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The effects of dopexamine on the cardiovascular system of the dog

R.A. Brown, J.B. Farmer, Janet C. Hall, R.G. Humphries, S.E. O'Connor & G.W. Smith[1]

Fisons plc, Pharmaceutical Division, Bakewell Road, Loughborough, Leicestershire LE11 0RH

1 The cardiovascular effects of dopexamine and dopamine were compared in the anaesthetized and conscious dog by the use of intravenous infusions over the dose range $3 \times 10^{-9} - 10^{-7}$ mol $kg^{-1} min^{-1}$.

2 In the anaesthetized dog, dopexamine produced a dose-related fall in blood pressure due to peripheral vasodilatation and a small rise in heart rate and contractility. By contrast, dopamine did not significantly reduce blood pressure but produced a larger dose-related increase in contractility. At the highest infusion rate (10^{-7} mol $kg^{-1} min^{-1}$) blood pressure and heart rate were increased by dopamine.

3 Dopexamine dilated the renal and mesenteric vascular beds with a potency similar to that of dopamine. Femoral vascular responses produced by both agents were inconsistent but the highest infusion rate of dopamine did produce vasoconstriction.

4 With the aid of selective receptor antagonists (haloperidol, propranolol and bulbocapnine) the vasodepressor activity of dopexamine was shown to be mediated by stimulation of DA_2-, β- and DA_1-receptors. The cardiac stimulation and renal vasodilatation produced by both compounds were due to stimulation of β-adrenoceptors and DA_1-receptors respectively.

5 In the conscious dog, intravenous infusion of dopexamine caused a dose-related fall in blood pressure, renal vasodilatation and an increase in cardiac contractility and heart rate. Dopamine also increased cardiac contractility, and renal blood flow due to renal vasodilatation but without affecting heart rate. At the highest infusion rate, blood pressure was increased.

6 Dopexamine and dopamine produced a similar incidence of panting and repetitive licking at 3×10^{-8} mol $kg^{-1} min^{-1}$ and emesis at 10^{-7} mol $kg^{-1} min^{-1}$, due to stimulation of dopamine receptors in the chemoreceptor trigger zone.

7 Dopexamine produces a different cardiovascular profile from dopamine in the anaesthetized and conscious dog. Both compounds reduce renal vascular resistance, but in contrast to dopamine, dopexamine reduces afterload and produces only mild inotropic stimulation. These differences reflect contrasting activity at adrenoceptors.

Introduction

Dopamine is used in the management of acute heart failure as discussed in the previous paper (Brown *et al.*, 1985). This use of dopamine is, however, sometimes restricted by undesirable effects, such as α-adrenoceptor-mediated vasoconstriction, leading to an increase in blood pressure and even producing gangrene (Makabali *et al.*, 1982; Rajfer & Goldberg, 1982). The production of arrhythmias, excessive tachycardia and precipitation of anginal attacks are probably related to the ability of dopamine to stimulate cardiac β_1-adrenoceptors (Rajfer & Goldberg, 1982).

Dopexamine hydrochloride is a structural analogue of dopamine which retains agonist activity at peripheral dopamine receptors, but only weakly stimulates β_1-adrenoceptors and is not an agonist at postjunctional α_1- or α_2-adrenoceptors. In addition, it is approximately sixty times more potent than dopamine in stimulating β_2-adrenoceptors (Brown *et al.*, 1985). The pharmacological profile displayed by dopexamine might therefore confer certain advantages over dopamine in the treatment of acute heart failure. The cardiovascular effects of dopexamine were examined and compared with dopamine in pentobarbitone-anaesthetized and in conscious dogs. A

[1]Author for correspondence

preliminary account of this work was presented to the British Pharmacological Society (Brown *et al.*, 1984).

Methods

Haemodynamic studies in the anaesthetized dog

Male beagle dogs (10–15 kg) were anaesthetized with pentobarbitone (30 mg kg^{-1} i.v. with supplementary infusion) and respired artificially by constant stroke volume, after creation of a pneumothorax. A double pressure sensor tipped catheter (5F, Gaeltec, UK or Millar, USA) passed down the left carotid artery, was used to measure aortic blood pressure (BP) and left ventricular pressure (LVP). Heart rate (HR) and contractility, measured as LV $dP/dt\,P^{-1}$ (Wolk *et al.*, 1971) were derived from the latter. The left renal artery was exposed via a flank incision and an electromagnetic flow probe (2.0–3.0 mm, Narco Biosystems, USA) placed around the vessel to record renal blood flow (RBF). Electronic division of mean BP by mean RBF gave a continuous recording of renal vascular resistance (RVR). In some of these dogs the superior mesenteric artery and the left femoral artery were exposed and fitted with electromagnetic flow probes to record mesenteric blood flow (MBF) and femoral blood flow (FBF) respectively, and their resistances calculated as above. Cardiac output (CO) was measured by thermal dilution using a thermistor catheter (Cardiovascular Instruments Limited, UK) positioned in the aortic arch via the right femoral artery. Saline at room temperature (5 ml) was rapidly injected into the right atrium via a jugular vein catheter and the CO measured by a thermal dilution computer (St Thomas' Hospital, Model 3750). Total peripheral resistance (TPR) was calculated by division of mean BP by CO and these values were measured 5 min before and after 15 and 25 min of infusion. Lead 2 ECG was recorded continuously.

