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COMPARISON OF THE VASODILATOR ACTION OF DOPAMINE AND DOPAMINE AGONISTS IN THE RENAL AND CORONARY BEDS OF THE DOG

The late W.J. LANG & O.L. WOODMAN[1]

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

1 The effects of dopamine and the dopamine receptor agonists, SK&F 38393 and bromocriptine, on renal and coronary blood flow in the anaesthetized dog were examined. Dopamine was found to dilate both vascular beds, whereas SK&F 38393 increased renal blood flow but did not have any dilator activity in the coronary vasculature. Bromocriptine did not cause vasodilatation in either vascular bed.

2 The vasodilator responses to dopamine and SK&F 38393 were significantly reduced by the dopamine receptor antagonists, ergometrine or metoclopramide.

3 It is proposed that the selective action of SK&F 38393 on the renal vasculature suggests that the dopamine receptors of the renal and coronary vascular beds may be of different types.

Introduction

There is now considerable evidence to suggest that there is more than one type of dopamine receptor in the central nervous system (for reviews, Cools & van Rossum, 1976; 1980; Kebabian & Calne, 1979; Costall & Naylor, 1981). This raises the possibility that there may also be multiple dopamine receptors in the periphery. We have recently shown that 2-(3,4-dihydroxyphenylimino)-imidazolidine (DPI) can cause vasodilatation by activating dopamine receptors in the coronary vasculature of the dog (Woodman, Medgett, Lang & Rand, 1981). However, unlike dopamine, DPI does not have any action in the renal vasculature of the dog or rat, suggesting that the dopamine receptors in the renal and coronary vasculature may be of different types.

To examine further the existence of different receptors, the actions of two dopamine receptor agonists, SK&F 38393 and bromocriptine, together with dopamine itself, have been compared in the renal and coronary vascular beds of the anaesthetized dog. SK&F 38393 has previously been shown to dilate the renal and mesenteric vasculature of the dog (Pendleton, Salmer, Kaiser & Ridley, 1978; Roby & Orzechowski, 1979; Hahn & Wardell, 1980) and the vasculature of the isolated perfused kidney of the rat (Woodman, Rechtman & Lang, 1980). It has been suggested, therefore, that SK&F 38393 has a specific dilator action in the renal bed not seen in the remainder of the vascular system as a whole (Pendleton *et al.*, 1978). However, there are no previously described studies of its actions on other vasculatures than those of the renal or mesenteric beds.

Bromocriptine has been shown to cause vasodilatation in the isolated kidney of the rat (Imbs, Schmidt, Ehrhardt & Schwartz, 1979; Schmidt & Imbs, 1979; Woodman *et al.*, 1980) and to increase renal blood flow following intra-arterial injection in the dog (Schmidt & Imbs, 1979). In contrast, Volkman & Goldberg (1976) reported that the intra-arterial injection of bromocriptine did not affect dog renal blood flow. Although intravenous infusions of dopamine increase renal blood flow in the dog (Clark, Sholtysik & Fluckiger, 1978; Lokhandwala, Tadepalli & Jandhyala, 1979), Lokhandwala *et al.* (1979) have suggested that this is due to a neurogenic mechanism rather than to stimulation of vascular dopamine receptors.

Methods

Mongrel or greyhound dogs of either sex weighing 12–30 kg were anaesthetized with α-chloralose (70 mg/kg, i.v.) following induction with thiopentone sodium. A cannula was passed up a branch of the right femoral artery into the abdominal aorta to allow the measurement of systemic blood pressure with a Statham P23Db pressure transducer. Standard limb leads were attached subcutaneously to monitor the electrocardiogram, which was integrated with a cardiotachometer coupler to provide a continuous record of heart rate.

Dogs were randomly selected for renal or coronary

[1]Present address: Department of Medicine, University of Melbourne, Austin Hospital, Heidelberg, Victoria 3084 Australia.

