Br. J. Pharmac. (1972), **44**, 442–450.

Effects of dopamine on the conductance of perfused vascular beds of the chloralosed cat

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Summary

1. Dopamine produced vasoconstriction followed by secondary vasodilatation in the perfused cat hindquarters and splanchnic region. Low doses produced only vasodilatation in the splanchnic region.

2. Phenoxybenzamine abolished, while desipramine and cocaine potentiated, the vasoconstrictor and secondary dilator actions of dopamine.

3. After phenoxybenzamine, dopamine produced only vasodilatation in both the hindquarters and splanchnic region, being more effective in the latter.

4. Haloperidol, but not propranolol, atropine or mepyramine, antagonized dopamine-induced vasodilatation.

5. Dopamine differs from other catecholamines in that, while its cardiac effects are mediated by a β-adrenoceptive mechanism, its vasodilator effects are not.

6. The results support the concept of a specific receptor mediating dopamine vasodilatation.

Introduction

Although the catecholamines adrenaline and isoprenaline elicit vasodilatation by a β-adrenoceptive mechanism, dopamine produces vasodilatation in the dog by several different mechanisms (Eble, 1964 ; McNay & Goldberg, 1966 ; Yeh, McNay & Goldberg, 1968 ; Schuelke, Mark, Schmidt & Eckstein, 1969). The existence of specific receptors mediating dopamine vasodilatation in this species has been suggested (Eble, 1964). Ross & Brown (1967) studied the effects of intravenous dopamine on the blood flow of various vascular beds of the cat and also suggested that this amine activated receptors, which were not β-adrenoceptive.

The present study was aimed at the characterization of the action of dopamine by direct arterial injection in perfused vascular beds of the cat.

Methods

Cats of either sex, 2·2–3·0 kg body wt., were anaesthetized with chloralose, 100 mg/kg intraperitoneally. Systemic blood pressure (1 mmHg≡1·333 mbar) was recorded from a carotid artery and heart rate was monitored.

The method of continuous recording of vascular conductance in selected vascular beds has been described previously (Gardiner, Hamilton & Parkes, 1971). Blood flow was measured by an electromagnetic flow meter (Statham E-3002), using an extra-corporeal flow probe, interposed in the abdominal aorta or superior mesenteric artery for measurement of conductance changes in the auto-perfused hindquarters

and splanchnic region respectively. Perfusion pressure was measured distal to the flow probe and the flow signal divided electronically by that for pressure to give a continuous record of changes of vascular conductance simultaneously with those of blood flow and perfusion pressure.

Heparinized saline, 5 mg/kg intravenously, was injected immediately after cannulation. Arterial injections were made into a side arm in the perfusion circuit, in a volume of 0·1 or 0·2 ml, and washed into the blood-stream with 0·1 ml 0·9% saline.

Drugs used were atropine sulphate (B.D.H.), cocaine hydrochloride (May & Baker), desmethylimipramine hydrochloride (Geigy), dopamine hydrochloride (Sigma), mepyramine maleate (May & Baker), papaverine hydrochloride (McFarlan Smith), phenoxybenzamine hydrochloride (S.K.F.), phentolamine methane-