Eight dogs were used to assess the effects of 30 min infusions of dopexamine (3×10^{-9}, 10^{-8}, 3×10^{-8} and 10^{-7} mol kg^{-1} min^{-1} i.v.) allowing a minimum of 30 min between infusions and four other dogs were used to examine dopamine over the same dose-range.

Mechanisms of action in the anaesthetized dog

These were investigated by studying the effects of dopexamine and dopamine in the presence of various receptor antagonists. Four male beagle dogs (10–15 kg) were prepared as described above for the measurement of BP, HR, $dP/dt\,P^{-1}$, RBF and RVR. Dopexamine and dopamine were given alternately by cumulative 5 min infusions (3×10^{-9}–10^{-7} mol kg^{-1} min^{-1} i.v.) before and after each receptor antagonist, allowing at least 30 min for recovery between both agonists. The contribution made by DA_2-(prejunctional), β- and DA_1-(vascular) receptors in producing cardiovascular responses was assessed in each dog by the successive intravenous administration of the respective receptor blockers given in the following order:- Haloperidol was given each hour to block DA_2-receptors at a dose (50 μg kg^{-1}) which does not antagonise the DA_1-receptor response (Shepperson *et al.*, 1982). The β-adrenoceptors were blocked by propranolol (0.5 mg kg^{-1} and 0.25 mg kg^{-1} h^{-1}), and bulbocapnine (3 mg kg^{-1} over 15 min) was used to prevent DA_1-receptor stimulation (Setler *et al.*, 1975).

Haemodynamic studies in the conscious dog

Seven male beagle dogs were selected for this study and prepared as described previously (O'Connor *et al.*, 1982). Under pentobarbitone anaesthesia, catheters (Tygon, 2.4 mm OD, 0.8 mm ID) were positioned in the right carotid or a femoral artery to allow measurement of arterial blood pressure. Another catheter placed in the right jugular vein was used to administer drugs. Both catheters were led subcutaneously to the nape of the neck and exteriorised by means of titanium skin buttons with teflon taps. Electromagnetic flow probes (2.5–3.0 mm, Narco Biosystems, USA) were implanted around the left renal artery in four of these dogs and led to the back of the neck. Electronic division of mean BP by mean

Table 1 Anaesthetized dog: resting values for blood pressure, heart rate, renal, mesenteric and femoral blood flows and their respective vascular resistances and cardiac output before drug administration

	BP	*HR*	*RBF*	*RVR*	*MBF*	*MVR*	*FBF*	*FVR*	*CO*
Dopexamine	110 ± 6*	158 ± 5*	79 ± 10*	1.66 ± 0.32*	157 ± 47	0.96 ± 0.24	72 ± 18	2.32 ± 0.70	1.89 ± 0.34†
Dopamine	118 ± 9	158 ± 7	56 ± 9	1.87 ± 0.65	205 ± 51	0.74 ± 0.21	87 ± 27	2.11 ± 0.87	2.45 ± 0.29†

Values are mean ± s.e.mean of blood pressure (BP, mmHg), heart rate (HR, beats min^{-1}), renal, mesenteric and femoral blood flows (RBF, MBF and FBF, ml min^{-1}), their respective vascular resistances (RVR, MVR and FVR, mmHg min ml^{-1}) and cardiac output (CO, l min^{-1}).
$n = 4$ with the exception of $n = 8$ (*) and $n = 3$ (†)

RBF gave a continuous measurement of renal vascular resistance (RVR). The dogs were used after a minimum of one week's recovery.

In preliminary experiments dopexamine was examined by intravenous bolus injection (3×10^{-9}–10^{-6} mol kg^{-1}) and the selective DA_2-receptor blocker sulpiride (0.5 mg kg^{-1} i.v., Shepperson *et al.*, 1982) was used to evaluate the involvement of DA_2-receptor stimulation in producing the behavioural response. The effects of dopexamine or dopamine were examined by intravenous infusion for 30 min (3×10^{-9}, 10^{-8}, 3×10^{-8} and 10^{-7} mol kg^{-1} min^{-1}). BP, HR, RBF and RVR were measured, and an indirect assessment of contractility was made using the QA interval. This, the time interval between the beginning of the Q-wave of the ECG (lead 2) to the beginning of the systolic BP pulse, has been shown to be inversely proportional to contractility (Jackson, 1974).

Dopexamine was also administered orally, as a powder in gelatine capsules (3×10^{-6} mol kg^{-1}, $n = 2$, and 10^{-5} mol kg^{-1}, $n = 3$) or as a solution by stomach tube in one dog (10^{-5} mol kg^{-1}), to assess oral activity of the compound.

Results

Haemodynamic studies in the anaesthetized dog

The resting values for each cardiovascular parameter in the two groups of dogs used to examine dopexamine and dopamine were similar, as shown in Table 1. Results are expressed as percentage changes of these resting values to take into account the variation in basal blood flows and vascular resistances found between these dogs.

