Br. J. Pharmac. (1976), **58**, 505–515

CARDIOVASCULAR EFFECTS OF DOPAMINE AFTER CENTRAL ADMINISTRATION INTO CONSCIOUS CATS

M.D. DAY[1] & A.G. ROACH[2]

Pharmacological Laboratories, Department of Pharmacy, University of Aston, Birmingham, B4 7ET

1 Dopamine (30 and 45 μg) administered intracerebroventricularly (i.c.v.) to a group of 10 conscious normotensive cats caused dose-related increases in blood pressure and heart rate. In 4 of these animals the initial cardiovascular stimulant effects of i.c.v. dopamine were followed by hypotension and bradycardia.

2 α-Methyldopamine (30 and 45 μg i.c.v.) produced qualitatively similar responses to dopamine except that the cardiovascular stimulant effects were smaller and the secondary depressant effects somewhat more prolonged.

3 Both stimulant and depressant effects of i.c.v. dopamine and α-methyldopamine were greatly inhibited by autonomic ganglion blockade or by adrenergic neurone blockade.

4 The cardiovascular stimulant effects of both i.c.v. dopamine and i.c.v. α-methyldopamine were selectively inhibited by β-adrenoceptor blocking agents whilst the cardiovascular depressant effects of these substances were abolished by the α-adrenoceptor blocker phentolamine or by the dopamine-β-hydroxylase inhibitor disulfiram.

5 Haloperidol by either i.c.v. or the intravenous route abolished both cardiovascular stimulant and depressant effects of i.c.v. dopamine, whilst pimozide by either route inhibited only the cardiovascular stimulant effects.

6 In 2 cats, injection of dopamine into the cisterna magna produced predominantly depressant effects on the cardiovascular system except with a higher dose which induced biphasic responses.

Introduction

Numerous reports have appeared in recent years concerning the mechanism of the cardiovascular depressant effects usually seen after the central administration of noradrenaline and related sympathomimetic amines in conscious and anaesthetized cats and rats (for instance, Henning, 1973; 1975; Van Zwieten, 1973; Day & Roach, 1974a,b; de Jong, Nijkamp & Bohus, 1975; Struyker-Boudier, Smeets, Brouwer & van Rossum, 1975). In general, it appears that hypotension and bradycardia result from stimulation of α-adrenoceptors in the lower brain stem (see references above) and in the anterior hypothalamus (Toivola & Gale, 1970; Struyker-Boudier, Smeets, Brouwer & van Rossum, 1974). In addition, β-adrenoceptors may also be concerned in the central control of blood pressure since intracerebroventricular (i.c.v.) isoprenaline in conscious cats usually caused cardiovascular stimulant effects (Day & Roach, 1972; 1973; 1974a).

Dopamine is the immediate physiological precursor of noradrenaline, and in addition, itself possesses neurotransmitter functions in the brain. However, little work has been reported concerning a possible role for dopamine in the central regulation of blood pressure. McCubbin, Kaneko & Page (1960) found that i.c.v. dopamine in anaesthetized dogs had no effect on blood pressure unless monoamine oxidase had previously been inhibited when it produced hypotension, bradycardia and marked impairment of the carotid sinus pressor reflex. Intracerebroventricular dopamine has been reported to cause hypotension and bradycardia in rats and cats (Baum & Shropshire, 1973; Heise & Kroneberg, 1973; Finch, Hersom & Hicks, 1975), and also when applied to the ventral surface of the brain stem (Bloch, Bousquet, Feldman, Velly & Schwartz, 1974). Finch *et al.* (1975) found that inhibition of dopamine-β-hydroxylase abolished the cardiovascular depressant effects of α-methyldopamine in conscious rats suggesting that these effects were mediated via formation of α-methylnoradrenaline. This observation casts doubt on

[1] Present address: Department of Physiology and Pharmacology, University Hospital and Medical School, Nottingham NG7 2UH.

[2] Present address: Laboratoires d'Etudes et de Recherches Scientifiques, 58 Rue de la Glacière, Paris 75013, France.

the validity of previous reports concerning the central actions of dopamine since part, at least, of any observed effects may have been due to the formation of noradrenaline.

We have studied the effects of centrally-administered dopamine on the blood pressures and heart rates of conscious normotensive cats both before and after inhibition of dopamine-β-oxidase.

Methods

Ten cats of either sex, weighing between 2.5–4.5 kg were used in this study. Under halothane anaesthesia arterial and venous cannulae were inserted by the method of Day & Whiting (1972). The blood pressure recording system consisting of catheters, valve and transducer were tested to ensure that the frequency response of the system was adequate to give reliable measurements of both systolic and diastolic pressures. The system was tested with an electromagnetic pressure generator (Ardill, Fentem & Wellard, 1967). The recording system used in the cat experiments gave no damping of sinusoidal pulses with frequencies up to 5 Hz when compared with a similar transducer connected directly to the pulse generator. In the present experiments resting heart rates were of the order of 100–130 beats/min and rarely exceeded 200 beats/min in response to drugs and thus the system was considered adequate for the measurement of both systolic and diastolic pressures. A modified Collison Cannula (Cooling, Day & Roach, 1974) was implanted in the left lateral cerebral ventricle (i.c.v.) as described by Feldberg & Sherwood (1953). At least seven days elapsed following operation before each cat was used in an experimental study.

Injections into the cisterna magna

Two cats previously cannulated for i.c.v. injection were additionally cannulated for injections into the cisterna magna (i.c.m.). A cannula guide was made from a No. 0 hypodermic needle based upon the guide described by Feldberg, Myers & Veale (1970). The needle shaft was cut and filed to a length of 18 mm. The guide was cemented to the skull so that its tip rested just above the atlanto-occipital membrane. A No. 1 gauge hypodermic needle was inserted into the guide until it punctured the membrane; cerebrospinal fluid rose up the needle. The injection needle was fixed in this position with quick drying epoxyresin and capped with a sealed piece of polyethylene tubing.

Drugs

Drugs infused i.c.v. or i.c.m. were dissolved in sterile 0.9% w/v NaCl solution (saline) ('Steriflex', Allen & Hanbury's Ltd) except where otherwise stated. Intracerebroventricular and i.c.m. drug administrations were made in volumes of 100 and 50 µl respectively and were infused over a 4 min period with a constant infusion pump (Scientific and Research Instruments Ltd).