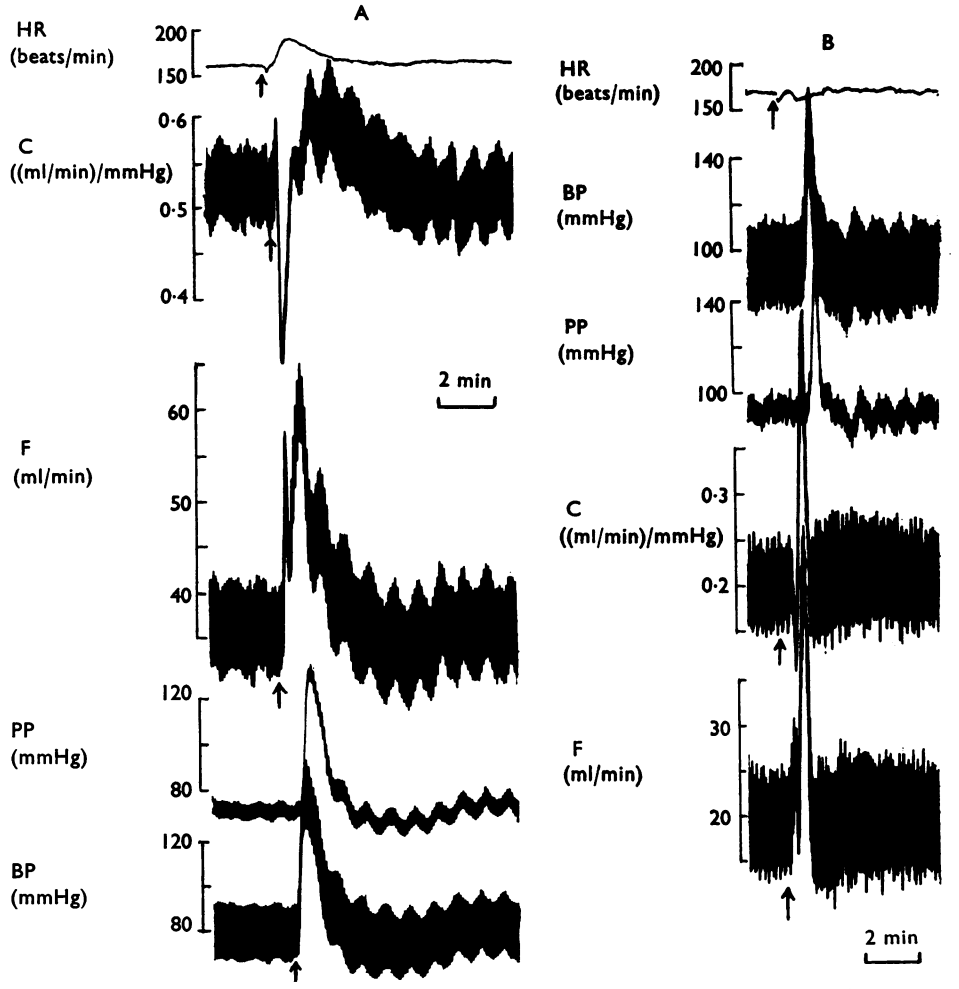

FIG. 1. (A), Part of recording of hindquarters perfusion in a chloralosed cat. (B), Part of a recording of splanchnic region perfusion in a chloralosed cat. Traces: heart rate (HR); vascular conductance (C); blood flow (F); perfusion pressure (PP); carotid blood pressure (BP). At each set of arrows, dopamine, 20 μg/kg was injected intravenously: these show corresponding points on the traces and indicate the offset of the recording pens. Time intervals are shown on the record.

sulphonate (Ciba) and propranolol hydrochloride (I.C.I.). These were dissolved in saline and their doses are expressed as the salt. Haloperidol (Searle) was dissolved in dilute citric acid and the dose is expressed as that of the base.

Isoprenaline (Burroughs Wellcome) and adrenaline (B.D.H.) were prepared from stock ampoules of the sulphate and tartrate respectively and their doses expressed in terms of the base.

Results

Intravenous injection

Effect on systemic blood pressure and heart rate

Dopamine, 2–10 μg/kg, caused slight and variable changes in heart rate. In three preparations dopamine, 20 μg/kg, produced a transient fall in heart rate but tachycardia, susceptible to β-adrenoceptive blockade, in three others.

Doses of dopamine less than 2 μg/kg did not affect systemic blood pressure, despite small changes in conductance in the hindquarters and splanchnic region, while larger doses produced a rise in blood pressure, sometimes followed by a secondary depressor response. In only one of twelve preparations in which systemic blood pressure effects were examined was dopamine depressor over the dose range 2–20 μg/kg.

Changes in vascular conductance

In the hindquarters (Fig. 1A), the systemic pressor response was initially accompanied by an increase in flow, with or without a slight increase in conductance. Later, as the drug reached the hindquarters, conductance fell, representing the vasoconstrictor action of dopamine in this bed. As a result, though the pressor response was maintained, the flow in this region decreased. In the final stage, conductance increased during the secondary depressor response.

In the splanchnic region (Fig. 1B) during the systemic pressor response, a biphasic decrease, followed by increase, of conductance occurred in this bed, the latter component often being prolonged and contributing to the secondary systemic depressor effect. In some preparations there was no initial constrictor phase.

Arterial injection

In the perfused hindquarters, doses of dopamine less than 1 μg did not affect resting conductance but larger doses produced dose-dependent vasoconstriction (Fig. 2 and Table 1) of approximately 30 s duration, this often being followed by a secondary dilatation (increase in conductance) of up to 6 min duration after high doses (10 and 20 μg).