Effects of dopexamine (Figures 1 and 2)

A typical example of the effects of dopexamine is shown in Figure 1. Blood pressure (BP) was reduced in a dose-dependent manner over the dose range of 3×10^{-9}–10^{-7} mol kg^{-1} min^{-1} (i.v.) and fell by virtually half at the highest infusion level. Cardiac output (CO) was unchanged, except for a small but significant ($P < 0.05$) rise at 3×10^{-8} mol kg^{-1} min^{-1} of 8 ± 2%. Consequently, the reduction in BP was solely due to a fall in peripheral resistance. Accompanying these changes were dose-dependent increases in HR and LV dP/dt P^{-1} of up to 10% and 40% respectively. The renal vascular bed showed a dose-related vasodilatation with a maximum reduction of 47% in RVR resulting in an increase in RBF at 3×10^{-8} mol kg^{-1} min^{-1}. At the highest infusion level (10^{-7} mol kg^{-1} min^{-1}) RBF fell because of the large fall in BP (Figure 2). The mesenteric vascular bed also showed a significant and dose-dependent vasodilatation in response to dopexamine, falling by 8 ± 5%, 28 ± 2%, 34 ± 4%, and 41 ± 8% for each of the infusion levels, resulting in a rise in MBF of 20 ± 5% at 10^{-8} mol kg^{-1} min^{-1}, but with a fall in MBF at the highest infusion. The effects of dopexamine were rapid in onset, well maintained and quickly reversed on termination of the infusion as shown in Figures 1 and 2. No consistent femoral vascular response occurred.

Effects of dopamine (Figure 3)

Dopamine infusion produced no alteration of BP except at the highest infusion rate (10^{-7} mol kg^{-1} min^{-1}) when it rose in each of the four dogs. CO

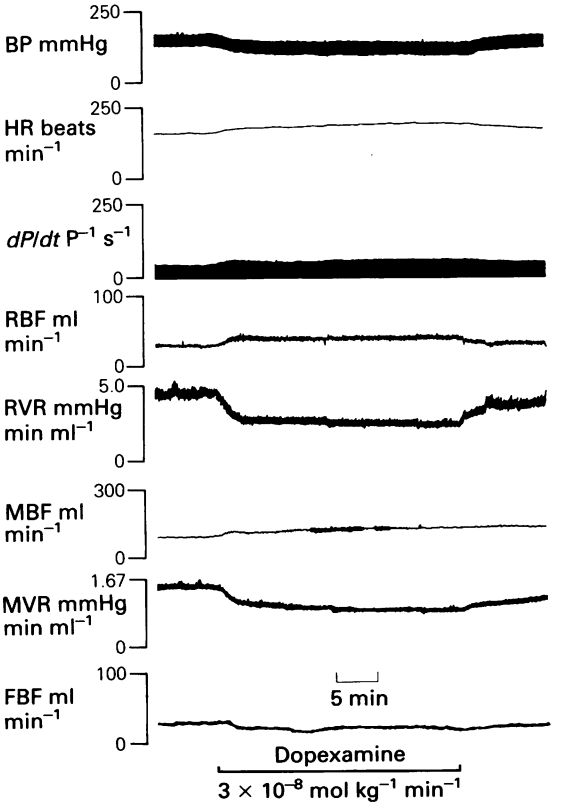

Figure 1 Anaesthetized dog: effects of a 30 min infusion of dopexamine (3×10^{-8} mol kg^{-1} min^{-1}, i.v.) on blood pressure (BP), heart rate (HR), left ventricular contractility (dP/dt P^{-1}), mean renal, mesenteric and femoral blood flows (RBF, MBF and FBF respectively) and renal and mesenteric vascular resistances (RVR and MVR respectively).

rose significantly at the two higher infusion rates by 12 ± 3% with 3×10^{-8} mol kg^{-1} min^{-1} and 23 ± 6%, with 10^{-7} mol kg^{-1} min^{-1}, without altering calculated TPR. The rise in CO was probably due to the increases in contractility and heart rate. The cardiac stimulation was of a greater magnitude than seen with dopexamine and occurred gradually over the 30 min infusion period. The decrease in RVR produced by dopamine resulted in a greater rise in RBF than that produced by dopexamine (86 ± 40% with 10^{-7} mol kg^{-1} min^{-1}) because of the presence of a pressor response. MVR fell by up to 20% and was accompanied by significant increases in MBF at 3×10^{-8} mol kg^{-1} min^{-1} (27 ± 6%) and 10^{-7} mol kg^{-1} min^{-1} (42 ± 15%). The femoral vascular bed however, was not consistently affected until the highest infusion rate, when a significant rise in FVR (75 ± 19%) occurred and FBF fell.

Comparison of dopexamine with dopamine (Figure 3)

The changes in BP, HR, contractility and RVR produced by dopexamine and dopamine at the end of each 30 min infusion are compared in Figure 3. Whereas dopexamine was equipotent with dopamine as a renal vasodilator, it produced comparatively less cardiac stimulation, reaching a maximal effect at 3×10^{-8} mol kg^{-1} min^{-1}. Dopexamine produced a dose-related fall in BP of up to 50% at the highest infusion, whereas dopamine only increased BP.