The drugs used were: dopamine hydrochloride (Sigma), (–) α-methyldopamine hydrochloride (Merck, Sharp & Dohme), isoprenaline sulphate (BDH), pempidine tartrate (May & Baker), hexamethonium bromide (Koch-Light Labs.), tetramethylammonium chloride (BDH), bethanidine sulphate (Burroughs Wellcome), guanethidine monosulphate (Ciba), (+) and (±)-propranolol (ICI), (+) and (±)-alprenolol (Astra), lignocaine hydrochloride (BDH), procaine hydrochloride (BDH), phentolamine methane sulphonate (Ciba), haloperidol and pimozide (Janssen Pharmaceuticals) and disulfiram (tetraethylthiuram disulphide, BDH).

The doses in the text of (+)-alprenolol, haloperidol and pimozide are quoted as base and all other doses as the salts mentioned above. Disulfiram was injected intraperitoneally as a suspension in sterile saline using compound powder of Tragacanth BPC as the suspending agent. Haloperidol was dissolved in dilute lactic acid and the pH of the solution adjusted to 4.8 with 0.1 N NaOH. Pimozide was dissolved in 0.1% w/v tartaric acid and the pH adjusted to 5.5 with 0.1N NaOH.

Table 1 Maximal increases in blood pressure and heart rate (mean ± s.e.) induced by two dose levels of each of dopamine and α-methyldopamine administered into the lateral cerebral ventricles of a group of conscious cats which responded to both drugs with simple cardiovascular stimulation

Agonist	Total dose (µg i.c.v.)	No. of responses	Arterial blood pressure increase (mmHg) Systolic	Arterial blood pressure increase (mmHg) Diastolic	Heart rate increase (beats/min)	No. of cats
Dopamine	30	18	27.6 ± 3.1	25.4 ± 3.2	15.1 ± 3.6	6
	45	12	36.8 ± 4.0	30.7 ± 4.1	20.9 ± 3.8	
α-Methyldopamine	30	4	13.2 ± 1.7	11.0 ± 1.4	10.9 ± 2.1	1
	45	4	18.6 ± 1.9	17.2 ± 1.8	14.3 ± 1.9	

Results

Cardiovascular effects of i.c.v. dopamine and α-methyldopamine

The resting blood pressures and heart rates of the 10 animals used in this study were initially similar and remained virtually constant throughout the period of the study. Three control recordings of each cat were made on separate days and the group mean pressures were 114.3 ± 2.3 mmHg (systolic) and 82.6 ± 3.2 mmHg (diastolic) and the heart rate 139.7 ± 4.1 beats/minute.

Dopamine (30 and 45 μg i.c.v.) produced dose-related increases in blood pressure and heart rate in 6 cats and biphasic responses consisting of initial stimulant followed by prolonged depressor effects in the remaining 4. In those cats responding with pure stimulant effects the diastolic and systolic pressures were increased to a similar extent and the peak rises in blood pressure and heart rate occurred within 10 min of starting the drug infusion and had subsided within 30–45 min (Table 1). In those cats responding biphasically to i.c.v. dopamine the initial stimulant effects were over within 30 min of the infusion and were followed by depressor effects which reached a maximum 45–60 min post infusion with control levels of blood pressure and heart rate regained by 90 min (Table 2).

α-Methyldopamine (30 and 45 μg) was administered i.c.v. to 3 cats. In one cat it produced only stimulant effects on blood pressure and heart rate (Table 1) whilst in the remaining 2 it regularly produced biphasic responses (Table 2). The pressor and heart rate components of the responses to α-methyldopamine were smaller than those produced by the same dose of dopamine in each cat tested whilst the depressor effects were similar (Tables 1 and 2).

Effect of autonomic ganglion blockade

Autonomic ganglion blockade was produced either by pempidine (5 to 7.5 mg/kg i.v.) or by hexamethonium (5 to 10 mg/kg). These dose levels were sufficient to abolish completely the pressor responses produced by the autonomic ganglion stimulant tetramethylammonium bromide (75 μg/kg i.v.). After ganglion blockade the pressor responses to i.c.v. dopamine and α-methyldopamine were abolished as were the secondary depressor components in those animals responding biphasically. Figure 1 illustrates an experiment in a cat which responded with a simple pressor response to i.c.v. dopamine (45 μg) with little change in heart rate. The pressor response was abolished 45 min after hexamethonium (10 mg/kg i.v.).

Effect of adrenergic neurone blockade

The cardiovascular effects of i.c.v. dopamine (30 and 45 μg) were markedly reduced or abolished after

Table 2 Maximal initial increases and secondary decreases in blood pressure and heart rate (mean ± s.e.) induced by two dose levels of each of dopamine and α-methyldopamine administered into the lateral cerebral ventricles of a group of conscious cats which responded biphasically to both drugs

Agonist	Total dose (μg i.c.v.)	No. of responses	Arterial blood pressure initial increase (mmHg) Systolic	Arterial blood pressure initial increase (mmHg) Diastolic	Heart rate initial increase (beats/min)	Arterial blood pressure secondary decrease (mmHg) Systolic	Arterial blood pressure secondary decrease (mmHg) Diastolic	Heart rate secondary decrease (beats/min)	No. of cats
Dopamine	30	12	+23.1 ± 2.9	+22.0 ± 3.1	+14.2 ± 3.8	−12.2 ± 2.6	−12.7 ± 2.7	−16.6 ± 3.0	4
	45	12	+30.8 ± 3.2	+29.5 ± 3.3	+19.9 ± 3.9	−18.6 ± 2.9	−18.9 ± 3.0	−23.2 ± 3.2	
α-Methyldopamine	30	8	+10.6 ± 2.4	+ 9.9 ± 2.5	+11.2 ± 3.1	−11.1 ± 2.0	−11.9 ± 2.3	−13.7 ± 3.1	2
	45	8	+19.3 ± 2.8	+17.8 ± 3.5	+15.9 ± 3.8	−16.7 ± 3.3	−17.0 ± 3.4	−20.2 ± 4.0	

