Br. J. Pharmac. (1979), **66**, 235–240

CARDIOVASCULAR RESPONSES PRODUCED BY THE INJECTION OF DOPAMINE INTO THE CEREBRAL VENTRICLES OF THE UNANAESTHETIZED DOG

W.J. LANG & O.L. WOODMAN

Department of Pharmacology, University of Melbourne, Parkville, Victoria, 3052, Australia

1 The injection of dopamine (100 to 500 μg) into the cerebral ventricles (i.c.v.) of 10 unanaesthetized dogs produced a dose-dependent increase in arterial blood pressure and heart rate. The dogs licked, swallowed, sometimes vomited and became sedated.

2 Autonomic ganglion blockade with hexamethonium (10 mg/kg, i.v.) abolished cardiovascular responses to i.c.v. dopamine, indicating that dopamine was exerting its effect within the central nervous system.

3 The dopamine receptor antagonists, haloperidol (500 μg), chlorpromazine (200 μg) and ergometrine (500 μg), each given i.c.v., subsequently abolished the cardiovascular responses to dopamine.

4 Pretreatment with either the β-adrenoceptor antagonist, propranolol (600 μg) or the α-adrenoceptor antagonist, phentolamine (1 mg) given i.c.v. had no significant effect on the response to dopamine.

5 It is suggested that dopamine injected into the cerebral ventricles of the unanaesthetized dog causes hypertension and tachycardia by activating central dopamine receptors.

Introduction

During the past few years considerable evidence has been accumulated supporting the role of dopamine as a neurotransmitter substance in the central nervous system (Vogt, 1973; Carlsson, 1974). Recently it has been suggested that central dopaminergic pathways may be involved in cardiovascular regulation (Bolme, Fuxe & Lidbrink, 1972) but there have been few reported studies investigating this possibility.

The intraventricular injection of dopamine has been shown to decrease both heart rate and blood pressure in the anaesthetized rat and cat (Baum & Shropshire, 1973; Heise & Kroneberg, 1973; Heise, 1976), and it was found by Heise (1976) that this depressor response could be abolished by the dopamine receptor antagonists, haloperidol and pimozide, but not by the α-adrenoceptor antagonist, phentolamine. However, in the anaesthetized dog, little or no response was produced by intraventricular injections of dopamine (McCubbin, Kaneko & Page, 1960).

In contrast, the injection of dopamine into the cerebral ventricles of unanaesthetized cats produced an increase in both blood pressure and heart rate which, in some cases, was followed by prolonged hypotension and bradycardia (Day & Roach, 1976). It was also found that the increases in blood pressure and heart rate produced by dopamine were abolished by the dopamine receptor antagonists, haloperidol and pimozide.

The present series of experiments was performed in unanaesthetized dogs with guide cannulae implanted above the lateral cerebral ventricles so that the effects of intracerebroventricular (i.c.v.) injections of dopamine could be compared with those previously reported in unanaesthetized cats, and in anaesthetized dogs. The specific nature of any action in the central nervous system was determined with various pharmacological agents.

Methods

Dogs of either sex and weighing between 10 to 15 kg were used. Arterial blood pressure was recorded by a method similar to that described by Lang, Gershon & Holan (1963). Dogs which had been surgically prepared with carotid arteries exteriorized in skin loops, were trained to stand in harness in a Pavlov-type stand. To record arterial blood pressure an Intramedic (R) PE50 polythene cannula was passed through an 18 gauge thin-walled needle into the carotid artery and held in place with a skin suture. Arterial pressure was measured in mmHg with a Statham P23Db pressure transducer. The ECG was obtained from standard limb leads, and integrated with a cardiotachometer coupler to provide a continuous record of heart rate. Both blood pressure and heart

0007-1188/79/060235-06 $01.00

rate were recorded on a Beckman Type R-411 dynograph and the dog's behaviour during the experiments was observed from outside the experimental room through a one-way mirror.