Mechanism of action in the anaesthetized dog (Figure 4)

Cumulative 5 min infusions of dopexamine (3×10^{-9}–10^{-7} mol kg^{-1} min^{-1}) produced a dose-related reduction in BP and RVR, with an increase in HR and dP/dt P^{-1}, consistent with responses obtained using 30 min infusions. Dopamine, however, showed only a dose-related fall in RVR; cardiac contractility, HR and BP were virtually unaffected by these short infusions. Administration of a dose of haloperidol (50 μg kg^{-1}, i.v., repeated each hour) to block DA_2- but not DA_1-receptors, resulted in an attenuation of the dopexamine-induced depressor response and

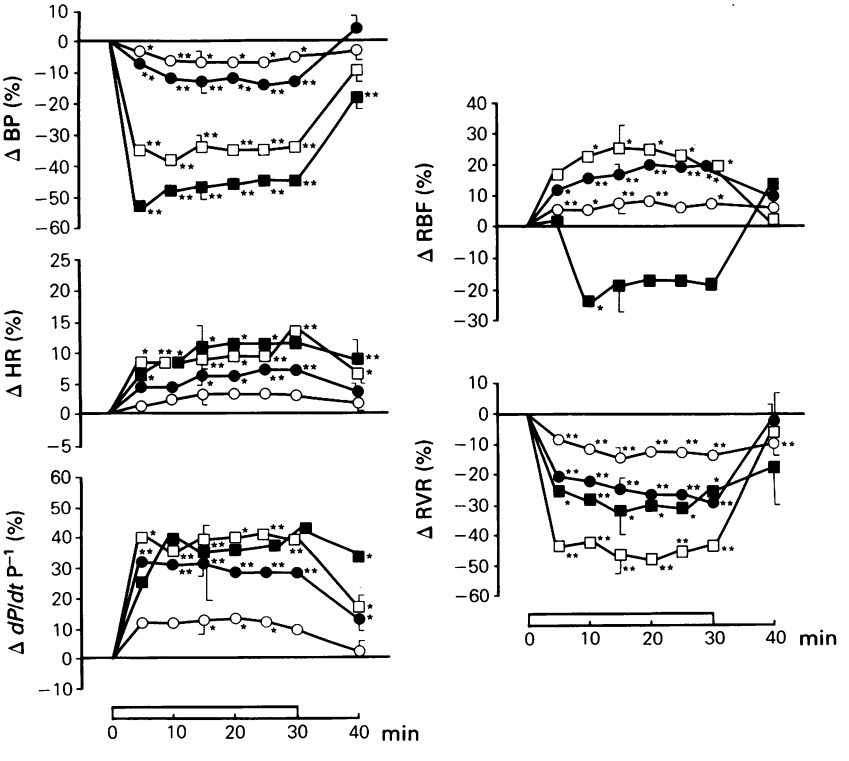

Figure 2 Anaesthetized dog: time-and-dose-dependent effects of dopexamine infused for 30 min at 3×10^{-9} (○), 10^{-8} (●), 3×10^{-8} (□) and 10^{-7} (■) mol kg^{-1} min^{-1} (iv) in eight dogs, on blood pressure (BP), heart rate (HR), contractility (dP/dt P^{-1}), renal blood flow (RBF) and renal vascular resistance (RVR). Percentage changes are shown as mean values with bars showing s.e.mean. $*P < 0.05$; $**P < 0.01$ (paired two-tailed t test).

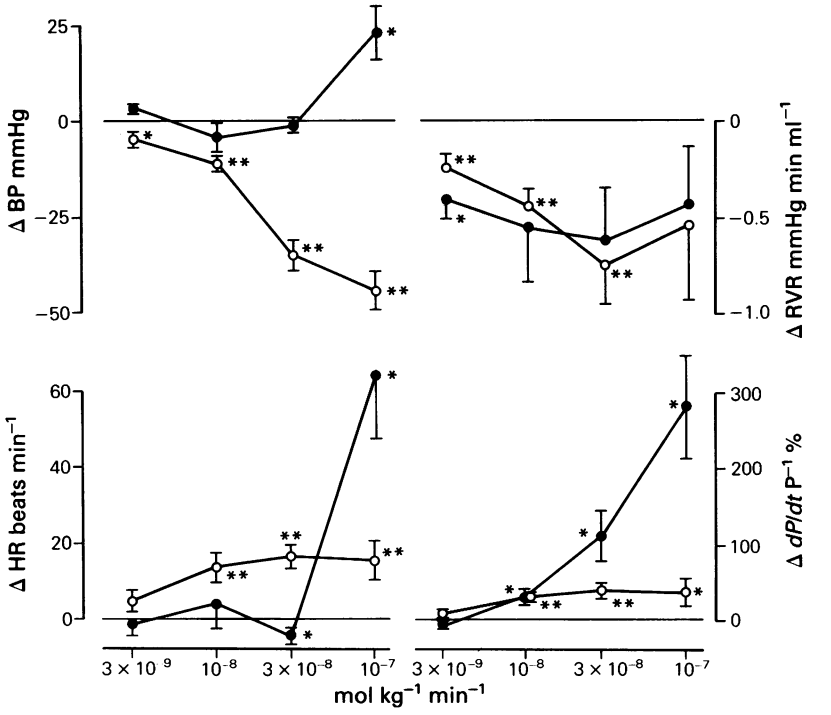

Figure 3 Anaesthetized dog: comparison of the effects of infusions (after 30 min) of dopexamine (○, $n = 8$) with dopamine (●, $n = 4$) on blood pressure (BP), heart rate (HR), renal vascular resistance (RVR) and contractility (dP/dt P^{-1}); $*P<0.05$; $**P<0.01$.

potentiation of the cardiac stimulation but no alteration of the renal vascular changes. The cardiovascular and renal responses produced by dopamine were unaffected by haloperidol.

Following haloperidol, propranolol (0.5 mg kg^{-1} and 0.25 mg kg^{-1} h^{-1}, i.v.) was given to block β-adrenoceptors, resulting in a significant fall in BP (from 136 ± 4 to 118 ± 7 mmHg) and HR (from 178 ± 7 to 132 ± 5 beats min^{-1}). The depressor response produced by dopexamine was attenuated, and the cardiac stimulation evoked by both dopexamine and dopamine was abolished but the renal vascular effects of dopexamine and dopamine were unaffected by the presence of propranolol.