In most preparations in which the splanchnic region was perfused, doses of dopamine less than 1 μg produced a slight vasodilatation, but this was not dose-dependent and, in one case, dilatation was observed with a dose of 10 μg. In ten other experiments, dopamine produced a dose dependent vasoconstriction in doses greater than 1 μg (Fig. 2 and Table 1), this being followed by a prolonged or transient secondary dilatation with doses greater than 2 μg (Figs. 3 & 4).

Table 1 shows that the dose of dopamine required for a given proportional change in vascular conductance was the same for the two beds.

α-Adrenoceptor blockade

Preliminary experiments indicated that phentolamine, 2–4 mg/kg intravenously, reduced or abolished both the vasoconstrictor and secondary dilator actions of dopamine in both the hindquarters and splanchnic region, converting these to a dose dependent vasodilatation of 30 s duration. However, the extent and duration of reversal varied from one cat to another, biphasic responses frequently being observed, and depending on the degree of α-adrenoceptor blockade. Phentolamine

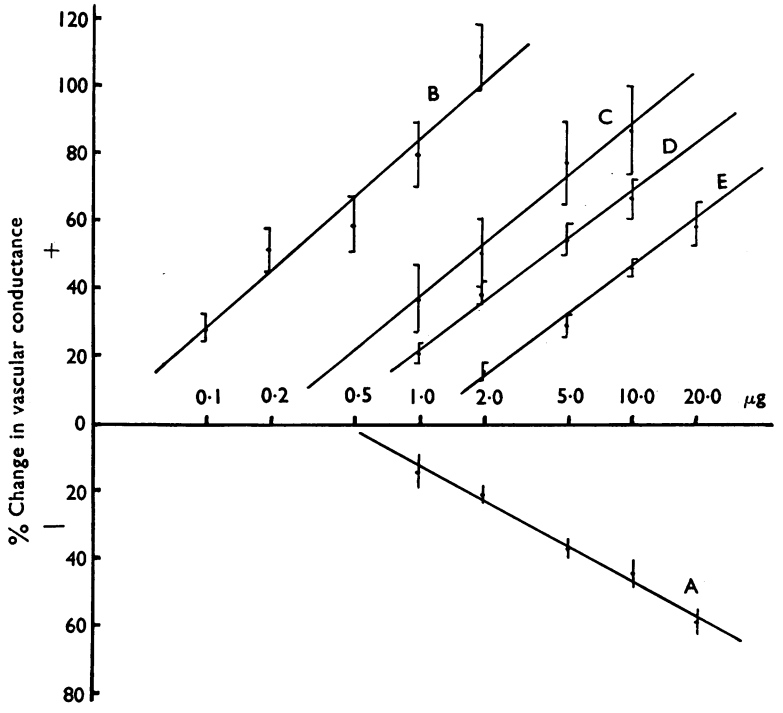

FIG. 2. Dose-response relations for the vasoconstrictor effect of dopamine, injected intra-arterially in the chloralosed cat hindquarters (A) and for the vasodilator effect of dopamine, after 5 mg/kg phenoxybenzamine intravenously, in both the splanchnic region before (B) and after (C), 1 mg haloperidol intra-arterially; and in the hindquarters before (D) and after (E), 3 mg haloperidol intra-arterially. Responses were measured as percentage increase or decrease of vascular conductance from the predose level. Vertical bars extend to mean ± S.E. of the values. Regression lines are computed (see Tables 1 & 2).

TABLE 1. *Vasoconstrictor effect of dopamine in the perfused cat hindquarters and splanchnic region*

	From dose-response regression relations (Fig. 1)		
	n	b±Sb	ED50 (95% fiducial limits) μg intra-arterially
Hindquarters	25	35·0±3·9	12·0 (9·1–15·8)
Splanchnic region	24	37·7±3·5	12·3 (9·9–15·5)

n represents the total number of values used to calculate each regression line. Six cats were used for each vascular bed. ED50 is the dose producing a 50% fall in vascular conductance.

augmented the vasodilatation due to small doses of dopamine in the splanchnic region.

After phenoxybenzamine, 2–5 mg/kg intravenously, dopamine produced dose-dependent vasodilatation in both the hindquarters and splanchnic region, being more effective in the latter (Fig. 2, Fig. 3 and Table 2).