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blood flow experiments. To measure renal blood flow, the left kidney was exposed by a flank incision and blunt dissection allowing the renal nerves to remain intact. A cuff-type electromagnetic flow probe (Devices) was used to monitor flow in the left renal artery. Close arterial injections of drugs were made through a cannula placed in the renal artery distal to the flow probe. The cannula consisted of Dural SP28 polythene tubing tipped with the shaft of a 25 gauge needle bent to an angle of approximately 90°.

To measure coronary blood flow, the heart was exposed by a left thoracotomy in the fourth intercostal space; the pericardium was cut and its edges sutured to the wall of the thorax to construct a pericardial sling. A portion of the left circumflex coronary artery was then dissected free from surrounding tissue and a cuff-type flow probe placed in position. Close arterial injections of drugs were made directly into the circumflex coronary artery distal to the flow probe using the same cannula as described above. Blood pressure, heart rate and blood flow were continuously recorded on a Beckman R411 dynograph.

Dopamine was injected intra-arterially in all dogs, and these dogs were then randomly selected to receive further injections of SK&F 38393 or bromocriptine. These experiments were of 4 to 6 h duration.

Drugs used were: bromocriptine mesylate (Sandoz); dopamine hydrochloride (Calbiochem); ergometrine maleate (David Bull); isoprenaline hydrochloride (Sterling); (−)-noradrenaline acid tartrate (Winthrop); phentolamine mesylate (Ciba-Geigy); metoclopramide hydrochloride (Beecham); propranolol hydrochloride (I.C.I.); 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine (SK&F 38393 Smith Kline & French) and yohimbine hydrochloride (Sigma). Doses in the text refer to the above salts, with the exception of noradrenaline, where the equivalent dose of the base is given. Solutions of isoprenaline, noradrenaline, phentolamine and propranolol were diluted in 0.9% w/v NaCl solution (saline) from the contents of ampoules. Bromocriptine was dissolved in 0.2 ml dimethyl sulphoxide (pure solution) and then diluted in saline. The intra-arterial injection of the vehicle alone had no effect on blood flow. All other drugs were dissolved in saline on the day on which they were to be used.

Results were assessed by two statistical tests as appropriate. The significance of difference of means was assessed using Student's t test for unpaired data. In addition, regression functions were estimated for dose-response curves (Documenta Geigy, 1970). Evaluation of the variances of the regression parameters for each curve revealed that these lines did not differ significantly from linearity or parallelism, making it possible to test for any significant shift using linear regression analysis.

Results

Renal blood flow

The average resting blood flow in the left renal artery of anaesthetized dogs was 5.1 ± 0.5 ml min^{-1}kg^{-1} ($\pm$ s.e.mean, $n = 15$). Initial flow rates were well maintained throughout the duration of the experiments.

Dopamine, SK&F 38393 and bromocriptine were administered in the presence of α-adrenoceptor blockade with phentolamine (0.5 mg/kg, i.v.), as described by Bell, Conway & Lang (1974). The α-adrenoceptor blockade was checked by the intra-arterial injection of noradrenaline (1 μg) and additional phentolamine was administered as necessary to prevent any vasoconstrictor response. Both dopamine (5–50 μg) and SK&F 38393 (0.05–1 mg) were found to produce dose-dependent increases in renal blood flow (Figure 1) without any effect on heart rate or systemic blood pressure when injected directly into the renal artery. The maximal responses to dopamine and SK&F 38393 were of similar magnitude. However, to produce equivalent increases in blood flow, the dose of SK&F 38393 required was approximately ten times greater than that of dopamine. Bromocriptine (5–500 μg) had no significant effect on renal blood flow (Table 1), heart rate or systemic blood pressure.

Dopamine receptor blockade was produced by intra-arterial injection of ergometrine (0.5 mg) or metoclopramide (5 mg). Both antagonists caused a transient reduction in renal blood flow, but this returned to control level within 3 min. Ergometrine was found to produce effective antagonism for approximately 20 min, while it was necessary to inject metoclopramide before each administration of the agonists. Both ergometrine and metoclopramide reduced the dilator responses to all doses of dopamine and SK&F 38393, causing a significant shift to the right of all dose-response curves (Figure 1).