The successive administration of the selective DA_1-receptor antagonist bulbocapnine (3 mg kg^{-1} given over 15 min, i.v.) in the presence of haloperidol, produced only a transient rise in BP but a significant and long lasting bradycardia (from 132 ± 5 to 106 ± 4 beats min^{-1}). In the presence of bulbocapnine, the dopexamine-induced falls in BP and RVR were antagonized. The renal vasodilatation produced by dopamine was reversed to produce vasoconstriction. The tachycardia produced by dopexamine, which was previously abolished by propranolol, reappeared after the administration of bulbocapnine.

Haemodynamic studies in the conscious dog

Resting values from the seven dogs used in this study, before the administration of dopexamine (four with renal artery flow probes) are shown in Table 2. The highest infusion of dopexamine and dopamine (10^{-7} mol kg^{-1} min^{-1}) was given only to five of these dogs.

Effects of dopexamine (Figure 5) Dopexamine infusions produced rapid and well maintained effects over the 30 min of infusion, with rapid recovery on termination of the infusions. There was a dose-related reduction in BP, except at the highest infusion rate. These effects were accompanied by a dose-dependent increase in HR (doubled at 3×10^{-8} mol kg^{-1} min^{-1}), and cardiac contractility (fall in the QA interval). The renal vascular bed dilated in response to dopexamine, RVR falling by up to a third at 10^{-8} and 3×10^{-8} mol kg^{-1} min^{-1}, resulting in a significant rise in RBF (Figure 5). Behavioural changes occurred at