To enable the injection of drugs into the cerebral ventricles, a modified Collison cannula was stereotaxically implanted into the skull to act as a permanent guide tube, by the method of Lang & Rush (1973). The cannula was positioned above the left lateral ventricle, at a point 15 mm anterior to the inter-aural plane and 5 mm lateral to the saggital suture. The guide tube was fixed to the skull with dental acrylic cement and two stainless steel screws. Before each experiment a 25 guage needle was passed down the cannula guide and lowered into the brain until a fall in pressure was recorded, indicating that the end of the needle was situated within the cerebral ventricle. Drugs were injected with a volume of 0.1 ml which was washed in with 0.2 ml of sterile 0.9% w/v NaCl solution (saline).

The site of injection into the lateral cerebral ventricle was confirmed at the end of the series of experiments in each dog by injection of 0.3 ml of 1% Evan's blue solution and examination of the staining of the cerebral ventricles at *post mortem*. Staining was apparent in both lateral ventricles as well as the third and fourth ventricles, indicating correct positioning of the cannulae.

Drugs used were: chlorpromazine hydrochloride (Largactil, May & Baker), dopamine hydrochloride (3-hydroxytryptamine hydrochloride, Calbiochem), ergometrine maleate (Burroughs Wellcome), haloperidol (Serenace, Searle), hexamethonium bromide (Sigma), isoprenaline hydrochloride (Sterling), phentolamine mesylate (Regitine, CIBA-Geigy), propranolol hydrochloride (Inderal, ICI). Doses quoted are in terms of the above salts. Dopamine, ergometrine, hexamethonium and isoprenaline solutions were made up on the day of the experiment in sterile saline. Chlorpromazine, haloperidol, phentolamine and propranolol solutions were taken from sterile ampoules. Similar volumes of saline or of the vehicles used to dissolve the drugs had no apparent effect when injected into the cerebral ventricles. The significance of difference of means was assessed with Student's t test.

Results

The resting blood pressures and heart rates of 10 dogs used in this study did not change significantly over the period of experiments; the control mean blood pressure was 107 $\pm$ 3 mmHg (mean $\pm$ s.e. mean) and the control mean heart rate was 102 $\pm$ 3 beats/min.

Effect of intraventricular injection of dopamine

Dopamine was injected into the cerebral ventricles of a series of 10 unanaesthetized dogs over the dose range of 100 to 500 μg. Nine dogs were given 100 μg dopamine, which produced an increase in blood pressure and heart rate in four of them. Of the 5 dogs in which this dose had no effect, 2 showed a pressor response to the injection of 200 μg dopamine, and all 5 responded to an injection of 500 μg dopamine. A typical experimental record is shown in Figure 1. The 10th dog in the series did not respond to either 200 or 500 μg dopamine. The dose of 200 μg was chosen for use in the subsequent experiments to determine the effect of various antagonists upon the response to dopamine.

The onset of the cardiovascular response to dopamine occurred between 2 and 15 min after administration and the duration of the responses was between