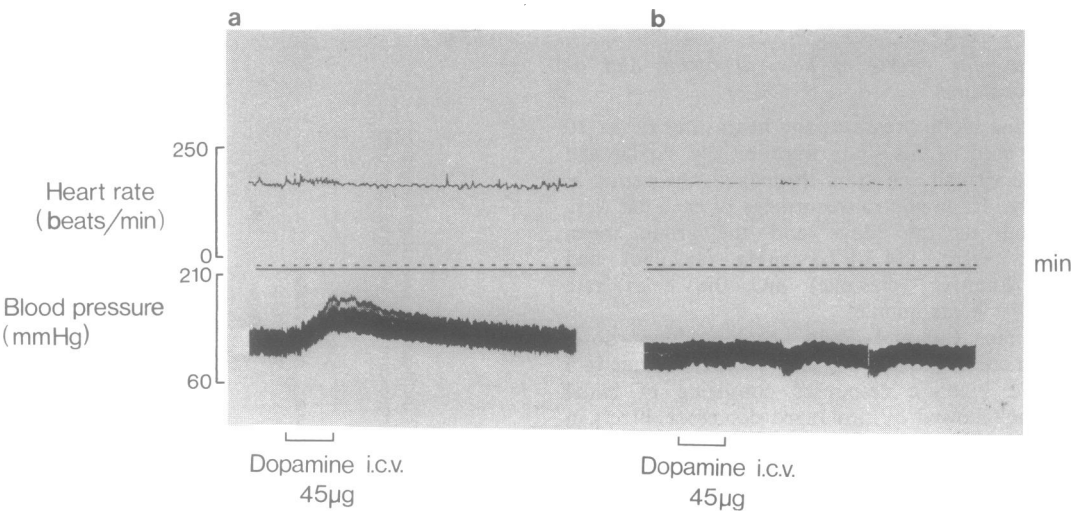

Figure 1 Conscious cat; blood pressure and heart rate recordings. In (a) i.c.v. dopamine (45 μg) produced a large rise in blood pressure with little change in heart rate. This effect was abolished in (b) 45 min after ganglion blockade with hexamethonium (10 mg/kg, i.v.). Time-marker in this and subsequent figures is in one minute intervals.

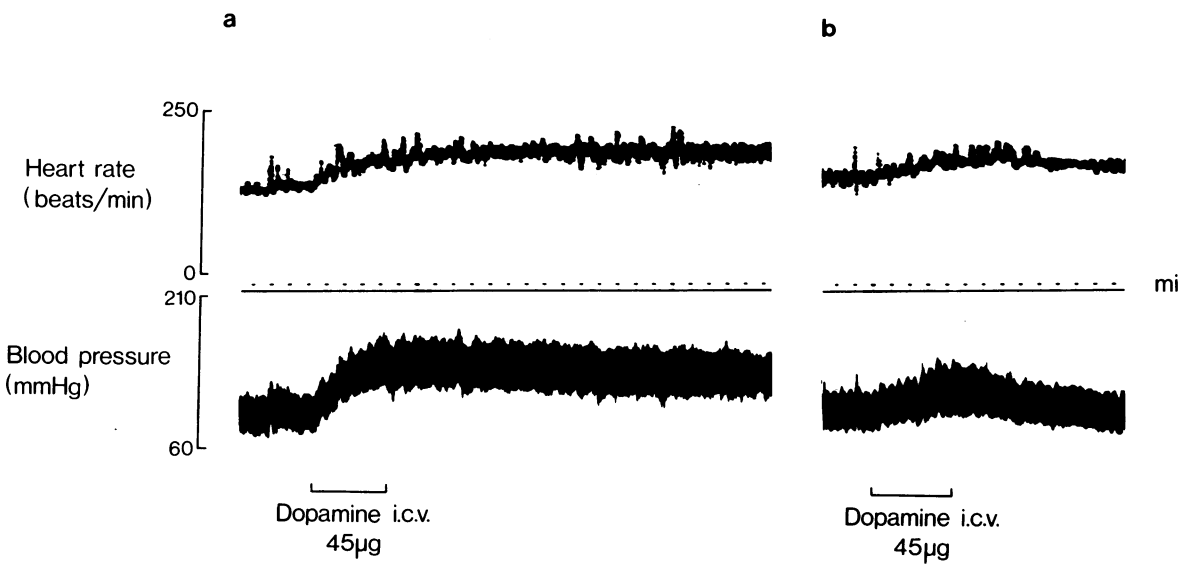

Figure 2 Conscious cat; blood pressure and heart rate recordings. The pressor response and tachycardia produced by i.c.v. dopamine (45 μg) in (a) were markedly reduced in (b) 2 h after adrenergic neurone blockade with bethanidine (5 mg/kg i.v.)

adrenergic neurone blockade with bethanidine (5 mg/kg i.v.) in each of 10 cats tested. Figure 2 illustrates an experiment in which the pressor effect and tachycardia produced by i.c.v. dopamine (45 μg) were considerably reduced 2 h after the administration of bethanidine (5 mg/kg i.v.). Guanethidine was used in 2 cats (7.5 and 10 mg/kg i.v. respectively) and virtually abolished all the cardiovascular changes induced by i.c.v. dopamine.