Coronary blood flow

The average resting blood flow in the left circumflex coronary artery of the anaesthetized dog was 3.3 ± 0.2 ml min^{-1}kg^{-1} ($n = 31$). Initial flow rates were well maintained throughout the duration of the experiments.

The intra-arterial injection of dopamine (5–50 μg) caused biphasic changes in coronary blood flow. The initial decreases in flow could be abolished by α-adrenoceptor blockade with phentolamine (0.5 mg/kg, i.v.). The secondary increase in flow was

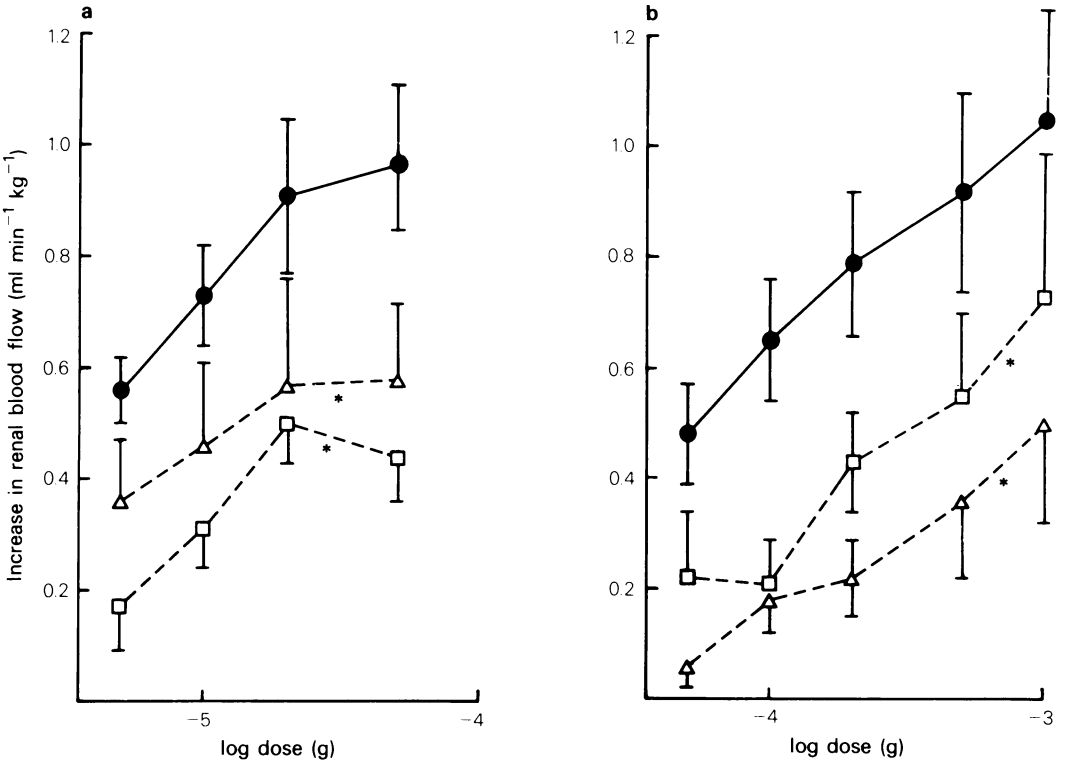

Figure 1 Increases in renal blood flow produced by the intra-arterial injection of (a) dopamine and (b) SK&F 38393. The control responses (●) are compared with those in the presence of ergometrine 0.5 mg i.a. (□) or metoclopramide 5 mg i.a. (△). Each point represents the mean of at least four experiments. The error bars represent the s.e.mean. Significant parallel shift of regression curve compared to control; linear regression analysis: $*P < 0.05$.

larger and more prolonged, lasting up to 5 min (Table 2). The changes in blood flow were accompanied by increases in heart rate (Table 2), but there was no effect on systemic blood pressure.

