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The cardiovascular actions of dopexamine hydrochloride, an agonist at dopamine receptors and β_2-adrenoceptors in the dog

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The receptor pharmacology of the cardiovascular effects of dopexamine hydrochloride in the anaesthetized dog (given by i.v. infusion of 3×10^{-9}–10^{-7} mol kg^{-1} min^{-1}) has been analysed by the use of selective receptor antagonists and of ganglionic blockade. The increases in cardiac output, contractility, and rate were antagonized by the β_2-adrenoceptor antagonist, ICI 118551. Renal blood flow rose secondary to reduction in renal vascular resistance and this was antagonized by SCH 23390, a highly selective DA_1-receptor antagonist. Peripheral vasodilation and reduction of blood pressure were mediated by a combination of DA_1- and DA_2-receptor and β_2-adrenoceptor stimulation. In a separate group of dogs, the cardiac stimulant effects of dopexamine HCl were partially reflex and were reduced by ganglion block, revealing responses due to stimulation of cardiac β_2-adrenoceptors. Thus the β_2-adrenoceptor agonist action of dopexamine HCl is not only partly responsible for afterload reduction but also leads to direct cardiac stimulation. From its cardiovascular profile, dopexamine HCl is likely to be of use in acute treatment of heart failure.

Dopexamine hydrochloride (DopacardR, Fisons plc) is a novel catecholamine designed to enhance the desirable cardiovascular therapeutic actions of dopamine. Its receptor and cardiovascular pharmacology has previously been reported (Brown et al 1985a, b). Specifically we reported dopexamine HCl to be a peripheral dopamine receptor agonist, one third the potency of dopamine at the vascular DA_1-receptor, but 60 times as potent in stimulating the β_2-adrenoceptor. The present paper describes further studies carried out in the anaesthetized dog to analyse the receptors responsible for the cardiovascular effects of dopexamine HCl, with particular reference to the heart, using more highly selective antagonists than those used previously. In addition, the direct effect of dopexamine HCl on the heart has been studied after autonomic ganglionic blockade to abolish reflex influences. This was particularly important since dopexamine HCl is a vasodilator and has been shown to exhibit β_1-adrenoceptor-mediated cardiac stimulant effects (prevented by propranolol, a non-selective β-adrenoceptor antagonist, Brown et al 1985b) despite possessing only very weak β-adrenoceptor agonist activity (Brown et al 1985a).

MATERIALS AND METHODS

Beagles of either sex (10–15 kg, n = 8) were anaesthetized with pentobarbitone (30 mg kg^{-1} i.v. with supplementary infusion, Brown et al 1985b). Briefly, blood pressure (BP), left ventricular (LV) pressure (Gaeltec, UK or Millar, USA, 5F pressure sensor tipped catheter), heart rate, left ventricular end diastolic pressure (LVEDP) and the index of contractility LVdP/dt.P^{-1} max (dP/dt.P^{-1}) were recorded. An electromagnetic flow probe (2·5–3·0 mm, Narco Biosystems, USA) was positioned via a midline laparotomy around the left renal artery to allow measurement of renal blood flow. Electronic division of mean blood pressure by mean renal blood flow gave a continuous record of renal vascular resistance.

In four of the dogs (receptor antagonist study), cardiac output was also measured using a 14 or 16 mm electromagnetic flow probe placed around the ascending aorta via a midline sternotomy. From cardiac output we derived stroke volume (SV, i.e. CO divided by HR) and total peripheral resistance (TPR, i.e. mean BP divided by mean CO).