In 3 cats adrenergic neurone blockade by

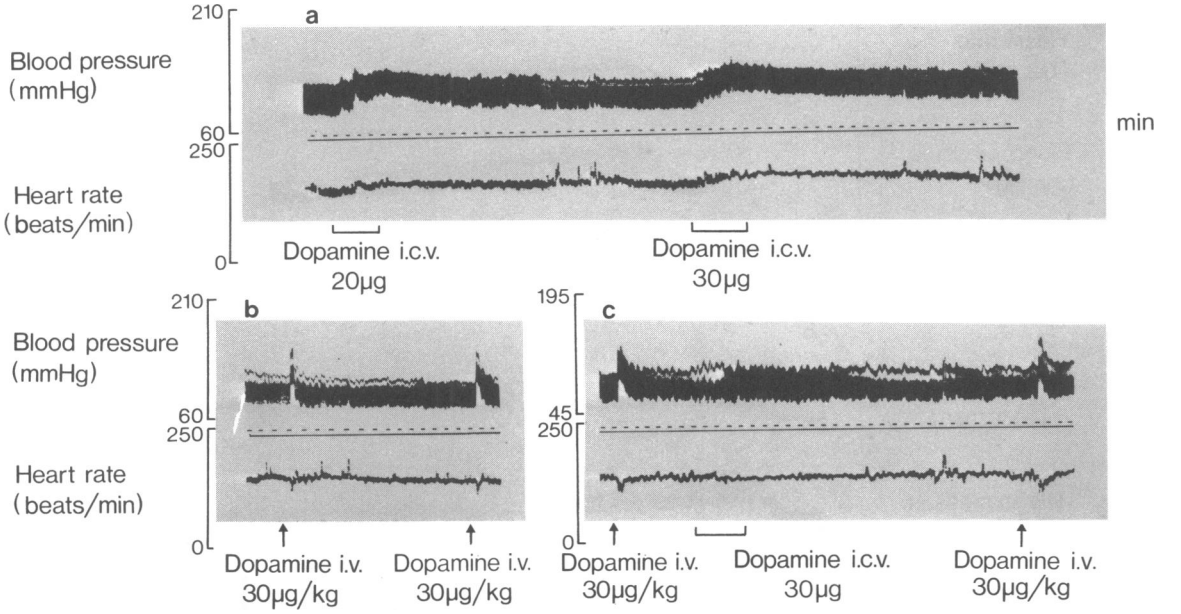

Figure 3 Conscious cat; blood pressure and heart rate recordings. In (a) i.c.v. dopamine, at two dose levels, produced pressor responses associated with tachycardia. In (b) are shown the responses induced by i.v. dopamine. Between (b) and (c) (±)-propranolol (0.75 mg) was infused i.c.v. and panel (c) which commences 30 min later shows the unaltered responses to dopamine by the i.v. route and the abolition of responses to i.c.v. dopamine.

bethanidine or guanethidine produced a similar inhibition of the cardiovascular effects of i.c.v. α-methyldopamine (45 μg).

Effect of i.c.v. pretreatment with β-adrenoceptor antagonists

In the 6 cats which responded regularly with pressor effects and tachycardia to i.c.v. dopamine these effects were markedly inhibited 45–60 min after (±)-propranolol or (±)-alprenolol (0.5 to 1.0 mg, i.c.v.). These i.c.v. doses of β-adrenoceptor blockers have been shown previously to abolish completely the cardiovascular effects of i.c.v. isoprenaline in this preparation (Day & Roach, 1974a). Figure 3 illustrates the total blockade of the cardiovascular stimulant effects of i.c.v. dopamine (30 μg) by (±)-propranolol (0.75 mg, i.c.v.). In this experiment the pressor effects and associated bradycardias produced by intravenous dopamine (30 μg/kg) were unaffected by the central β-adrenoceptor blockade indicating that in this experiment the effects of both dopamine and propranolol after i.c.v. administration are confined to the central nervous system.

In 4 cats in which i.c.v. dopamine produced biphasic blood pressure responses both (±)-propranolol and (±)-alprenolol inhibited the initial pressor responses and associated tachycardias but did not affect the secondary hypotensions and bradycardias. These β-adrenoceptor blocking agents produced similar effects on the stimulant responses to i.c.v. α-methyldopamine in 3 cats responding with simple cardiovascular stimulant effects and also in 2 others responding biphasically to this drug.

Administration of (+)-propranolol (0.25 to 0.5 mg i.c.v.) or (+)-alprenolol (0.25 to 0.75 mg) did not affect the cardiovascular effects of either dopamine or α-methyldopamine administered i.c.v. Similarly, the local anaesthetics lignocaine (0.75 to 1 mg i.c.v.) and procaine (1.5 to 2 mg i.c.v.) were ineffective.

Effect of i.c.v. pretreatment with an α-adrenoceptor antagonist

In the 6 cats responding with cardiovascular stimulation to i.c.v. dopamine the administration of the α-adrenoceptor antagonist phentolamine (0.5 to 0.75 mg i.c.v.) did not affect these responses. However, in the 4 cats responding biphasically to i.c.v. dopamine, i.c.v. phentolamine prevented the development of the secondary bradycardia and hypotension but did not affect the initial stimulant effects.

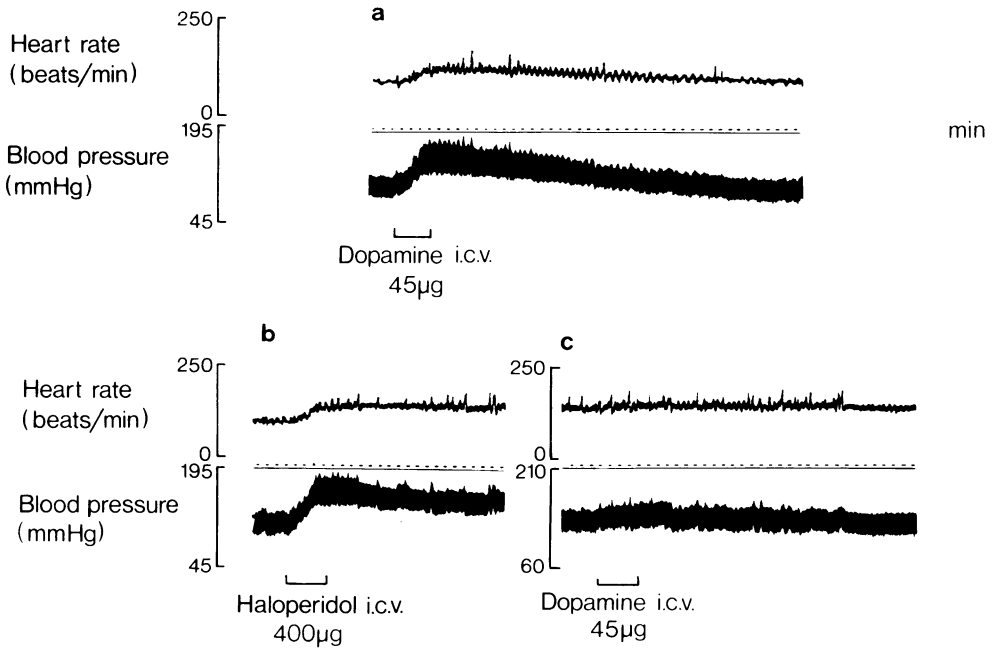

Figure 4 Conscious cat; blood pressure and heart rate recordings. In (a), i.c.v. dopamine (45 μg) produced a large pressor response and tachycardia. (b) Haloperidol (400 μg i.c.v.) produced similar initial cardiovascular stimulation as did dopamine and 60 min later in (c) the effects of i.c.v. dopamine were abolished.