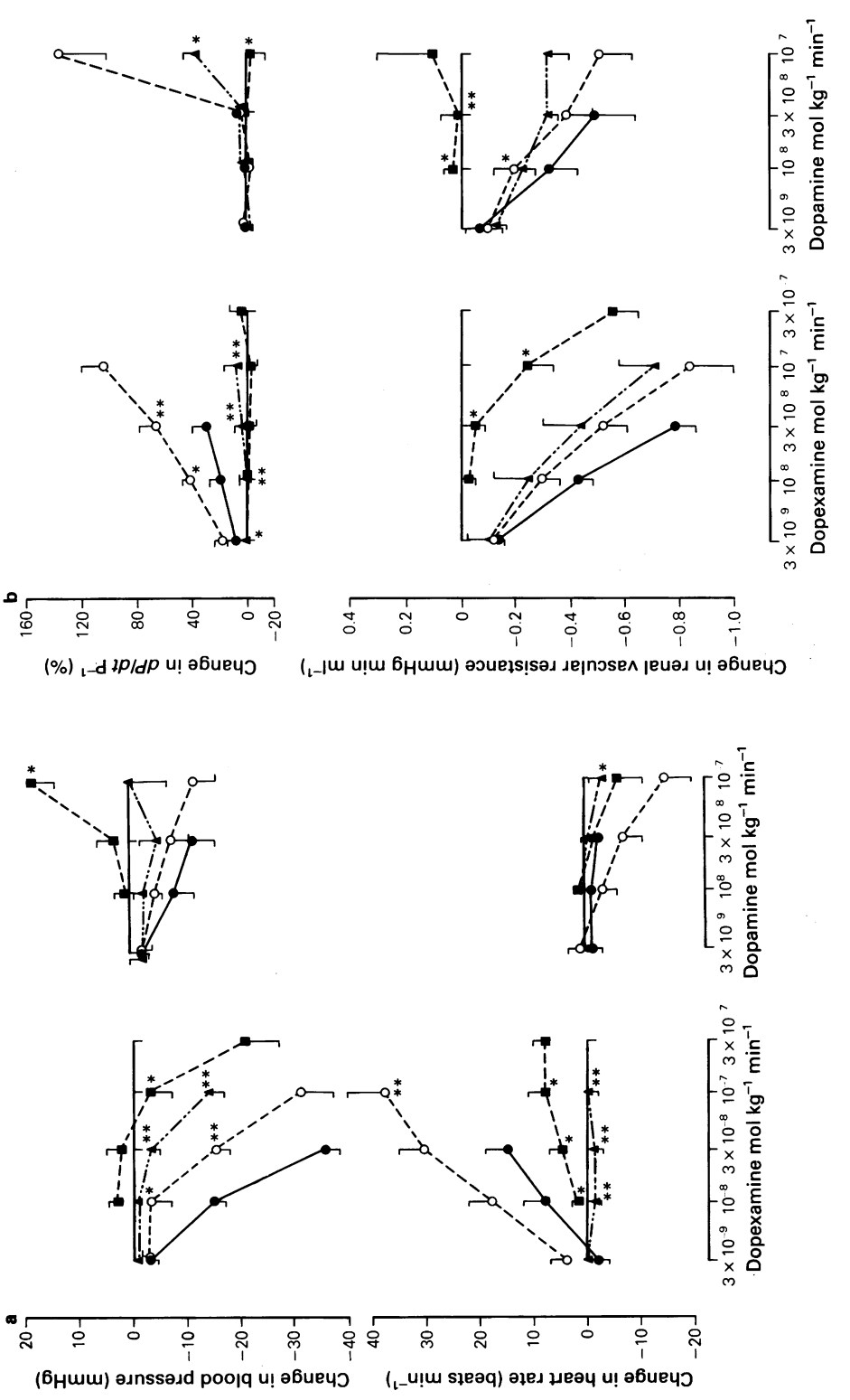

Figure 4 Anaesthetized dog: the responses produced by dopexamine and dopamine infusions before (●) and during the successive administration of the following antagonists: haloperidol (○, 50 μg kg^{-1}, each hour, to block DA_2-receptors), propranolol (▲, 0.5 mg kg^{-1} and 0.25 mg kg^{-1} h^{-1}, to block β-adrenoceptors) and bulbocapnine (■, 3 mg kg^{-1}, to block DA_1-receptors) on (a) blood pressure (BP) and heart rate (HR) and (b) contractility (dP/dt P^{-1}) and renal vascular resistance (RVR). Values shown are mean with bars showing s.e.mean. $^*P < 0.05$; $^{**}P < 0.01$ (paired, two-tailed t test).

Table 2 Conscious dog: resting values for blood pressure, heart rate, contractility, renal blood flow and renal vascular resistance before drug administration

	BP	*HR*	*QA*	*RBF*	*RVR*
Dopexamine	131 ± 6	99 ± 12	128 ± 11	124 ± 16	1.15 ± 0.18
Dopamine	117 ± 4	92 ± 7	116 ± 13	125 ± 14	1.23 ± 0.17

Values are mean ± s.e.mean of blood pressure (BP, mmHg), heart rate (HR, beats min^{-1}) contractility (QA, ms), renal blood flow (RBF, ml min^{-1}) and renal vascular resistance (RVR, mmHg min ml^{-1}) taken before infusion of 10^{-8} mol kg^{-1} min^{-1} of either dopexamine or dopamine ($n = 7$, except for RBF and RVR where $n = 4$).

the two higher infusion rates. At 3×10^{-8} mol kg^{-1} min^{-1}, two of the seven dogs displayed bouts of repetitive licking and panting, whilst three of the five dogs vomited on receiving 10^{-7} mol kg^{-1} min^{-1}. These effects subsided rapidly on terminating the infusions. In experiments where dopexamine was given by intravenous bolus (3×10^{-9}–10^{-6} mol kg^{-1}), repetitive licking and panting, characteristic of subemetic doses of DA_2-receptor agonists, were seen in two of the three dogs given 10^{-7} mol kg^{-1}, whilst the third dog vomited. All of these behavioural effects were prevented by prior administration of the DA_2-receptor antagonist, sulpiride (0.5 mg kg^{-1}, i.v.). Dopexamine (10^{-5} mol kg^{-1} i.e. 4.3 mg kg^{-1}) was

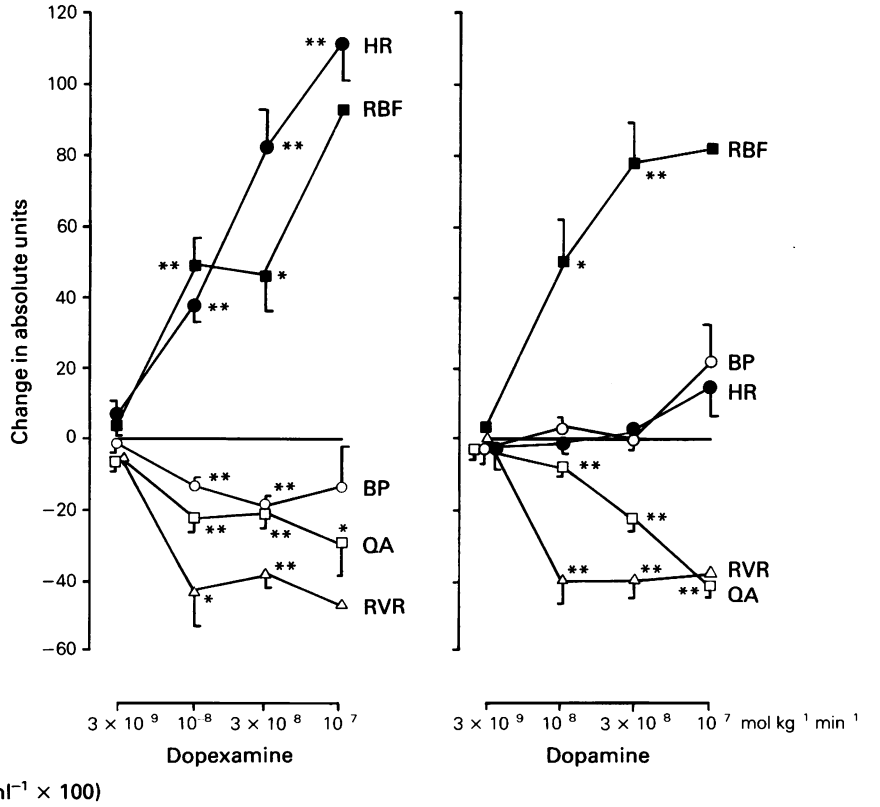

Figure 5 Conscious dog: comparison of the effects of 30 min infusions of dopexamine and dopamine on blood pressure (BP), heart rate (HR) and contractility (QA) in seven dogs and on renal blood flow (RBF) and renal vascular resistance (RVR) in four of these dogs. Values are mean with vertical bars showing s.e.mean. $*P < 0.05$; $**P < 0.01$ (paired, two-tailed t test).

inactive when given orally as a powder in gelatin capsules ($n = 3$) or by solution ($n = 1$).