Receptor antagonist study

Since the effects of dopexamine HCl infusions are rapidly attained (Brown et al 1985b), cumulative 5 min infusions were used to assess the influence of receptor antagonists upon the responses produced by dopexamine HCl. Control responses were obtained in four dogs with cumulative 5 min i.v. infusions of dopexamine HCl at 3×10^{-9}, 10^{-8}, 3×10^{-8} and 10^{-7} mol kg^{-1} min^{-1} before and after the successive i.v. administration of each of the selective receptor antagonists. This protocol was adopted in view of the

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multiplicity of receptors stimulated by dopexamine HCl. The antagonists were given in the order of ICI 118551 i.e. erythro-(±)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol (0·2 mg kg^{-1} and 0·2 mg kg^{-1} h^{-1}) to block β_2-adrenoceptors (Bilski et al 1983), SCH 23390 i.e. (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-d-benzazepine (0·02 mg kg^{-1}) to block DA_1-receptors (Goldberg et al 1984; Hilditch et al 1984) and domperidone (0·1 mg kg^{-1}) to block DA_2-receptors (Kohli et al 1983). In three of the dogs, atenolol (0·5 mg kg^{-1}) was given to block β_1-adrenoceptors. The doses were chosen to give reasonable and prolonged antagonism of receptor-mediated responses. We have previously satisfied ourselves that the effects of dopexamine HCl are reproducible over the experimental period of study in the absence of antagonist administration (unpublished observation).

Ganglion block study

In another four dogs, the effects of cumulative 5 min infusions of dopexamine HCl were compared with isoprenaline (3×10^{-11}, 10^{-10}, 3×10^{-10} and 10^{-9} mol kg^{-1} min^{-1}), included as a direct cardiac stimulant to assess the effect that changes in the baseline produced by ganglion block might have upon the drug-induced responses. Both agents were examined before and after ganglion block produced by the combined administration of chlorisondamine hydrochloride (1 mg kg^{-1}) and methylatropine bromide (2·5 mg kg^{-1}) to enable their direct actions on the heart to be assessed in the absence of reflex influences. The pure vasodilator, sodium nitroprusside (3·34, 1·0 and $3·4 \times 10^{-7}$ mol kg^{-1} min^{-1}), was included to confirm the effectiveness of ganglion block. Dopexamine HCl and isoprenaline were then examined in the presence of the β_2-adrenoceptor antagonist, ICI 118551 (0·2 mg kg^{-1} and 0·2 mg kg^{-1} h^{-1}).

Dopexamine dihydrochloride (Dr F. Ince, Fisons Medicinal Chemistry Department), was dissolved in saline containing ascorbic acid immediately before use. We gratefully acknowledge the gifts of ICI 118551 and atenolol (Imperial Chemical Industries), SCH 23390 (Schering-Plough Corp.) and domperidone (Janssen). Isoprenaline hydrochloride (Pharmax Ltd), sodium nitroprusside (BDH), chlorisondamine hydrochloride (May & Baker) and methylatropine bromide (Sigma) were purchased. Except for ICI 118551 which was dissolved in water and domperidone which was initially dissolved in an equivalent of 1 M lactic acid, the drugs were dissolved in 0·9% NaCl (saline).

Results are expressed as per cent changes from resting values (mean ± s.e.) and Student's *t*-test (paired single tailed) was used to assess significance.

RESULTS

Receptor antagonist study (Fig. 1 and Table 1)

In the absence of antagonists, dopexamine HCl infusions produced dose-related increases in heart rate and contractility accompanied by a fall in blood pressure while renal blood flow rose due to the fall in renal vascular resistance. These changes were accompanied by a dose-related fall in LVEDP (Table 1).

Table 1. The effect of successive administration of ICI 118551 and SCH 23390 to block β_2-adrenoceptors and DA_1-receptors, respectively, on the fall in left ventricular end diastolic pressure produced by dopexamine HCl.

Dopamine (mol kg^{-1} min^{-1})	Control	ICI 118551	SCH 23390
0	2·9 ± 0·5	5·1 ± 0·7†	5·4 ± 0·2
3×10^{-9}	−30 ± 7	−10 ± 6[b]	0 ± 0
10^{-8}	−41 ± 6	−17 ± 10[b]	+1 ± 1
3×10^{-8}	−56 ± 15	−26 ± 10[b]	−2 ± 2[a]
10^{-7}	−60 ± 13	−46 ± 15[a]	−29 ± 10

Values are mean ± s.e. (n = 4) of absolute control values (mmHg) and of per cent changes caused by dopexamine HCl. † A significant rise in basal LVEDP occurred after ICI 118551. [a] ($P < 0·05$) and [b] ($P < 0·01$) demonstrate the significance of the attenuation of the dopexamine HCl response caused by each antagonist.