The responses to i.c.v. α-methyldopamine were altered in the same way by i.c.v. phentolamine.

Effect of central dopamine receptor blockade

Haloperidol (400 μg, i.c.v.) produced a marked rise in blood pressure and heart rate in each of the 4 cats in which it was used. When these initial stimulant effects had subsided it was found that both stimulant and depressor effects of i.c.v. dopamine were abolished. These effects of haloperidol are illustrated in Figure 4. Since haloperidol was dissolved in an acid vehicle the effect of this alone was tested in 2 cats. The injection vehicle itself caused only a small pressor effect after i.c.v. infusion and did not affect the cardiovascular changes induced by i.c.v. dopamine.

Intravenous haloperidol (1 mg/kg) produced only slight cardiovascular stimulant effects itself but was as effective by this route as by i.c.v. administration in blocking both stimulant and depressor phases of the i.c.v. dopamine responses in two cats responding biphasically.

Pimozide (100 to 200 μg i.c.v.) produced much smaller cardiovascular stimulant effects than did i.c.v. haloperidol, control blood pressure and heart rate levels being regained after approximately 10 minutes. In 2 cats which responded with simple pressor responses to i.c.v. dopamine (45 μg) these effects were abolished 60 min after i.c.v. pimozide (200 μg). In 2 other cats which responded biphasically to i.c.v. dopamine the initial stimulant but not the secondary depressor phase of the response was abolished by i.c.v. pimozide. The vehicle in which pimozide was dissolved had no effects on the cardiovascular system which infused i.c.v. in similar volumes to those used for drug administration.

Intravenous pimozide (1 mg/kg) effectively inhibited the cardiovascular stimulant effects of i.c.v. dopamine (45 μg). Figure 5 illustrates an experiment with a cat which initially responded biphasically to the i.c.v. administration of dopamine. One hour after pimozide (1 mg/kg i.v.) the cardiovascular stimulant effects of i.c.v. dopamine (45 μg) were abolished, but the secondary hypotension and bradycardia still occurred.

Effect of dopamine-β-hydroxylase inhibition

Each of the 4 cats which responded biphasically to i.c.v. dopamine was pretreated for 3 days with the dopamine-β-hydroxylase inhibitor disulfiram (1st day 2 × 100 mg/kg i.p. separated by 12 h; 2nd and 3rd day 100 mg/kg i.p.). These cats were used 4 h after the final dose on the third day and it was found that

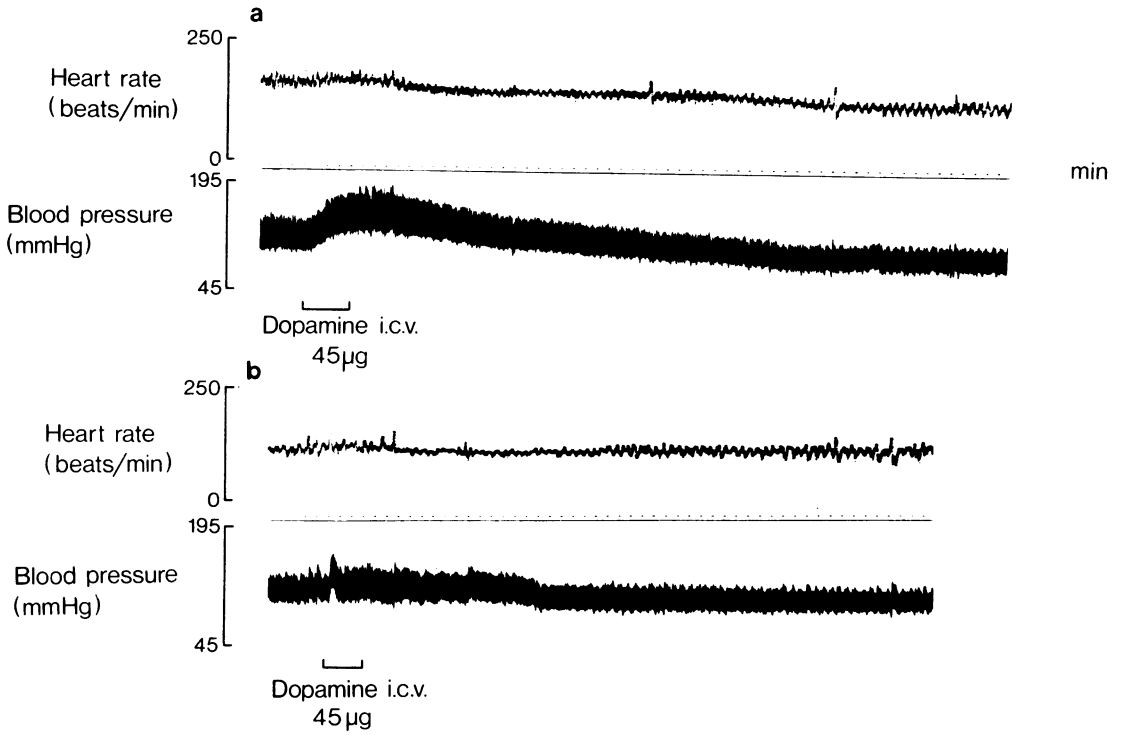

Figure 5 Conscious cat; blood pressure and heart rate recordings. (a) Dopamine (45 μg i.c.v.) produced an initial rise in blood pressure and heart rate which later subsided into a hypotension with slight bradycardia. (b) The dopamine response repeated 60 min after i.v. pimozide (1 mg/kg); the initial stimulant effect of dopamine is absent but there is still a prolonged hypotensive response.

resting blood pressures and heart rates were unchanged from control levels. Dopamine (45 μg i.c.v.) produced slightly increased initial pressor responses and tachycardias in these animals compared with control responses. However, the secondary falls in blood pressure and heart rate normally occurring in these animals were absent after disulfiram. α-Methyldopamine (30 μg i.c.v.) was tested in one of these animals and, like dopamine, was found to produce only cardiovascular stimulation.