Effects of dopamine (Figure 5) Dopamine infusions did not affect BP or HR in the conscious dog until the highest infusion rate when small rises occurred. Contractility (QA interval) by contrast, showed a dose-dependent rise. Renal vasodilatation occurred at infusions above 3×10^{-9} mol kg^{-1} min^{-1}, RVR falling by up to a third at 10^{-8}–3×10^{-8} mol kg^{-1} min^{-1}, with RBF rising as a consequence. In one dog given 3×10^{-8} mol kg^{-1} min^{-1}, repetitive licking and panting was seen, and two of the five dogs infused with 10^{-7} mol kg^{-1} min^{-1} vomited.

Discussion

Dopexamine has been shown to produce a reduction of blood pressure in the conscious and the anaesthetized dog, a consequence of peripheral vasodilatation. Despite the fall in organ perfusion pressure and with little change in cardiac output, dopexamine produced a rise in renal and mesenteric blood flows, suggesting that the degree of vasodilatation in these organs exceeded that of the general circulation. Both these vascular beds have been shown to contain vascular dopamine (DA_1)-receptors, the stimulation of which causes vasodilatation (McNay & Goldberg, 1966; Yeh *et al.*, 1969; Crumley *et al.*, 1976; Hilditch & Drew, 1983) and since the location of DA_1-receptors is highly regionalized (Goldberg, 1972), local effects would be expected to predominate. In the anaesthetized dog, it was confirmed that dopexamine-induced renal vasodilatation resulted from this mechanism, since the selective DA_1-receptor antagonist, bulbocapnine (Setler *et al.*, 1975; Shepperson *et al.*, 1982) attenuated the response. This activity is consistent with the finding that dopexamine is an agonist at renal vascular DA_1-receptors, where it has one third the potency of dopamine (Brown *et al.*, 1985). In this study, dopamine also dilated the renal vasculature, but the increase in RBF in the anaesthetized dog exceeded that produced by dopexamine because blood pressure also rose.

Dopamine produced only a mild mesenteric vasodilatation in the anaesthetized dog. This, in addition to the absence of peripheral vasodilatation, may be due to the opposing α-adrenoceptor vasoconstrictor property of dopamine (Farmer, 1966; Goldberg, 1972). This activity may also explain the reversal of the renal vasodilatation after DA_1-receptor block. Dopamine has been shown to produce α_2-adrenoceptor-mediated vasoconstriction in the canine mesenteric vascular bed (Shepperson *et al.*, 1982) and α_1-adrenoceptor-mediated vasoconstriction of the renal vascular bed (Duval *et al.*, 1984). Since dopexamine lacks stimulant properties at either postjunctional α_1- or α_2-adrenoceptors (Brown *et al.*, 1985) vasoconstrictor and pressor effects do not occur.

Stimulation of prejunctional DA_2-receptors found on sympathetic nerve endings, results in a reduction in the release of noradrenaline (Dubcovich & Langer, 1980). As a consequence, DA_2-receptor agonists produce a reduction in BP (Cavero *et al.*, 1981a; Clapham & Hamilton, 1982; O'Connor *et al.*, 1982) and HR (Cavero *et al.*, 1981b; Taylor *et al.*, 1983), although under certain circumstances reflex compensation can prevail, leading to baroreflex-mediated tachycardia (O'Connor *et al.*, 1982). Dopexamine is an agonist at the DA_2-receptor with a potency four to six times less than that of dopamine (Brown *et al.*, 1985) and the DA_2-receptor stimulant effect of dopexamine played a role in reducing BP in the anaesthetized dog and in attenuating the tachycardia and positive inotropic effects. By contrast, dopamine did not reduce BP in either the anaesthetized or the conscious dog, despite the presence of DA_2-receptor stimulant activity. This may have been due to the masking effect of α-adrenoceptor stimulation, combined with the presence of a functional neuronal catecholamine uptake system, which limits the neural effect of dopamine.

In the conscious dog, large bolus doses of dopexamine or high infusion rates of dopexamine and dopamine led to panting, repetitive licking and eventually to episodes of emesis. Since the emetic effect of bolus injections of dopexamine was abolished by sulpiride, this was attributable to stimulation of D_2-receptors within the chemoreceptor trigger zone of the brain (Stefanini & Clement-Cormier, 1981). These receptors are not protected by the blood brain barrier, and resemble pharmacologically the peripheral DA_2-receptors found in the rabbit ear artery (Brown *et al.*, 1983) and in the cat heart (Drew *et al.*, 1982). Dopexamine therefore resembles dopamine in producing emesis in the dog.

The tachycardia and positive inotropy produced by dopexamine in the anaesthetized dog were much less than those caused by dopamine and the dose-response curves were not as steep. Dopamine is know to stimulate cardiac β_1-adrenoceptors directly as well as indirectly by displacement of neuronal noradrenaline (Farmer, 1966; Tsai *et al.*, 1966). By contrast, dopexamine is a weak stimulant of β_1-adrenoceptors, with an intrinsic activity only one sixth that of dopamine (Brown *et al.*, 1985). Despite a rise in chronotropy and inotropy, dopexamine produced only a small rise in cardiac output, possibly due to the presence of venodilatation.