Infusion of ICI 118551 to block β_2-adrenoceptors produced only a small rise in LVEDP (Table 1). The increase in heart rate, contractility and cardiac output produced by dopexamine HCl were abolished by β_2-adrenoceptor block, with significant attenuation of the falls in total peripheral resistance and LVEDP. The blood pressure and renal vascular resistance responses were, however, unaffected, and there was a small potentiation of the renal blood flow rise at 3×10^{-8} mol kg^{-1} min^{-1}. In the presence of ICI 118551, the DA_1-receptor antagonist, SCH 23390 produced no change in resting parameters but attenuated the reductions in blood pressure and total peripheral resistance caused by dopexamine HCl. In addition, the small fall in LVEDP was abolished. DA_1-receptor block also resulted in attenuation of the renal responses produced by dopexamine HCl. Being an antagonist at DA_2-receptors, domperidone had no effect on its own in the β_2-adrenoceptor- and DA_1-receptor-blocked dogs, but abolished the remaining falls in total peripheral resistance and blood pressure and unmasked weak positive inotropic and chronotropic effects caused by dopexamine HCl. In the three dogs, also given the β_1-adrenoceptor antagonist, atenolol, the weak cardiac stimulation and renal vasodilation produced by

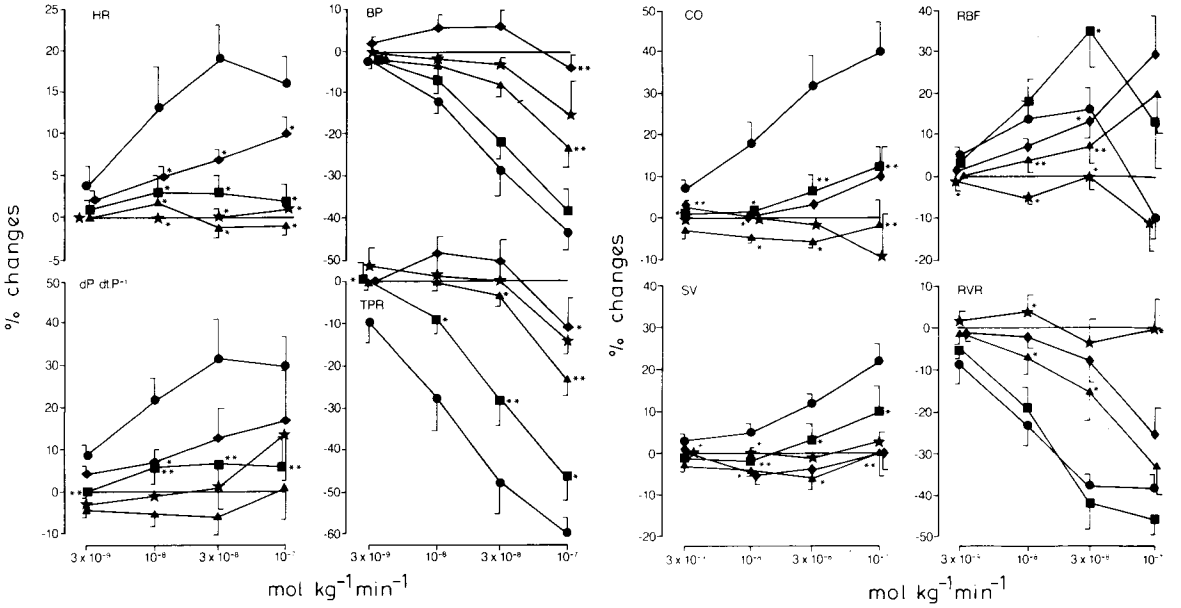

FIG. 1. The effects of selective receptor antagonists on the cardiovascular responses to dopexamine HCl (cumulative 5 min infusions of 3×10^{-9}–10^{-7} mol kg^{-1} min^{-1}, i.v.) in four dogs. Responses are per cent changes (mean ± s.e.) of heart rate (HR), contractility ($dP/dt.P^{-1}$), mean blood pressure (BP) total peripheral resistance (TPR), cardiac output (CO), stroke volume (SV), renal blood flow (RBF) and renal vascular resistance (RVR). The effects shown are under control conditions (●), and then after each successive administration of receptor antagonists given in the order: ICI 118551 (■) to block β_2-adrenoceptors, SCH 23390 (▲) to block DA_1-receptors, domperidone (◆) to block DA_2-receptors and in three dogs, atenolol (★) to block β_1-adrenoceptors. The significance of the effect of each antagonist on the dopexamine HCl-induced response is indicated by * ($P < 0.05$) and ** ($P < 0.01$) using a paired Student's *t*-test to compare the dopexamine HCl responses in the presence of the antagonist with those obtained immediately before the antagonist. Basal values were unchanged after each antagonist except after atenolol (see text).