Comparison of the cardiovascular effects of dopamine and isoprenaline by i.c.v. administration

Since it appeared that β-adrenoceptors may be involved in the cardiovascular responses produced by i.c.v. dopamine, the cardiovascular effects produced by i.c.v. administration of this substance were compared with those produced by isoprenaline in the 10 cats used in the present study. In the 6 cats which responded to i.c.v. dopamine with simple cardiovascular stimulation 4 responded to i.c.v. isoprenaline (30 μg) with pressor responses and tachycardia whilst in the other 2 there was a fall in blood pressure associated with tachycardia. Of the 4 cats which responded biphasically to i.c.v. dopamine, isoprenaline (30 μg i.c.v.) produced pressor responses with associated tachycardia in two, hypotension with tachycardia in one and tachycardia without blood pressure change in the last animal. Pressor, depressor and heart rate changes induced by i.c.v. isoprenaline were all abolished by (±)-propranolol (0.5 to 1 mg i.c.v.).

Neither pimozide (1 mg/kg i.v.) nor haloperidol (1 mg/kg i.v.) affected the cardiovascular changes induced by i.c.v. isoprenaline.

Effect of dopamine administered into the cisterna magna (i.c.m.)

Two cats previously used for i.c.v. administration of dopamine were additionally cannulated to allow of drug infusion into the cisterna magna. One cat responded to i.c.v. dopamine with a simple pressor response and tachycardia whilst the other responded biphasically. Infusion into the cisterna magna of

dopamine (30 and 45 μg) produced dose-related falls in blood pressure accompanied by bradycardia in each cat.

However, a higher dose (75 μg) of dopamine by this route produced an initial pressor response and tachycardia followed by prolonged hypotension and bradycardia in each cat. This higher dose of dopamine usually induced vomiting by the i.c.m. route which it never did i.c.v. The mean initial stimulant and subsequent depressor effects of the 75 μg i.c.m. dose of dopamine are summarized in Table 3. Phentolamine (0.5 mg i.c.m.) did not affect resting blood pressure or heart rate, but it abolished the inhibitory effects of the lower dopamine doses and also the inhibitory component of the response to the highest dopamine dose without significantly affecting the pressor component of the response. In one experiment dopamine did not induce vomiting following phentolamine suggesting that the pressor effect of dopamine by this route is not secondary to the stress of vomiting.

The initial pressor but not the secondary depressor effects of i.c.m. dopamine (75 μg) were absent 1.5 h after i.c.m. administration of (±)-propranolol (0.5 mg) in each cat. Neither cat vomited in response to i.c.m. dopamine after (±)-propranolol treatment.

Table 3 Maximal initial increases and secondary decreases in blood pressure and heart rate (mean ± s.e.) induced by 75 μg dopamine infused into the cisterna magna (i.c.m.) of two conscious cats

Agonist	Total dose (μg i.c.m.)	No. of responses	Arterial blood pressure initial increase (mmHg) Systolic	Arterial blood pressure initial increase (mmHg) Diastolic	Heart rate initial increase (beats/min)	Arterial blood pressure secondary decrease (mmHg) Systolic	Arterial blood pressure secondary decrease (mmHg) Diastolic	Heart rate secondary decrease (beats/min)	No. of cats
Dopamine	75	4	+20.1 ± 5.9	+18.8 ± 6.1	+27.1 ± 5.2	−24.8 ± 4.5	−25.3 ± 4.7	−31.7 ± 5.6	2

Discussion

The central administration of dopamine and its α-methyl analogue to several species has been reported to produce falls in arterial blood pressure with associated bradycardia (McCubbin *et al.*, 1960; Baum & Shropshire, 1973; Heise & Kroneberg, 1973; Bloch *et al.*, 1974; Finch *et al.*, 1975). Heise & Kroneberg (1973), using anaesthetized cats reported that the hypotension in response to i.c.v. α-methyldopamine was blocked by i.c.v. phentolamine or yohimbine although that to i.c.v. dopamine was relatively unaffected by i.c.v. phentolamine. Finch *et al.* (1975) analysed the mechanism of hypotension produced by i.c.v. α-methyldopamine in conscious spontaneously hypertensive rats. They reported that the hypotension induced by i.c.v. α-methyldopamine was prevented by i.c.v. phentolamine or desmethylimipramine but not by systemic haloperidol. Inhibition of central dopamine β-hydroxylase abolished the depressor effect of i.c.v. α-methyldopamine. These data suggest that in the rat i.c.v. α-methyldopamine produces hypotension by acting as a precursor for the formation of α-methylnoradrenaline which stimulates inhibitory α-adrenoceptors within the brain (van Zwieten, 1973). However, Finch *et al.* (1975) did not produce corroborative data for this hypothesis from their work in anaesthetized cats since, in their experiments, both noradrenaline and α-methylnoradrenaline by the i.c.v.

route produced increases in blood pressure, results in direct conflict with previous reports in conscious cats (Day & Roach, 1973; 1974a).

The mechanisms whereby the dopamine receptor stimulant apomorphine produces its cardiovascular responses are similarly confused. Barnett & Fiore (1971) reported that apomorphine lowered blood pressure in anaesthetized cats and that this effect was abolished by either spinal section or haloperidol treatment. These workers concluded that the hypotensive effect of apomorphine was due to stimulation of central dopamine receptors. However, Finch & Haeusler (1973) could not abolish the hypotensive effects of apomorphine in rats with haloperidol, spiroperidol or sulpiride, all substances reported to possess potent dopamine receptor blocking activity. Finch & Haeusler (1973) suggested that the hypotensive response to apomorphine in their experiments was due to increased efferent vagal activity and was not mediated through activation of central dopamine receptors.