β-Adrenoceptor blockade

Propranolol, when injected intra-arterially or intravenously in a dose greater than that required to block the vasodilatation due to adrenaline, did not affect that due to dopamine in either the hindquarters or splanchnic region (Table 3 and Fig. 3).

TABLE 2. *Effect of haloperidol on the vasodilator response to dopamine in the perfused cat hindquarters and splanchnic region, in the presence of 5 mg/kg phenoxybenzamine*

	From dose-response regression relations (Fig. 1)		
	n	b ± Sb	ED50 (95% fiducial limits) μg intra-arterially
Hindquarters	22	46·2 ± 5·6	4·1 (3·3 – 4·9)
After 3 mg haloperidol	19	47·2 ± 2·9	11·8 (9·9 –14·1)
Splanchnic region	27	55·5 ± 7·9	0·24 (0·17– 0·34)
After 1 mg haloperidol	17	51·2 ± 14·9	1·75 (1·2 – 2·65)

n represents the total number of values used to calculate each regression line. Ten cats were used for each vascular bed. ED50 is the dose producing a 50% increase in vascular conductance.

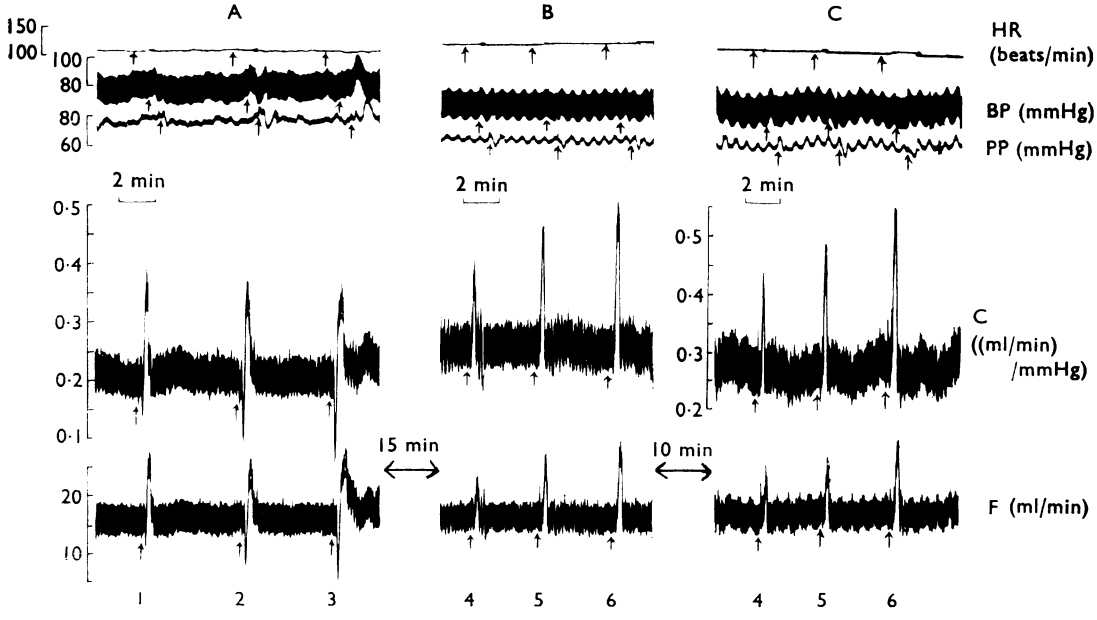

FIG. 3. Part of recording of splanchnic region perfused in a chloralosed cat. Traces, from above downwards: heart rate (HR); carotid blood pressure (BP); perfusion pressure (PP); vascular conductance (C); blood flow (F). At each set of arrows, an injection of dopamine was made into the perfusion circuit: these show corresponding points on the traces and indicate the offset of the recording pens. The doses of dopamine were as follows: at 1, 2 μg; at 2, 5 μg; at 3, 10 μg; at 4, 0·5 μg; at 5, 1 μg; at 6, 2 μg. Between panels A and B, phenoxybenzamine 2 mg/kg, was injected and between B and C, propranolol, 0·5 mg/kg, both intravenously. Time intervals are shown on the record.