dopexamine HCl were abolished. However, on its own, atenolol significantly depressed heart rate (136 ± 7 to 110 ± 3 beats min^{-1}), $dP/dt.P^{-1}$ (37 ± 3 to 29 ± 5 s^{-1}), cardiac output (858 ± 85 to 720 ± 76 mL min^{-1}), blood pressure (106 ± 13 to 84 ± 9 mmHg) and renal vascular resistance (1·44 ± 0·14 to 1·21 ± 0·07 mmHg min mL^{-1}).

Ganglion block study (Fig. 2)

Before ganglion blockade, dopexamine HCl reduced blood pressure and LVEDP and increased heart rate and contractility. Renal blood flow was increased by a maximum of 30 ± 12% due to a fall in renal vascular resistance of 49 ± 4% (not shown). Isoprenaline produced slightly smaller reductions in blood pressure and LVEDP but larger rises in $dP/dt.P^{-1}$ and heart rate, and did not change renal blood flow or renal vascular resistance. Sodium nitroprusside also reduced blood pressure (8 ± 2 to 32 ± 4%) and LVEDP to a similar degree but the maximal rises in heart rate (6 ± 2% max) and $dP/dt.P^{-1}$ (29 ± 8% max) were approximately half those produced by dopexamine HCl indicating that cardiovascular reflexes, though weak, were still present. Despite a fall in renal vascular resistance (31 ± 6% max), renal blood flow did not change.

Ganglion block caused a sustained fall in blood pressure (129 ± 8 to 74 ± 4 mmHg), heart rate (160 ± 7 to 116 ± 6 beats min^{-1}), $dP/dt.P^{-1}$ (48 ± 4 to 33 ± 3 s^{-1}), renal blood flow (71 ± 10 to 59 ± 10 mL min^{-1}) and renal vascular resistance (2·10 ± 0·56 to 1·46 ± 0·43 mmHg min mL^{-1}). The increases in inotropy and chronotropy produced by sodium nitroprusside were abolished by ganglion block whilst the depressor response was potentiated (maximum of 42 ± 3% from a control of 32 ± 4%).

The cardiac stimulation produced by low infusions of dopexamine HCl was attenuated by ganglion block, but the effects produced by higher infusion rates were unaffected, or even potentiated. The tachycardia caused by the highest infusion was significantly potentiated in both percentage (28 ± 8 cf. 14 ± 3%) and absolute (31 ± 8 cf. 22 ± 6 beats min^{-1}) terms whilst the inotropic response was hardly affected (51 ± 6 cf. control 44 ± 7% and 15 ± 2 cf. control 18 ± 3 s^{-1}). Ganglion block also