In the systemic cardiovascular system dopamine has been reported to stimulate α and β-adrenoceptors and dopamine receptors (Goldberg & Whitsett, 1971). Intracerebroventricular dopamine in the present experiments caused increases in blood pressure with associated tachycardia in each of the 10 cats used. These cardiovascular stimulant effects were apparently mediated via the peripheral sympathetic system since they were absent after either ganglion blockade or adrenergic neurone blockade. Moreover, the effects of i.c.v. dopamine were abolished by i.c.v. β-adrenoceptor blockers or by i.c.v. dopamine antagonists. In 4 of the cats used, after the initial stimulant effects of i.c.v. dopamine had subsided they were replaced by a prolonged fall in both blood pressure and heart rate. These secondary depressor effects of i.c.v. dopamine were abolished by phentolamine and by disulfiram. Disulfiram has been shown to be an effective inhibitor of central dopamine β-hydroxylase (Musacchio, Goldstein, Anagnoste, Poch & Kopin, 1966). Thus it would appear that in these cats some of the i.c.v. dopamine was converted to noradrenaline which then produced typical centrally-mediated cardiovascular depressant effects (Day & Roach, 1974a).

Haloperidol inhibited all the cardiovascular changes induced by i.c.v. dopamine whilst pimozide only inhibited the stimulant effects. These results are not unexpected considering the published data on these compounds. Thus, haloperidol is less specific than pimozide and blocks both noradrenaline and dopamine receptors in the central nervous systems of rats (Carlsson & Lindqvist, 1963), cats and dogs (Janssen, 1967), whilst pimozide has been reported to block only dopamine receptors in rats, cats and dogs (Janssen, 1967; Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970).

Bolme & Fuxe (1971) reported that in the cat, spiroperidol and pimozide caused hypotension and bradycardia which were potentiated by clonidine. They suggested that these effects might have been mediated via removal of excitatory central dopaminergic tone. They further postulated the existence in the brain of opposing dopaminergic and noradrenergic mechanisms influencing the peripheral cardiovascular system. Contrasting data were reported by Bloch *et al.* (1974) who found that clonidine and large doses of dopamine applied to the ventral surface of the cat brain stem induced hypotension. The effects of each compound were antagonized by pimozide whilst noradrenaline applied to this area caused pressor responses. In the present experiments i.c.v. haloperidol produced pronounced cardiovascular stimulant effects. It is not clear what the mechanism of this effect is; it could be due to initial dopamine receptor stimulant activity, or conversely, to inhibition of noradrenergic depressant pathways. It was found in the present experiments and in those reported previously (Day & Roach, 1974a) that i.c.v. phentolamine caused increases in heart rate and blood pressure. Pimozide which is a more specific dopamine receptor antagonist produced only slight and transient cardiovascular stimulation after i.c.v. administration. The results obtained with two cats in which dopamine was administered into the cisterna magna suggested that its predominant effect at this site was to cause cardiovascular depressant effects, apparently mediated via formation of noradrenaline. Thus it would appear that the increase in blood pressure and heart rate produced by i.c.v. dopamine were caused by stimulation of supramedullary structures.

Both dopamine and isoprenaline produce cardiovascular stimulant effects after i.c.v. infusion in conscious cats (Day & Roach, 1974a). These effects of both drugs are abolished by β-adrenoceptor blocking agents and tempt the speculation that both are mediated via the same receptors. However, the evidence from the present experiments, although not inconsistent with this possibility, lends it little support. Thus, although there was considerable variation in the responses to isoprenaline and dopamine in different cats the response to each agent remained constant within individual cats and qualitative differences in the responses were regularly found. Isoprenaline produced a more marked rise in systolic than diastolic pressure whilst dopamine increased both equally. Furthermore the pressor responses to i.c.v. isoprenaline were always accompanied by more marked tachycardias than were similar pressor responses to dopamine. These observations are not inconsistent with a similar action of dopamine and isoprenaline on blood pressure regulating centres with the possibility of a more marked effect of isoprenaline on centres controlling heart rate. The fact that pimozide selectively abolished dopamine responses suggests that the actual receptors mediating blood pressure responses to dopamine and isoprenaline are different but does not preclude the possibility that a common neural pathway, possibly

terminating in β-adrenoceptors, is involved in both responses.

The published evidence concerning the function of brain noradrenaline in cardiovascular control suggests that its role is inhibitory to the sympathetic outflow (see reviews by van Zwieten, 1973; Day & Roach, 1974b). The report of decreased noradrenaline synthesis and content of the brain stem and hypothalamus of spontaneously hypertensive rats (Yamori, Lovenberg & Sjoerdsma, 1970) supports this concept as does the finding of decreased turnover rate of noradrenaline in the brain stem of DOCA/saline hypertensive rats (Nakamura, Gerold & Thoenen, 1971).

Yamabe, de Jong & Lovenberg (1973) reported increased dopamine levels in the telencephalon of spontaneously hypertensive rats whilst Spring & Winkelmuller (1975) have recently produced evidence in favour of dopamine participation in the pressor response of anaesthetized cats to electrical stimulation of the ventral mid-brain. These observations together with those presented here are consistent with a role for brain dopamine as a mediator concerned with cardiovascular stimulation via activation of the peripheral sympathetic nervous system.

The authors are grateful to Merck, Sharpe and Dohme Ltd., West Point, Pennsylvania, U.S.A. for a gift of (–)-methyldopamine and to the Medical Research Council for a training award to one of us (A.G.R.).

References

ANDÉN, N.E., BUTCHER, S.G., CORRODI, H., FUXE, K. & UNGERSTEDT, U. (1970). Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.*, **11**, 303–314.

ARDILL, B.L., FENTEM, P.H. & WELLARD, M.J. (1967). An electromagnetic pressure generator for testing the frequency response of transducers and catheter systems. *J. Physiol., Lond.*, **192**, 19–21P.

BARNETT, A. & FIORE, J.W. (1971). Hypotensive effects of apomorphine in anaesthetised cats. *Eur. J. Pharmac.*, **14**, 206–208.

BAUM, T. & SHROPSHIRE, A.T. (1973). Reduction of sympathetic outflow by central administration of L-dopa, dopamine and norepinephrine. *Neuropharmacology*, **12**, 49–56.

BLOCH, R., BOUSQUET, P., FELDMAN, J., VELLY, J. & SCHWARTZ, J. (1974). Action hypotensive de la clonidine appliquée sur la surface ventrale du bulbe rachidien: analogie avec la dopamine. *Thérapie*, **29**, 251–259.