SK&F 38393, over the same dose range that produced vasodilatation in the renal vasculature (0.05–1 mg), decreased coronary blood flow. α-Adrenoceptor blockade with either phentolamine (0.5 mg/kg, i.v.) or yohimbine (0.5 mg/kg, i.v.) abolished the vasoconstriction produced by SK&F 38393, but there was no evidence of vasodilatation in the coronary vasculature (Table 3). SK&F 38393 injected directly into the coronary artery had no significant effect on either heart rate or systemic blood pressure. The intra-arterial injection of bromocriptine had no significant effect on coronary blood flow, heart rate or systemic blood pressure, either before or after α-adrenoceptor blockade (Table 3).

Table 1 Changes in renal blood flow (ml min^{-1} kg^{-1} body wt.) produced by the intra-arterial injection of bromocriptine in the presence of phentolamine (0.05 mg/kg, i.v.)

Bromocriptine (μg)	*Change in blood flow* (ml min^{-1} kg^{-1})
5	−0.24 ± 0.24 (3)
10	−0.28 ± 0.20 (6)
20	−0.17 ± 0.10 (6)
50	−0.45 ± 0.41 (6)
100	−0.49 ± 0.22 (4)
200	−0.74 ± 0.28 (4)
500	−0.78 ± 0.27 (3)

Values given are the mean ± s.e.mean. The number of experiments is given in parentheses. No change in blood flow induced by bromocriptine was significant.

Dopamine receptor blockade was produced by intra-arterial injection of ergometrine (0.5 mg). In 4 of the 10 dogs in which ergometrine was used, this caused a decrease in coronary blood flow but the flow returned to control level within 3 min. Pretreatment with ergometrine abolished the dilator response to the lowest dose of dopamine (5 μg) and caused a significant reduction in the responses to higher doses (Table 2).

Table 2 Increase in coronary blood flow (ml min^{-1} kg^{-1} body wt.) and heart rate (beats/min) produced by intra-arterial injection of dopamine before and after the administration of propranolol (0.1 mg/kg, i.v.) and ergometrine (0.5 mg. i.a.)

Dopamine (μg)	*Increase in coronary blood flow*		
	Control	*After propranolol*	*After ergometrine*
5	0.36 ± 0.05 (26)†	0.24 ± 0.08 (6)†	0 (6)**
10	0.53 ± 0.07 (27)†	0.34 ± 0.08 (6)†	0.08 ± 0.08 (6)**
20	0.69 ± 0.07 (27)†	0.66 ± 0.27 (6)†	0.13 ± 0.08 (6)**
50	0.92 ± 0.08 (26)†	0.64 ± 0.17 (6)†	0.33 ± 0.18 (6)**
	Increase in heart rate		
	Control	*After propranolol*	
5	7.7 ± 2.3 (26)	0 (6)	
10	11.0 ± 3.7 (27)	0 (6)	
20	22.3 ± 4.4 (27)	0 (6)*	
50	27.0 ± 4.0 (26)	0 (6)**	

Values given are mean ± s.e.mean. The number of experiments is given in parentheses.
Significant vasodilatation: †$P < 0.05$; significantly different from control: *$P < 0.05$; **$P < 0.01$.

Pretreatment with the β-adrenoceptor antagonist propranolol (0.1 mg/kg, i.v.) abolished the increase in heart rate produced by dopamine, but did not significantly affect the vasodilator response (Table 2).

Discussion

In these experiments, intra-arterial injections of dopamine were found to increase renal and coronary blood flow, an effect that is now well recognized. Although it has been established that dopamine produces renal vasodilatation through stimulation of a specific dopamine vascular receptor, there is some disagreement regarding the involvement of dopamine receptors in coronary vasodilatation (Parrat, 1980). Brooks, Stein, Matson & Hyland (1969) first reported that intravenous injection of dopamine increased both coronary blood flow and myocardial oxygen consumption and they therefore concluded that the increased blood flow was secondary to myocardial oxygen requirements, rather than the result of a direct vasodilator action of dopamine. However, in subsequent studies in which dopamine has been administered in the presence of α- and β-adrenoceptor blockade, increases in coronary blood flow have been observed in the absence of changes in myocardial oxygen consumption (Schuelke, Mark, Schmid & Eckstein, 1971; Cobb,

Table 3 Changes in coronary blood flow (ml min^{-1} kg^{-1} body wt.) produced by the intra-arterial injection of bromocriptine and SK&F 38393 before and after α-adrenoceptor blockade with phentolamine (0.5 mg/kg, i.v.) or yohimbine (0.5 mg/kg, i.v.)