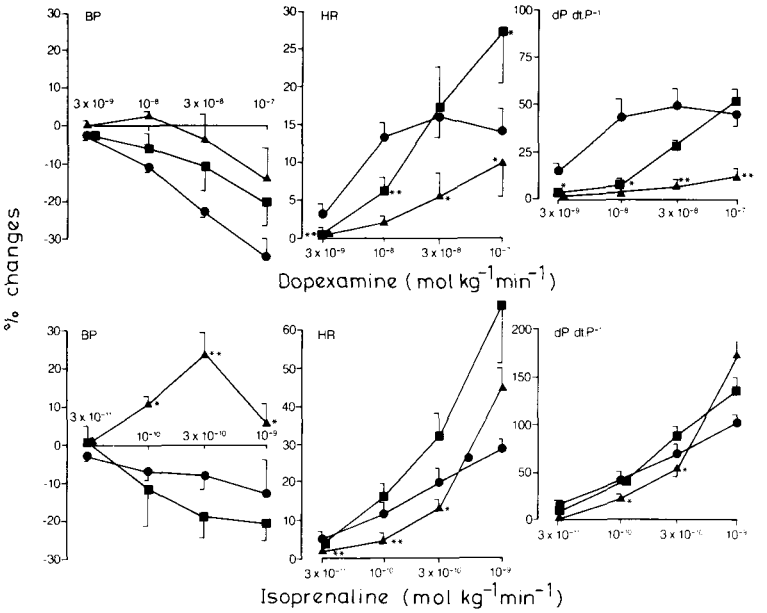

FIG. 2. The effects of dopexamine HCl and isoprenaline on BP, HR and dP/dt.P^{-1} (n = 4) on their own (●), during ganglion block produced by (■) chlorisondamine and methylatropine and after the additional block of β_2-adrenoceptors by ICI 118551 (▲). Values are the mean ± s.e. of per cent changes. The significance of the effect on the dopexamine HCl response of ganglion block alone or with ICI 118551, is indicated by * ($P < 0.05$) and ** ($P < 0.01$) using a paired Student's *t*-test to compare the responses to dopexamine HCl after ganglion block or ICI 118551 administration with those immediately before each intervention. Ganglion block significantly reduced BP, HR and dP/dt.P^{-1} (see text), but no further change was produced by the additional administration of ICI 118551. *Note* the difference in scales for HR and dP/dt.P^{-1} between dopexamine HCl and isoprenaline.

significantly attenuated the dopexamine HCl-induced fall in LVEDP, from 24 ± 7% to 15 ± 3% at the highest dose. However, neither the depressor nor the renal effects of dopexamine HCl were impaired. The cardiac stimulation produced by isoprenaline was unaffected by ganglion block. The depressor response of both agents was also unaffected by ganglion block.

In the presence of ganglion block, ICI 118551, inactive on its own, significantly antagonized the cardiac stimulation and abolished the falls in LVEDP and blood pressure produced by dopexamine HCl without affecting the renal responses. By contrast, the cardiac effects of isoprenaline were only slightly attenuated and the depressor response was reversed.

DISCUSSION

The principal cardiovascular effects of dopexamine HCl in the anaesthetized dog consist of increases in cardiac output, cardiac contractility, heart rate and renal blood flow with a fall in blood pressure. These responses were similar to our previous findings (Brown et al 1985b). However, important new observations were made in the present study regarding the cardiac actions of dopexamine HCl. The elevations in cardiac output and stroke volume and fall in cardiac filling pressure (LVEDP) induced by dopexamine HCl were abolished by ICI 118551, inferring the stimulation of β_2-adrenoceptors. Part of this response would be expected to be reflexly mediated since dopexamine HCl produced vasodilation through stimulation of vascular β_2-adrenoceptors. Prevention of reflex compensation by ganglion block resulted in attenuation of the heart rate and contractility effects of low infusions of dopexamine HCl; the residual cardiac responses were still blocked by ICI 118551. Although the β_1-adrenoceptor is the main cardiac adrenoceptor, confirmed by the resistance of the cardiac stimulant effect of isoprenaline to ICI 118551 (this study and Bilski et al 1983), the existence of cardiac β_2-adrenoceptors has recently been demonstrated by functional and radioligand binding studies in a variety of species (O'Donnell & Wanstall 1979; Hedberg et al 1980; Johansson & Persson 1983; Gustafsson & Borkman 1984), including the dog (Engel et al 1985).