BOLME, P. & FUXE, K. (1971). Pharmacological studies on the hypotensive effects of clonidine. *Eur. J. Pharmac.*, **13**, 168–174.

CARLSSON, A. & LINDQVIST, M. (1963). Effect of chlorpromazine or haloperidol on the formation of 3-methoxytryptamine and normetanephrine in mouse brain. *Acta pharmac. tox.*, **20**, 140–144.

COOLING, M.J., DAY, M.D. & ROACH, A.G. (1974). A modified cannula for intracerebroventricular injections in conscious cats. *Lab. Pract.*, **23**, 439.

DAY, M.D. & ROACH, A.G. (1972). Adrenoceptors in the central nervous system concerned with cardiovascular control. *J. Pharm. Pharmac.*, **24**, 148P.

DAY, M.D. & ROACH, A.G. (1973). β-Adrenergic receptors in the central nervous system of the cat concerned with control of arterial blood pressure and heart rate. *Nature, New Biol.*, **242**, 30–31.

DAY, M.D. & ROACH, A.G. (1974a). Central α- and β-adrenoceptors modifying arterial blood pressure and heart rate in conscious cats. *Br. J. Pharmac.*, **51**, 325–333.

DAY, M.D. & ROACH, A.G. (1974b). Central adrenoceptors and the control of arterial blood pressure. *Clin. exp. Pharm. Physiol.*, **1**, 347–360.

DAY, M.D. & WHITING, R.L. (1972). An improved valve device for the continuous measurement of arterial blood pressure in the conscious unrestrained cat. *J. Pharm. Pharmac.*, **24**, 263–264.

DE JONG, W., NIJKAMP, F.P. & BOHUS, B. (1975). Role of noradrenaline and serotonin in the central control of blood pressure in normotensive and spontaneously hypertensive rats. *Arch. int. Pharmacodyn. Thér.*, **213**, 272–284.

FELDBERG, W., MYERS, R.D. & VEALE, W.L. (1970). Perfusion from central ventricle to cisterna magna in the unanesthetised cat. Effect of calcium on body temperature. *J. Physiol., Lond.*, **207**, 403–416.

FELDBERG, W. & SHERWOOD, S.L. (1953). A permanent cannula for intraventricular injections in cats. *J. Physiol., Lond.*, **120**, 3–5P.

FINCH, L. & HAEUSLER, G. (1973). The cardiovascular effects of apomorphine in the anaesthetised rat. *Eur. J. Pharmac.*, **21**, 264–270.

FINCH, L., HERSOM, A. & HICKS, P. (1975). Studies on the hypotensive action of α-methyldopamine. *Br. J. Pharmac.*, **54**, 445–452.

GOLDBERG, L.I. & WHITSETT, T.L. (1971). Cardiovascular effects of levodopa. *J. Am. Med. Ass.*, **218**, 1921–1923.

HEISE, A. & KRONEBERG, G. (1973). Central nervous α-adrenergic receptors and the mode of action of α-methyldopa. *Naunyn-Schmiedebergs Arch. Pharmac.*, **279**, 285–300.

HENNING, M. (1973). Receptor regulation studies: significance of central catecholamine receptors in cardiovascular control. In *Frontiers in Catecholamine Research*, ed. Usdin, E. & Snyder, S., pp. 595–600. New York: Pergamon Press.

HENNING, M. (1975). Central sympathetic transmitters and hypertension. *Clin. Sci. Mol. Med.*, **48**, 195–203S.

JANSSEN, P.A.J. (1967). Haloperidol and related butyrophenones. In *Psychopharmacological Agents*, Vol. II, ed. Gordon, M., pp. 199–248. New York, London: Academic Press.

McCUBBIN, J.W., KANEKO, Y. & PAGE, I.H. (1960). Ability of serotonin and norepinephrine to mimic the central effects of reserpine on vasomotor activity. *Circulation Res.*, **8**, 849–858.

MUSACCHIO, J.M., GOLDSTEIN, M., ANAGNOSTE, B., POCH, G. & KOPIN, I.J. (1966). Inhibition of dopamine-β-hydroxylase by disulfiram *in vivo*. *J. Pharmac. exp. Ther.*, **152**, 56–61.

NAKAMURA, K., GEROLD, M. & THOENEN, H. (1971). Experimental hypertension of the rat: Reciprocal changes of norepinephrine turnover in heart and brainstem. *Naunyn-Schmiedebergs Arch. Pharmac.*, **268**, 125–139.

SPRING, A. & WINKELMULLER, W. (1975). Ventral midbrain stimulation, blood pressure responses and their relation to the dopaminergic nigro-striatal pathways. *Pflügers Arch. Eur. J. Physiol.*, **358**, 339–348.

STRUYKER BOUDIER, H.A.J., SMEETS, G.W.M., BROUWER, G.M. & VAN ROSSUM, J.M. (1974). Hypothalamic alpha adrenergic receptors in cardiovascular regulation. *Neuropharmacology*, **13**, 837–846.

STRUYKER BOUDIER, H.A.J., SMEETS, G.W.M., BROUWER, G.M. & VAN ROSSUM, J.M. (1975). Central nervous system α-adrenergic mechanisms and cardiovascular regulation in rats. *Arch. int. Pharmacodyn. Thér.*, **213**, 285–293.

TOIVOLA, P. & GALE, C.C. (1970). Effect on temperature of biogenic amine infusion into hypothalamus of baboon. *Neuroendocrinology*, **6**, 210–219.

VAN ZWIETEN, P.A. (1973). The central action of antihypertensive drugs, mediated via central α-receptors. *J. Pharm. Pharmac.*, **25**, 89–95.

YAMABE, H., DE JONG, W. & LOVENBERG, W. (1973). Further studies on catecholamine synthesis in the spontaneously hypertensive rat: Catecholamine synthesis in the central nervous system. *Eur. J. Pharmac.*, **22**, 91–98.

YAMORI, Y., LOVENBERG, W. & SJOERSDMA, A. (1970). Norepinephrine metabolism in brain stem of spontaneously hypertensive rats. *Science*, **170**, 544–546.

(Received February 20, 1976.
Revised May 13, 1976.)