Agonist (μg)	*Control*	*After α-adrenoceptor blockade*
Bromocriptine		
50	− 0.03 ± 0.03 (5)	− 0.11 ± 0.11 (3)
100	− 0.06 ± 0.06 (5)	0 (3)
200	0 (5)	+ 0.07 ± 0.77 (4)
500	− 0.03 ± 0.09 (5)	0 (3)
SK&F 38393		
50	− 0.05 ± 0.05 (6)	0 (3)
100	− 0.05 ± 0.05 (5)	+ 0.08 ± 0.08 (4)
200	− 0.17 ± 0.08 (5)	0 (3)
500	− 0.24 ± 0.19 (6)	− 0.05 ± 0.005 (4)
1000	− 0.27 ± 0.14 (4)	0 (3)

Values given are mean ± s.e.mean. The number of experiments is given in parentheses.

McHale, Bache & Greenfield, 1972). This has led to the conclusion that vascular dopamine receptors are involved directly in the coronary vasodilatation. In the present study, the intra-arterial injection of dopamine increased heart rate and caused an initial decrease in coronary blood flow, in addition to producing vasodilatation. The vasoconstriction and tachycardia were attenuated by α- and β-adrenoceptor antagonists, respectively, without having any significant effect on the dilator response to dopamine. The dopamine-induced increase in coronary blood flow was significantly reduced by ergometrine. Thus it appears that the most important mechanism in the increase in coronary blood flow produced by dopamine is a direct vasodilatation due to stimulation of vascular dopamine receptors.

The intra-arterial injection of SK&F 38393 increased renal blood flow, as has been observed in earlier studies in which it was administered by intravenous infusion (Pendleton *et al.*, 1978; Hahn & Wardell, 1980). The maximal responses to SK&F 38393 were approximately equal in magnitude to those produced by dopamine and were longer lasting, although the doses used were up to 20 times higher. The renal vasodilatation produced by SK&F 38393 was attenuated by ergometrine and metoclopramide, indicating that its dilator actions are produced by activation of vascular dopamine receptors.

Bromocriptine did not cause any vasodilatation in the kidney after intra-arterial injection. This agrees with the findings of Volkman & Goldberg (1976). In contrast, however, Imbs *et al.* (1979) observed that in the dog, intra-arterial injections of bromocriptine did increase renal blood flow, but they did note that bromocriptine was less potent in the dog than in the rat, where we also have observed bromocriptine-induced vasodilatation (Woodman *et al.*, 1980). This loss of activity in the dog may be due to species differences or differences inherent in *in vivo* as opposed to *in vitro* preparations.

SK&F 38393 and bromocriptine both lacked any vasodilator activity in the coronary vasculature, even in the presence of α-adrenoceptor antagonists. It appears therefore that although dopamine can stimulate receptors in both the renal and coronary circulation to produce vasodilatation, SK&F 38393 acts specifically on the renal vascular dopamine receptor. Together with our finding that DPI acts specifically on the coronary vascular dopamine receptor (Woodman *et al.*, 1981), this suggests that the dopamine receptors differ in the renal and coronary vasculatures.

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References

BELL, C., CONWAY, E.L. & LANG, W.J. (1974). Ergometrine and apomorphine as selective antagonists of dopamine in the canine renal vasculature. *Br. J. Pharmac.*, **52,** 591–595.

BROOKS, H.L., STEIN, P.D., MATSON, J.L. & HYLAND, J.W. (1969). Dopamine-induced alterations in coronary haemodynamics in dogs. *Circulation Res.*, **24,** 699–704.