All these findings are clinically relevant since β_2-adrenoceptors also produce positive inotropic

effects in human cardiac tissue (Ginsburg et al 1984; Wilson 1984; Ask et al 1985) and have been identified by radioligand binding with a $\beta_2:\beta_1$ ratio of between 20:80 (Brodde et al 1983; Ginsburg et al 1984) and 35:65 (Heitz et al 1983). Cardiac β_2-adrenoceptors may be of therapeutic importance since they appear less prone than cardiac β_1-adrenoceptors to the down-regulation associated with heart failure (Bristow et al 1984; Brodde et al 1986). Since dopexamine HCl is approximately sixty times more potent than dopamine as a β_2-adrenoceptor agonist, but has similar potency at dopamine receptors (Brown et al 1985a), the cardiac β_2-adrenoceptor-mediated stimulant property of dopexamine HCl may be important during its administration to heart failure patients.

Dopexamine HCl is a weak β_1-adrenoceptor agonist, with an intrinsic activity of only 0·1 (Brown et al 1985a) and this activity could be demonstrated in the anaesthetized dog only after blockade of β_2-adrenoceptors and prevention of the neuro-inhibitory effect of DA_2-receptor stimulation (Hahn 1984).

The renal vasodilation and increase in renal blood flow produced by dopexamine HCl were blocked by SCH 23390, a potent and highly selective DA_1-receptor antagonist (Goldberg et al 1984; Hilditch et al 1984) and this agrees with our earlier finding using bulbocapnine as a DA_1-receptor blocker (Brown et al 1985b). The vascular DA_1-receptor has a highly regional disposition and is particularly abundant in the renal vasculature (Goldberg 1972).

The apparent inability of dopexamine HCl to dilate the renal vasculature after atenolol probably reflects near maximal autoregulation of the kidney secondary to the large reduction in blood pressure and cardiac output induced by atenolol. In one dog, not included in this study, atenolol given in the absence of the other antagonists did not affect the resting renal vascular resistance or the DA_1-receptor renal vasodilator response of both dopexamine HCl and the specific DA_1-receptor stimulant, fenoldopam.

The fall in blood pressure produced by dopexamine HCl in the anaesthetized dog resulted from arterial vasodilation mediated by stimulation of vascular DA_1-receptors and indirectly through stimulation of prejunctional DA_2-receptors. β_2-Adrenoceptor blockade did not however affect the blood pressure fall, since attenuation of the total peripheral resistance reduction due to stimulation of this receptor was counterbalanced by the loss of the β_2-adrenoceptor-mediated rise in cardiac output.

In four experiments, not included in this study, in which the order of administration of the antagonists was different (domperidone, ICI 118551 and then SCH 23390), similar conclusions were reached. Consequently the order of administration of the antagonists did not influence the findings.

The present study extends our earlier observations (Brown et al 1985b). Of particular interest, we believe, is the finding that dopexamine HCl can increase contractility and cardiac output by an action on cardiac β_2-adrenoceptors. This effect was only evident after prevention of the baroreceptor reflex. In clinical use it is expected that the reflex component to afterload reduction will be less prominent since reflex mechanisms will, to a varying extent depending on the severity of the heart failure, have become attenuated (Goldstein et al 1975). By reducing afterload, improving renal blood flow, and increasing cardiac contractility, dopexamine HCl should be useful in the acute treatment of heart failure and other low output states.

These studies support the clinical findings that dopexamine HCl leads to haemodynamic improvement in patients (Dawson et al 1985; Jaski et al 1986) and, moreoever, elucidate the receptor mechanism likely to be responsible for these cardiovascular effects.

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