Haloperidol

Haloperidol, 3 mg intra-arterially, significantly reduced vasodilatation due to dopamine in the perfused hindquarters, while 1 mg, intra-arterially, reduced that in the splanchnic region (Fig. 2 and Table 2: Fig. 4). The vasodilator response to isoprenaline was not reduced (Fig. 4) nor was that to papaverine. Haloperidol did not reduce dopamine-induced vasoconstriction but increased it in some preparations (Fig. 4).

TABLE 3. *Effect of propranolol on the vasodilator response to dopamine in the perfused cat hindquarters, in the presence of 5 mg/kg phenoxybenzamine*

		From calculated regression lines	
			ED50 (95% fiducial limits)
	n	b±Sb	μg intra-arterially
Before propranolol	16	35·5± 9·36	3·4 (2·3–5·0)
After 500 μg propranolol	16	27·3±11·5	3·0 (2·0–4·6)

n represents the total number of values to calculate each regression line, from experiments in five cats. ED50 is the dose producing a 50% increase in vascular conductance.

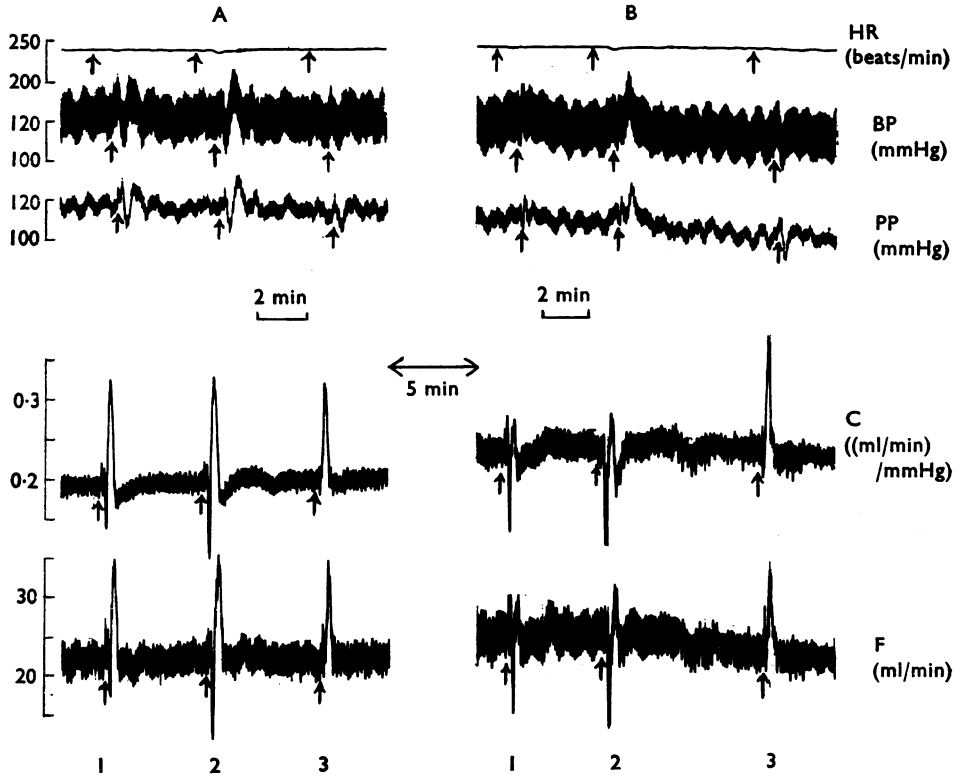

FIG. 4. Part of recording of splanchnic region perfusion in a chloralosed cat. Traces, from above downwards: heart rate (HR); carotid blood pressure (BP); perfusion pressure (PP); vascular conductance (C); blood flow (F). At each set of arrows an injection of dopamine or isoprenaline was made into the perfusion circuit: these show corresponding points on the traces and indicate the offset of the recording pens. The doses of dopamine were as follows: at 1, 5 μg; at 2, 10 μg. The dose of isoprenaline was: at 3, 0·01 μg. Between panels A and B, 1 mg haloperidol was injected into the perfusion circuit. Time intervals are shown on the record.

Desipramine and cocaine

Desipramine and cocaine, 2 mg/kg intravenously, potentiated both the vasoconstrictor and secondary dilator responses to dopamine in both the hindquarters and splanchnic region. Propranolol did not reduce the augmented secondary dilator effect.