CLARK, B.J., SCHOLTYSIK, G. & FLÜCKIGER, E. (1978). Cardiovascular actions of bromocriptine. *Acta Endocrin.*, Suppl. 216, **88,** 75–81.

COBB, F.R., McHALE, P.A., BACHE, R.J. & GREENFIELD, J.C. (1972). Coronary and systemic hemodynamic effects of dopamine in the awake dog. *Am. J. Physiol.*, **222,** 1355–1360.

COOLS, A.R. & VAN ROSSUM, J.M. (1976). Excitation-mediating and inhibition-mediating dopamine-receptors: a new concept towards a better understanding of electrophysiological, biochemical, pharmacological, functional and clinical data. *Psychopharmacologia*, **45,** 243–254.

COOLS, A.R. & VAN ROSSUM, J.M. (1980). Multiple receptors for brain dopamine in behaviour regulations: concept of dopamine-e and dopamine-i receptors. *Life Sci.*, **27,** 1237–1253.

COSTALL, B. & NAYLOR, R.J. (1981). The hypotheses of different dopamine receptor mechanisms. *Life Sci.*, **28,** 215–229.

DOCUMENTA GEIGY, 7TH EDITION (1970). ed. Diem, K. & Lentner, C. pp. 174–179. Basle: J.R.Geigy S.A.

HAHN, R.A. & WARDELL, J.R. (1980). Renal vascular activity of SK&F 38393 and dopamine in anaesthetized dogs. *J. cardiovasc. Pharmac.*, **2,** 583–593.

IMBS, J-L., SCHMIDT, M., EHRHARDT, J.D. & SCHWARTZ, J. (1979). Renal dopaminergic mechanisms. *Adv. Biosci.*, **20,** 331–342.

KEBABIAN, J.W. & CALNE, D.B. (1979). Multiple receptors for dopamine. *Nature*, **277,** 93–96.

LOKHANDWALA, M.F., TADEPALLI, A.S. & JANDHYALA, B.S. (1979). Cardiovascular actions of bromocriptine: evidence for a neurogenic mechanism. *J. Pharmac. exp. Ther.*, **211,** 620–625.

PARRATT, J.R. (1980). Effects of adrenergic activators and inhibitors on the coronary circulation. In *Handbook of Experimental Pharmacology*, Vol. 54(I), Adrenergic Activators and Inhibitors. ed. Szekeres, L. pp. 735–822. Berlin: Springer Verlag.

PENDLETON, R.G., SALMER, L., KAISER, C. & RIDLEY, P.T. (1978). Studies on renal dopamine receptors with a new agonist. *Eur. J. Pharmac.*, **51,** 19–28.

ROBY, A. & ORZECHOWSKI, R.F. (1979). Selective post-synaptic dopamine receptor stimulation by SK&F 38393 in canine mesenteric vasculature. *Pharmacologist*, **21,** 239.

SCHMIDT, M. & IMBS, J-L. (1979). Effets rénaux de la bromocriptine. *J. de Pharmacologie*, **10,** 525–532.

SCHUELKE, D.M., MARK, A.L., SCHMID, P.G. & ECKSTEIN,

J.W. (1971). Coronary vasodilatation produced by dopamine after adrenergic blockade. *J. Pharmac. exp. Ther.*, **176,** 320–327.

VOLKMAN, P.H. & GOLDBERG, L.I. (1976). Lack of correlation between inhibition of prolactin release and stimulation of dopaminergic renal vasodilatation. *Pharmacologist*, **18,** 130.

WOODMAN, O.L., MEDGETT, I.C., LANG, W.J. & RAND, M.J. (1981). Agonistic actions of DPI (2-(3,4-dihydroxyphenylimino)-imidazolidine) on α-adrenoceptors and dopamine receptors. *Eur. J. Pharmac.*, **75,** 11–19.

WOODMAN, O.L., RECHTMAN, M.P. & LANG, W.J. (1980). A comparison of the response to some dopamine receptor agonists and antagonists in the isolated perfused rat kidney. *Archs. int. Pharmacodyn.*, **315,** 259–265.

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