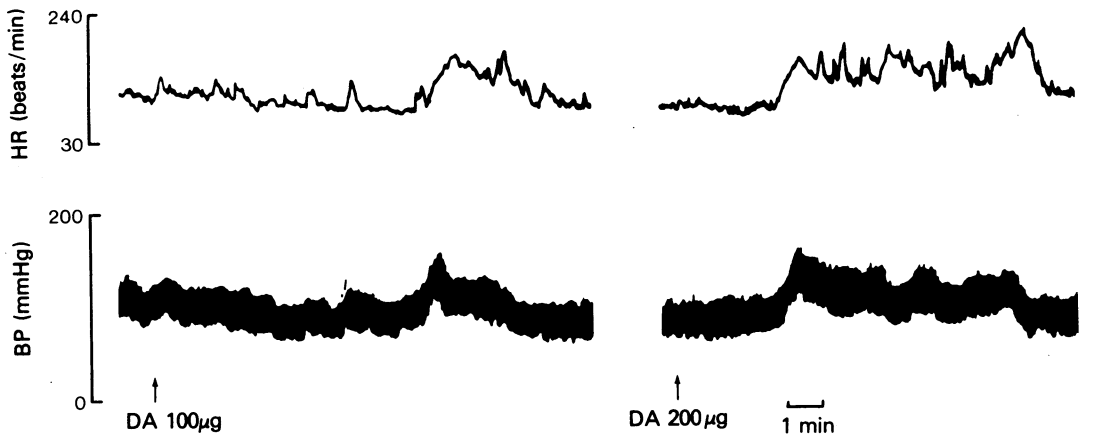

Figure 1 Heart rate (HR) and arterial blood pressure (BP) recorded from an unanaesthetized dog. The responses to two doses of dopamine (DA) injected into the cerebral ventricles of the same dog are illustrated.

2 and 10 min. After injection of dopamine the dogs were sometimes seen to lick and swallow. In 8 of the 10 dogs, vomiting occasionally occurred at the same time as the cardiovascular response. Dogs frequently appeared drowsy after i.c.v. dopamine and would hang in the restraining harness without supporting themselves, although they remained conscious.

Effect of pretreatment with hexamethonium

Autonomic ganglion blockade was produced in 5 dogs with hexamethonium (10 mg/kg i.v.) 10 min before injection of dopamine (200 μg, i.c.v.). Hexamethonium completely abolished the cardiovascular response to dopamine (Figure 2b). In one of these dogs vomiting occurred between 11 and 15 min after the injection of dopamine, but there were no changes in blood pressure or heart rate.

Effect of pretreatment with dopamine receptor antagonists

To study the effect of dopamine receptor antagonists on the response to dopamine, 3 of the dogs were injected with haloperidol (500 μg), 3 with chlorpromazine (200 μg) and 5 with ergometrine (500 μg), 10 min before the administration of dopamine (200 μg); all drugs being given i.c.v.

Neither haloperidol (500 μg) nor chlorpromazine (200 μg) affected heart rate or blood pressure. However, pretreatment with either antagonist abolished the cardiovascular response to the injection of 200 μg dopamine (Figure 2c).

In 2 of the dogs injected with ergometrine (500 μg) there occurred an increase in blood pressure and