The simple classification of beta receptors into β_1-cardiac and β_2-smooth muscle adrenoceptors is now in question since β_2-adrenoceptors have been identified in the heart of dog (Einstein *et al.*, 1979) and of man

(Brodde *et al.*, 1983; Wilson, 1984). Therefore the cardiac effects of dopexamine may also be due to stimulation of β_2-drenoceptors, since dopexamine is a relatively potent agonist at this receptor, sixty times more potent than dopamine (Brown *et al.*, 1985). It is also probable that a reflex component is present, in view of the depressor response.

In the conscious dog, dopexamine produced a smaller depressor response, accompanied by a larger dose-dependent tachycardia than seen in the anaesthetized dog. Since barbiturate anaesthesia is vagolytic and depresses cardiovascular reflexes (Chenoweth & Van Dyke, 1969; Strobel & Wollman, 1969), the response to drugs can differ depending on the integrity of the reflexes (O'Connor *et al.*, 1982). The presence of a powerful baroreflex in the conscious dog is the most likely explanation of the damped depressor response and increased tachycardia seen with dopexamine compared with the responses obtained in the anaesthetized dog. Evidence to support this has come from the observation in ganglion blocked conscious dogs, that dopexamine produces only a small increase in HR and a large fall in BP, both of which are prevented by the β_2-adrenoceptor antagonist, ICI 118551 (unpublished observations). Dopamine produced a dose-dependent increase in contractility but did not reduce BP or cause tachycardia in the conscious dog except at the highest infusion rate when a small increase in blood pressure and heart rate occurred. The mechanisms responsible for these effects were not analysed.

Dopamine is used in the treatment of acute heart failure, primarily because it provides inotropic stimulation, and in addition improves renal blood flow and induces diuresis and natriuresis (Goldberg, 1972; Bergovich *et al.*, 1974; Makabali *et al.*, 1982). Its use is generally restricted to i.v. infusions over the range of $1-10\,\mu g\,kg^{-1}\,min^{-1}$, ($5\times10^{-9}-5\times10^{-8}$ $mol\,kg^{-1}\,min^{-1}$). At higher infusion rates, various undesirable effects occur, such as arrhythmias, anginal attacks, vasoconstriction (Rajfer & Goldberg, 1982), and headache, nausea and tachycardia have been reported (Makabali *et al.*, 1982). In addition, dopamine is ineffective in reducing preload (Rae *et al.*, 1983) and may even raise left heart filling pressure (Timmis *et al.*, 1981). Many of these side-effects are likely to be a consequence of stimulation of cardiac β_1-adrenoceptors and vascular α-adrenoceptors.

Since dopexamine lacks significant activity at the cardiac β_1-adrenoceptor and is inactive at the α-adrenoceptor, most, if not all of the above disadvantages seen with dopamine, should be absent. The tachycardia produced by dopexamine in the conscious dog is an exception, but it is known that baroreflex tachycardia is depressed in heart failure patients (Cohn & Franciosa, 1977; Chatterjee & Parmley, 1980). Although not measured in this study, dopexamine has been found in subsequent experiments to reduce left ventricular end diastolic pressure (unpublished observations), unlike dopamine which increases filling pressure in the anaesthetized dog due to α-adrenoceptor stimulation (Hsieh & Goldberg, 1979).

Dobutamine, another dopamine analogue has comparable inotropic and chronotropic activity to dopamine in the anaesthetized dog, but is a weaker vasoconstrictor than dopamine. However, unlike dopexamine or dopamine it does not stimulate DA_1-receptors thereby failing to cause renal vasodilatation (Robie & Goldberg, 1975). In the conscious dog, dobutamine increases skeletal muscle blood flow at the expense of renal and visceral blood flows (Vatner *et al.*, 1974).

Reduction of afterload by means of vasodilators, has been shown to offer a useful therapeutic alternative to inotropic stimulation in the treatment of heart failure, allowing myocardial oxygen consumption to be lowered despite an increased cardiac output (Chatterjee & Parmley, 1980). The reduction in afterload produced by dopexamine in the anaesthetized dog is probably a consequence of stimulation of β_2-adrenoceptors and dopamine receptors. In heart failure patients, effective afterload reduction has been demonstrated with β_2-adrenoceptor agonists (Sharma & Goodwin, 1978; Fowler *et al.*, 1982, Weber *et al.*, 1982) and a DA_2-receptor agonist (Fennell *et al.*, 1983). Sodium nitroprusside, a non-specific vasodilator used in heart failure therapy reduces pre- and afterload (Cohn & Franciosa, 1977), but only has a weak renal vasodilator effect such that renal blood flow falls (Fennell *et al.*, 1980, O'Connor, *et al.*, 1982).

In conclusion, dopexamine retains the useful feature of dopamine in stimulating peripheral dopamine receptors, the main effect of which is to enhance renal blood flow and maintain blood flow to other DA_1-receptor-containing vascular beds such as the mesenteric circulation. Improvement of cardiac output is likely to follow afterload reduction caused by the combined stimulation of vascular β_2-adrenoceptors as well as of prejunctional DA_2- and vascular DA_1-receptors. In view of the lack of activity at α-adrenoceptors and the weak activity at cardiac β_1-adrenoceptors, dopexamine is unlikely to display the undesirable cardiovascular side-effects seen with high infusions of dopamine.

Cardiovascular activity has been confirmed with dopexamine in human volunteers (Foulds & Simpson, personal communication) and in patients with heart failure (Dawson *et al.*, 1984).

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