of the McN-A-343 responses when the animals were tilted after treatment with mecamylamine. The effect, therefore, is not due to local effects of McN-A-343 on the intestinal vasculature, splenic volume or catecholamine release from the adrenal glands.

However, the potentiation of the McN-A-343 response is dependent on the venous distension caused by tilting and the resultant impairment of venous return and cardiac output. The phenomenon was most marked and consistent during orthostatic hypotension and venous pooling following ganglionic blockade. It did not occur in mecamylamine-treated cats when they were tilted head-down, which would improve rather than impair venous return. Finally both the orthostatic hypotension and the increase in the McN-A-343 pressor responses seen in tilted cats were promptly abolished when positive pressure was applied to the lower part of the body counteract the venous distension.

Lower body compression itself raised blood pressure, and this mechanical response was also potentiated when the cats were tilted to the head-up position, demonstrating that a mechanical reduction in venous capacity is also more effective in raising blood pressure with the animal tilted rather than horizontal. This effect of change of posture on the pressor response to McN-A-343 is not confined to cats. It occurred in dogs treated with mecamylamine but not in rats with sympathetic nerve activity abolished by either mecamylamine or by destruction of the brain and spinal cord. The lack of effect in rats may be due to the meagre drop in hydrostatic pressure that occurs when such a small animal is tilted from the horizontal. However, others have observed brief falls in diastolic and systolic blood pressure when pentobarbitone anaesthetized rats were tilted to the head-up position (Liu, Anderson, Lape & Rosenberg, 1967).

Thus, when the cardiac output is low because of poor venous return due to distension of capacitance vessels, McN-A-343 is much more effective in raising blood pressure than when the cardiac output is normal. Noradrenaline on the other hand is most effective when cardiac output and venous return are normal. These differences can be explained by the drugs increasing blood pressure by different mechanisms: McN-A-343 by predominantly increasing cardiac output and noradrenaline by increasing peripheral resistance. In turn these effects can be accounted for by McN-A-343 having a much greater effect in constricting capacitance vessels than resistance vessels and noradrenaline, in contrast, by predominantly constricting resistance vessels. Other vasoconstrictors, adrenaline, angiotensin and tyramine behave like noradrenaline. Angiotensin is known to be a selective constrictor of resistance vessels in preference to capacitance vessels and although noradrenaline and adrenaline constrict both pre- and post-capillary vessels (Folkow, Johansson & Mellander, 1961; Haddy, Molnar, Borden & Texter, 1962; DePasquale & Burch, 1963; Texter, Chou, Merrill, Laureta & Frohlich, 1964), some selectivity may result from the precapillary drug concentration being greater than the post capillary concentration since catecholamines are taken up by tissues on their passage through the capillaries (Vane, 1969). Although endogenously released noradrenaline may sometimes behave differently from injected noradrenaline (Glick, Epstein, Weschler Braunwald, 1969), in our experiments endogenous noradrenaline released by tyramine gave pressor responses which, like injected noradrenaline, were reduced when the cat was tilted.

McN-A-343 differs from the other vasconstrictors in another way, in addition to the vasconstrictor effect from sympathetic ganglionic stimulation; it also has a direct vasodilator action which is responsible for the initial depressor component of the overall blood pressure response (Roszkowski, 1961). If this vasodilator action was selective for precapillary resistance vessels and the vasconstrictor action was not, then the resultant response would be selective constriction of post-capillary vessels. This seems unlikely, since in experiments using isovolaemic perfusion of the vascular bed of the cat intestine (Fielden, Owen & Taylor, 1974) McN-A-343 was equally effective in dilating both resistance and capacitance vessels (unpublished results).

This phenomenon of enhanced pressor responses in the tilted position also occurs when blood pressure is raised by reflex stimulation of muscarinic sympathetic ganglion sites, since the mecamylamine-resistant, atropine-sensitive component of the carotid occlusion reflex is greater in tilted than in supine cats.

Thus, stimulation of sympathetic ganglia at muscarinic sites may selectively constrict capacitance

vessels to raise blood pressure by increasing venous return and cardiac output. Whether or not stimulation of vasomotor ganglia at nicotinic sites also selectively constricts capacitance vessels is not clear. Neither DMPP nor bilateral carotid occlusion gave greater pressor responses in tilted than in supine cats not pretreated with mecamylamine, but under these conditions neither did McN-A-343. However, in one experiment, when an untreated cat was tilted and orthostatic hypotension occurred DMPP gave greater responses when the cat was tilted than when it was supine. Further work is, therefore, needed to establish whether selective constriction of capacitance vessels is a general property of sympathetic nerve stimulation (Mellander, 1966) or whether there may be a functional separation of muscarinic and nicotinic sites so that muscarinic sites selectively innervate post capillary vessels. Anatomical separation of muscarinic and nicotinic pathways have been demonstrated in the dog left ventricle (Chinn & Hilton, 1976).

More practically, muscarinic ganglion stimulants may be more effective clinically in raising low blood pressure than are noradrenaline or angiotensin. Blood pressure would be raised by mobilizing venous blood to increase venous return and cardiac output so that blood flow to vital organs would be increased, an action preferable to increasing peripheral resistance at the expense of blood flow.

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