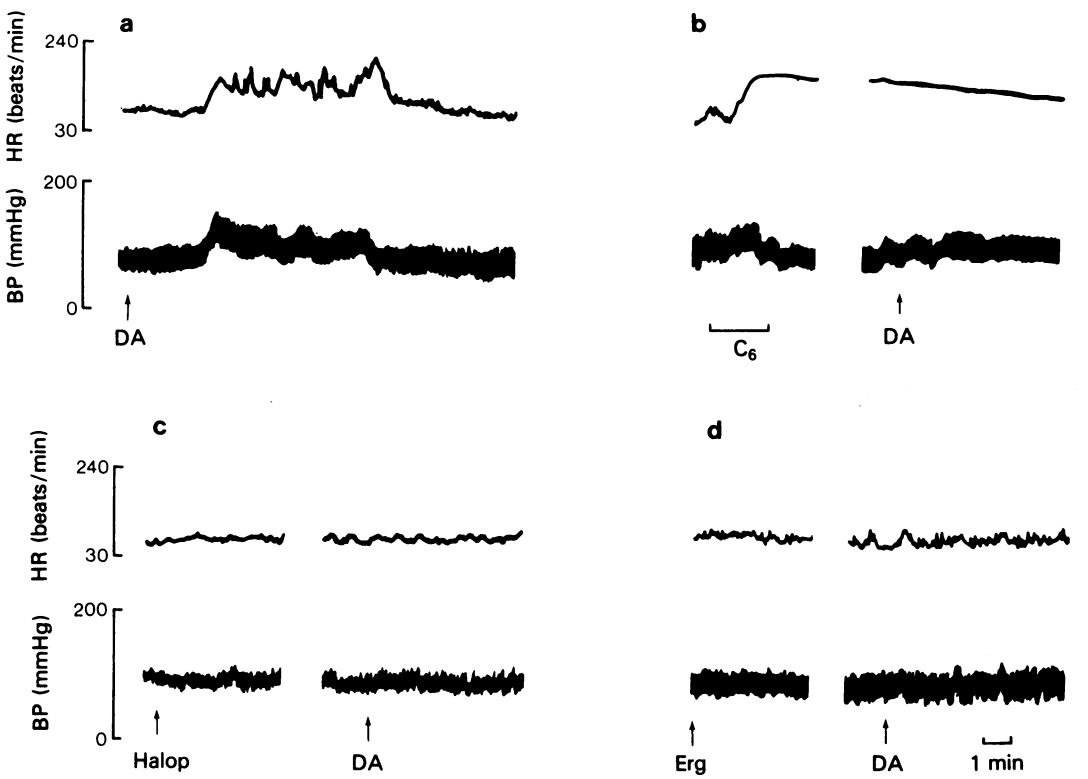

Figure 2 Heart rate (HR) and arterial blood pressure (BP) of an unanaesthetized dog. In (a) the control response to the intraventricular injection of 200 μg dopamine (DA) is illustrated; (b) shows the response to the same dose of dopamine on a subsequent day 10 min after intravenous injection of 10 mg/kg hexamethonium (C_6). The response to dopamine (200 μg) on subsequent experimental days after the intraventricular injection of 500 mg of dopamine receptor antagonists haloperidol (Halop) and ergometrine (Erg) is shown in records (c) and (d) respectively.

heart rate which lasted about 2 min and on both occasions vomiting accompanied the cardiovascular response. The remaining dogs showed no response to ergometrine. In all dogs the response to 200 μg dopamine was completely abolished by the pretreatment with ergometrine (Figure 2d).

Effect of pretreatment with propranolol

The β-adrenoceptor antagonist, propranolol (600 μg) was given i.c.v. to 6 dogs. This dose of propranolol has previously been reported to abolish the decrease in blood pressure and increase in heart rate observed in response to i.c.v. isoprenaline (100 μg) in this preparation (Conway & Lang, 1974). Similarly, in the present series of experiments there was no cardiovascular response to isoprenaline (100 μg) following pretreatment with propranolol (600 μg). The cardiovascular response to dopamine was unaffected by this pretreatment (Table 1.).

Effect of pretreatment with phentolamine

Blockade of central α-adrenoceptors was produced with phentolamine (1 mg, i.c.v.) in 6 dogs. The increase in blood pressure caused by i.c.v. dopamine (200 μg) was unaffected by the presence of phentolamine (Table 1). The increase in heart rate caused by this dose of dopamine following phentolamine was found to be 45 ± 15 beats/min (mean ± s.e. mean) compared with a control value of 67 ± 12 beats/min. This difference was not statistically significant.

Discussion

Dopamine injected into the cerebral ventricles of unanaesthetized dogs produced a dose-dependent increase in blood pressure and heart rate. The dogs appeared drowsy, would lick and swallow, and occasionally this was followed by vomiting.

In the anaesthetized cat, Heise (1976) found (a) that the maximal cardiovascular response to dopamine occurred when the anterior portion of the third ventricle was perfused; (b) that if only the posterior part of the third ventricle was perfused, the response to dopamine decreased; and (c) that if only the fourth ventricle was perfused, the response was very small. In our study the cardiovascular effects result from dopamine acting at a site in the central nervous system rather than through it escaping from the ventricles into the periphery since the response was abolished by pretreatment with hexamethonium. Examination of dye distribution in the brain at *post mortem* suggested that dopamine would have entered both lateral as well as the third and fourth ventricles. Dopamine could have been acting, therefore, on any of the brain regions lining these ventricles. Possible sites include caudate nucleus and hippocampus (which both form part of the wall of the lateral ventricles), the hypothalamus adjacent to the wall of the third ventricle and the medulla oblongata and pons which form the floor of the fourth ventricle. However, our experimental method does not allow any more precise localization.