Atropine and mepyramine

Neither atropine, 1 mg/kg intravenously, nor mepyramine, 2 mg/kg intravenously, affected the secondary dilator responses to dopamine nor the dilatation that occurred in the presence of phenoxybenzamine.

Discussion

In the dog changes in regional blood flow produced by dopamine have been reported to vary in different vascular beds. Vasoconstriction of the femoral artery was reversed by α-adrenoceptor blockade to a vasodilatation that was sensitive to β-adrenoceptor blockade in the experiments of McNay & Goldberg (1966) and of Goldberg, Sonneville & McNay (1968) but was less consistently blocked in those of Eble (1964). Dopamine-induced renal vasodilatation was, however, not sensitive to β-adrenoceptor blockade, though it was attenuated by haloperidol (Yeh *et al.*, 1968 ; 1969), a specific dopamine antagonist (Van Rossum, 1966). Chlorpromazine (Goldberg & Yeh, 1969) also reduced renal vasodilatation produced by dopamine.

Dopamine produced a biphasic change in flow through the superior mesenteric artery of the dog, a decrease being followed by an increase. Phenoxybenzamine abolished the constrictor and augmented the dilator effect, which was not affected by propranolol (Eble, 1964) but it was, however, attenuated by haloperidol (Yeh *et al.*, 1968). Schuelke *et al.* (1969) found that dopamine increased coronary artery flow and that propranolol reversed this to a decrease susceptible to block by phenoxybenzamine, revealing another dilator action of dopamine.

Dopamine has here been shown to produce vasoconstriction by an α-adrenoceptive mechanism in the perfused hindquarters and splanchnic region of the cat. After α-adrenoceptor blockade dopamine elicited vasodilatation in both vascular beds by a mechanism not susceptible to β-adrenoceptor blockade ; this confirms the observation of Ross & Brown (1967) on superior mesenteric artery flow.

The vasodilator effects of dopamine in the cat therefore differ from those of other catecholamines which are sensitive to β-adrenoceptor blockade (Shanks, 1967). However, dopamine resembles the other catecholamines in that it increases myocardial force of contraction and heart rate by mechanisms susceptible to β-adrenoceptor blockade in both the dog (McDonald & Goldberg, 1963) and cat (Ross & Brown, 1967). This difference may be related to the absence in dopamine of β-hydroxylation in the side chain, which as Lands (1949) points out, enhances β-stimulant activity. Nevertheless, the fall in blood pressure and renal vasodilatation due to tetrahydropapaveroline, a metabolite of dopamine, is susceptible to β-adrenoceptor blockade (Holtz, Stock & Westermann, 1964 ; McNay & Goldberg, 1966).

Haloperidol prevents the hypotensive action of dopamine in the cat (Van Rossum, 1966). In the study reported here, haloperidol blocked dopamine dilatation after

α-adrenoceptor blockade, in both the hindquarters and splanchnic region, and also that occurring in the splanchnic region in the absence of α-adrenoceptor blockade. However, haloperidol did not affect the dilatation due to isoprenaline or papaverine, which supports the concept of a specific receptor mediating the vasodilator action of dopamine, as suggested by Eble (1964) for the dog and by Ross & Brown (1967) for the cat.

Farmer (1966) considered that dopamine exerts its cardiovascular effects in the cat by both direct and indirect means, according to the distinction of Burn & Rand (1958), while Spiers & Calne (1969) attributed mydriasis with dopamine to an indirect action. Desipramine and cocaine have been shown here to augment both the vasoconstrictor and the secondary dilator action of dopamine, indicating that this effect of dopamine is normally limited by uptake of the amine, and is unlikely to be due to an indirect action.

Dopamine was commonly pressor in the chloralosed cat, despite a primary vasodilatation in the splanchnic region with low doses. The responses of the various vascular beds determine the type of systemic blood pressure change that occurs and in most preparations the effect of vasoconstriction occurring in the hindquarters (and possibly other beds) outweighed that of vasodilatation in the splanchnic bed (and possibly other beds) resulting in a pressor response, as suggested by Ross & Brown (1967). However, in the presence of phenoxybenzamine, dopamine was more active as a vasodilator in the splanchnic region than in the hindquarters and therefore it is likely that the depressor action produced by dopamine is principally due to this splanchnic dilatation.

I am indebted to Dr. M. W. Parkes for helpful advice and discussion in the preparation of the manuscript.

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(*Received August* 5, 1971)