The response to i.c.v. dopamine is qualitatively different from that observed after i.v. dopamine in the unanaesthetized dog. Doses of dopamine similar to, and higher than those injected into the cerebral ventricles in this study, have been reported to produce biphasic cardiovascular responses when injected intravenously into the unanaesthetized dog (Higgins, Millard, Braunwald & Vatner, 1973). In their experiments, a small and transient increase in blood pressure occurred followed by a prolonged decrease in pressure while heart rate showed an initial small decrease followed by a prolonged rise.

In the present experiments, pretreatment of the dogs with i.c.v. injections of the dopamine receptor antagonists haloperidol, chlorpromazine and ergometrine abolished the cardiovascular responses to i.c.v. dopamine. The specificity of ergometrine as an antag-

Table 1 Comparison of blood pressure and heart rate responses induced by intracerebroventricular injection of dopamine (200 μg) before and after pretreatment with propranolol (600 μg) or phentolamine (1 mg)

Pretreatment	*No. of responses*	*Mean blood pressure increase (mmHg)*	*Heart rate increase (beats/min)*	*No. of dogs*
Control	10	23 ± 4	67 ± 12	6
Propranolol (600 μg i.c.v.)	6	21 ± 5	65 ± 18	6
Phentolamine (1 mg i.c.v.)	6	20 ± 3	45 ± 15	6

Values are mean ± s.e. mean

onist of dopamine in the peripheral vasculature has been previously reported in experiments on the hindlimb of the anaesthetized dog where it was found to have no effect on the dilator response to isoprenaline, acetylcholine, histamine, 5-hydroxytryptamine or bradykinin (Bell, Conway, Lang & Padanyi, 1975). On the other hand, Woodruff, Elkhawad & Crossman (1974) proposed that ergometrine acts as a dopamine receptor agonist in the rat central nervous system. These authors found that in rats with unilateral 6-hydroxydopamine-induced lesions of the nigrostriatal pathway, the injection of ergometrine caused them to turn towards the denervated side, a response which has been previously interpreted as indicating dopamine receptor stimulation (Ungerstedt, 1971). In our unanaesthetized dogs, i.c.v. ergometrine caused an inconsistent increase in blood pressure and heart rate which was accompanied by vomiting. However, ergometrine consistently abolished the cardiovascular response to intraventricular dopamine, suggesting that in the central nervous system of the dog, ergometrine acts either as a dopamine receptor antagonist or partial agonist.

Although more usually regarded as potent dopamine antagonists, chlorpromazine and haloperidol are also known to act as antagonists at α-adrenoceptors (Byck, 1975). However, phentolamine a potent α-adrenoceptor antagonist, had no significant effect upon the cardiovascular responses to dopamine, and it is also of interest that the other dopamine receptor antagonist used in these experiments, ergometrine, is reported to have no α-adrenoceptor antagonist activity (Nickerson & Collier, 1975). The abolition of the responses to dopamine by chlorpromazine and haloperidol appears therefore to be due to an action on dopamine receptors. A specific effect on dopamine receptors is further supported by the finding that the i.c.v. injection of the β-adrenoceptor antagonist, propranolol, had no effect on the response to dopamine. In the unanaesthetized dog, injection of isoprenaline into the cerebral ventricles has been reported to cause a depressor response accompanied by tachycardia (Conway & Lang, 1974) in contrast to the pressor response and tachycardia found with i.c.v. dopamine. According to McNay & Goldberg (1966), in the dog dopamine is a much less potent agonist of β-adrenoceptors than is isoprenaline, being only 1/1000 times as active in the femoral vascular bed. In view of these differences between dopamine and isoprenaline it seems unlikely that the dopamine-induced pressor effects in the dog could be accounted for by activation of central β-adrenoceptors.

In the unanaesthetized cat, Day & Roach (1976) found that β-adrenoceptor antagonism with either intraventricular propranolol or alprenolol abolished the cardiovascular response to i.c.v. dopamine. However, this may have been due to a peripheral rather than a central effect. It has been reported that propranolol injected into the cerebral ventricles of the unanaesthetized rabbit rapidly escapes to the peripheral circulation by Anderson, Korner, Bobik & Chalmers, 1977. They found that the plasma concentration of propranolol 10 min after i.c.v. injection was 80% of the level reached after i.v. injection of the same dose. In the unanaesthetized dog i.c.v. propranolol was found to abolish the depressor response and tachycardia produced by i.v. isoprenaline (Conway & Lang, 1974). In the same study it was reported that hexamethonium potentiated the depressor response to i.c.v. isoprenaline indicating that isoprenaline also may have leaked into the periphery. In our experiments the cardiovascular response to dopamine was abolished by autonomic ganglion blockade.

The injection of doses of dopamine into the cerebral ventricles of the anaesthetized dog similar to those used in our experiments was reported to have little or no effect on arterial blood pressure (McCubbin *et al.*, 1960). The anaesthetic used by McCubbin *et al.* (1960), pentobarbitone, has been shown to reduce pressor responses to electrical stimulation of the mesencephalon in even lower doses than are used for anaesthesia (Price, 1960). It appears, therefore, that the response to i.c.v. dopamine was being masked by the anaesthetic.

In a recent study by Day & Roach (1976), the injection of dopamine into the cerebral ventricles of unanaesthetized cats caused an increase in blood pressure and heart rate. In some of the cats studied, the initial cardiovascular stimulant effects of i.c.v. dopamine were followed by hypotension and bradycardia. It was suggested by Day & Roach (1976) that the secondary depressor effect was due to the conversion of some of the dopamine to noradrenaline, as this secondary response was abolished by an inhibitor of dopamine-β-hydroxylase, disulphiram, and by α-adrenoceptor blockade with phentolamine. However, no such cardiovascular depressant phase was observed in the dogs in our study. Other studies in rats (Baum & Shropshire, 1973) and cats (Heise & Kroneberg, 1973; Dutta, Guha & Pradhan, 1975; Heise, 1976) have reported hypotension and bradycardia in response to the intraventricular injection of dopamine. It is possible that the responses in these latter experiments may have been modified by the presence of the anaesthetic.

Dopamine has been suggested to act as a transmitter in some central neuronal pathways involved in blood pressure regulation (Bolme *et al.*, 1972; Day & Roach, 1976), and the results obtained in the unanaesthetized dog support this possibility. That dopamine acts as a neurotransmitter in the central nervous system is well established, particularly in the dopaminergic pathways of the basal ganglia (for review, see Hornykiewicz, 1973) which are involved in sen-

sory motor integration. Dopamine also appears to be involved in the mechanism of vomiting. Apomorphine, which is structurally related to dopamine and has been shown to stimulate dopamine receptors (Goldberg, 1975; Buylaert, Willems & Bogaert, 1977), is well known to be an emetic. In the dog, apomorphine-induced emesis has been antagonized with pimozide, a specific dopamine receptor antagonist (Pendleton & Setler, 1977). Other dopamine receptor antagonists such as chlorpromazine and metoclopramide have been used as anti-emetics (Byck, 1975). In our experiments, although dopamine occasionally caused some dogs to vomit, this was not so after administration of the dopamine antagonists.

In the unanaesthetized dog, as in the cat, dopamine therefore has been found to cause hypertension and tachycardia through the stimulation of central dopamine receptors. These findings support the possibility that dopaminergic neurones may be involved in central nervous system control of the cardiovascular system.

This work was supported by the Australian Research Grants Committee. O.L.W. was in receipt of a University of Melbourne Postgraduate Scholarship.

References

ANDERSON, W.P., KORNER, P.I., BOBIK, A. & CHALMERS, J.P. (1977). Leakage of dl-propranolol from cerebrospinal fluid to the bloodstream in the rabbit. *J. Pharmac. exp. Ther.*, **202**, 320–325.

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

BELL, C., CONWAY, E.L., LANG, W.J. & PADANYI, R. (1975). Vascular dopamine receptors in the canine hindlimb. *Br. J. Pharmac.*, **55**, 167–172.

BOLME, P., FUXE, K. & LIDBRINK, P. (1972). On the function of central catecholamine neurons—their role in cardiovascular and arousal mechanisms. *Res. Commun. Chem. Pathol. Pharmac.*, **4**, 657–697.

BUYLAERT, W.A., WILLEMS, J.L. & BOGAERT, M.G. (1977). Vasodilatation produced by apomorphine in the hindleg of the dog. *J. Pharmac. exp. Ther.*, **201**, 738–746.

BYCK, R. (1975). Drugs and the treatment of psychiatric disorders. In *The Pharmacological Basis of Therapeutics*, 5th Edn. ed. Goodman, L.S. & Gilman, A. pp. 152–200. New York: MacMillan Publishing Co.

CARLSSON, A. (1974). Some aspects of dopamine in the central nervous system. *Adv. Neurol.*, **5**, 59–68.

CONWAY, E.L. & LANG, W.J. (1974). Cardiovascular responses produced by the injection of isoprenaline and propranolol into the cerebral ventricles of the unanaesthetized dog. *Clin. exp. Pharmac. Physiol.*, **1**, 59–64.

DAY, M.D. & ROACH, A.G. (1976). Cardiovascular effects of dopamine after central administration into conscious cats. *Br. J. Pharmac.*, **58**, 505–515.

DUTTA, S.N., GUHA, D. & PRADHAN, S.N. (1975). Cardiovascular effects of central microinjections of apomorphine in cats. *Archs int. Pharmacodyn. Ther.*, **315**, 259–265.

GOLDBERG, L.I. (1975). Comparison of putative dopamine receptors in blood vessels and the central nervous system. *Adv. Neurol.*, **9**, 53–56.

HEISE, A. (1976). Hypotensive action by central α-adrenergic and dopaminergic receptor stimulation. In *New Antihypertensive Drugs*, ed. Scriabine, A. & Sweet, C.S. pp. 135–145. New York: Spectrum Publications.

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.

HIGGINS, C.B., MILLARD, R.W., BRAUNWALD, E. & VATNER, S.F. (1973). Effects and mechanisms of action of dopamine on regional hemodynamics in the conscious dog. *Am. J. Physiol.*, **225**, 423–437.

HORNYKIEWICZ, O. (1973). Dopamine in the basal ganglia. its role and therapeutic implications (including the clinical use of l-dopa). *Br. med. Bull.*, **29**, 172–178.

LANG, W.J., GERSHON, S. & HOLAN, G. (1963). Some antagonists of atropine-like psychotomimetics. *J. Pharm. Pharmac.*, **15**, 831–840.

LANG, W.J. & RUSH, M.L. (1973). Cardiovascular responses to injections of cholinomimetic drugs into the cerebral ventricles of unanaesthetized dogs. *Br. J. Pharmac.*, **47**, 196–205.

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.

MCNAY, J.L. & GOLDBERG, L.I. (1966). Comparison of the effects of dopamine, isoproterenol, norepinephrine and bradykinin on canine renal and femoral blood flow. *J. Pharmac. exp. Ther.*, **151**, 23–31.

NICKERSON, M. & COLLIER, B. (1975). Drugs inhibiting adrenergic nerves and structures innervated by them. In *The Pharmacological Basis of Therapeutics*, 5th Edn. ed. Goodman, L.S. & Gilman, A. pp. 533–564. New York: MacMillan Publishing Co.

PENDLETON, P.G. & SETLER, P.E. (1977). Peripheral cardiovascular dopamine receptors. *Gen. Pharmac.*, **8**, 1–5.

PRICE, H.L. (1960). General anaesthesia and circulatory homeostasis. *Physiol. Rev.*, **40**, 187–218.

UNGERSTEDT, U. (1971). Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigrostriatal dopamine system. *Acta physiol. scand.*, Suppl. **367**, 69–93.

VOGT, M.L. (1973). Pharmacology of dopamine. *Adv. Neurol.*, **3**, 217–222.

WOODRUFF, G.M., ELKHAWAD, A.O. & CROSSMAN, A.R. (1974). Further evidence for the stimulation of rat brain dopamine receptors by ergometrine. *J. Pharm. Pharmac.*, **26**, 455–456.

(Received August 15, 1978. Revised October 17, 1978.)