Br. J. Pharmac. (1985), **85**, 599–608

Dopexamine: a novel agonist at peripheral dopamine receptors and β_2-adrenoceptors

R.A. Brown, J. Dixon, J.B. Farmer, Janet C. Hall, R.G. Humphries, F. Ince, S.E. O'Connor, W.T. Simpson & G.W. Smith[1]

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

1 Dopexamine is an agonist at peripheral dopamine receptors and at β_2-adrenoceptors.

2 Dopexamine has approximately one-third the potency of dopamine in stimulating the vascular DA_1-receptor in the dog, resulting in a fall in renal vascular resistance of 20% at 2.3×10^{-8} mol kg^{-1} (i.a.).

3 Prejunctional DA_2-receptors are also stimulated by dopexamine, resulting in a reduction of neurogenic vasoconstriction in the rabbit isolated ear artery (IC_{50} of 1.15×10^{-6} M) and of neurogenic tachycardia in the cat (ID_{50} of 5.4×10^{-8} mol kg^{-1}, i.v.), with a potency six and four times less respectively than that of dopamine.

4 By contrast, dopexamine is approximately 60 times more potent than dopamine as an agonist at the β_2-adrenoceptor of the guinea-pig isolated tracheal chain, with an EC_{50} of 1.5×10^{-6} M.

5 Both dopexamine and dopamine are weak agonists at the guinea-pig atrial β_1-adrenoceptor over the concentration range 10^{-7} to 10^{-4} M, but dopexamine has an intrinsic activity of only 0.16 relative to dopamine.

6 Dopexamine does not stimulate postjunctional α_1- or α_2-adrenoceptors in the canine isolated saphenous vein, whereas dopamine is an agonist, approximately 120 times less potent than noradrenaline.

7 Unlike dopamine and salbutamol, dopexamine does not cause arrhythmias in the guinea-pig isolated perfused heart at doses of up to 10^{-5} mol, which is a thousand times the minimum cardiostimulant dose.

8 The combination of agonist properties at peripheral dopamine receptors and at β_2-adrenoceptors, with little or no activity at α- and β_1-adrenoceptors gives dopexamine a novel pharmacological profile. This may confer advantages over dopamine in the treatment of acute heart failure.

Introduction

Dopamine displays agonist activity at several peripheral receptors giving rise to cardiovascular and renal effects (Goldberg, 1972). Consequently, it is used to treat acute heart failure (Goldberg, 1972; Goldberg *et al.*, 1977; Rajfer & Goldberg, 1982). The main mechanism involves an increase in inotropy by direct stimulation of cardiac β_1-adrenoceptors and through the release of noradrenaline (Farmer, 1966; Goldberg, 1972). Additional advantages stem from the increase in renal blood flow and natriuresis caused by dopamine receptor stimulation (McDonald *et al.*, 1964; Meyer *et al.*, 1967). However, the usefulness of dopamine in the treatment of acute heart failure is often seriously limited by vasoconstriction (α-adrenoceptor stimulation), excessive tachycardia and arrhythmias (β_1-adrenoceptor stimulation) (Goldberg *et al.*, 1977; Makabali *et al.*, 1982).

Over the last decade, reduction of afterload by means of vasodilator agents has been established as an alternative to the use of inotropic agents in the treatment of heart failure (Chatterjee & Parmley, 1980). One mechanism of reducing afterload is by stimulation of vascular β_2-adrenoceptors and the successful use of both salbutamol (Sharma & Goodwin, 1978) and pirbuterol (Weber *et al.*, 1982) has been reported. It was therefore argued that a drug which stimulated both vascular dopamine receptors and β_2-adrenoceptors, but did not affect α- and β_1-adren-

[1] Author for correspondence.

oceptors, might have advantages over dopamine in the treatment of acute heart failure. Dopexamine dihydrochloride (Figure 1), chosen from a series of N-alkylated dopamine analogues, is believed to meet these criteria.

A preliminary account of the pharmacology of this compound was presented to the British Pharmacological Society (Brown *et al.*, 1984a, b).

Methods

Renal vascular resistance of the dog

Adult beagle dogs (10–15 kg) of either sex, were anaesthetized with pentobarbitone sodium (30 mg kg^{-1}, i.v.) and intubated to allow artificial respiration by a constant stroke volume pump following creation of a pneumothorax. The dogs were prepared for the measurement of renal blood flow (RBF) after a modification of the method of McNay & Goldberg (1966) as briefly described previously (Brown *et al.*, 1983). RBF was recorded from the left renal artery using an electromagnetic flow probe (2.5–3.0 mm Narco Biosystems) and blood pressure (BP) was recorded from a catheter-tipped pressure transducer (Gaeltec, 5F) placed in the descending aorta via the left carotid artery. Renal vascular resistance (RVR) was continuously recorded, as the electronic division of mean BP by mean RBF. A 21G needle, bent through a right angle and inserted distally into the renal artery, allowed agonists and antagonists to be injected directly into the renal artery (i.a.), carried by a constant infusion of saline (0.8 ml min^{-1}). The saline was constantly infused throughout the experiment to keep the needle lumen patent. Phenoxybenzamine (10 mg kg^{-1} over 1–1.5 h, i.v.) was infused to block α-adrenoceptors irreversibly. In some dogs the non-selective β-adrenoceptor antagonist, propranolol (0.5 mg kg^{-1} and 0.25 mg kg^{-1} h^{-1}, i.v.) was given, whilst in other dogs, the selective β_2-adrenoceptor antagonist, ICI 118551 (Bilski *et al.*, 1983) was infused (0.2 mg kg^{-1} h^{-1}, i.a.). Prejunctional DA_2-receptors were selectively blocked either by haloperidol (Shepperson *et al.*, 1982) given each hour (50 μg kg^{-1}, i.v.) or by the specific DA_2-receptor blocker domperidone (Kohli *et al.*, 1983) at a dose of 0.1 mg kg^{-1} (i.v.). Following the establishment of control renal vasodilator responses, the effects of dopexamine and dopamine (i.a.) were re-examined after DA_1-receptor blockade produced by SCH 23390 (Hilditch *et al.*, 1984) at a dose of 10 μg kg^{-1} (i.v.). The doses of dopexamine and dopamine required to reduce RVR by 20% (referred to as ED_{20} doses) were calculated before and after DA_1-receptor blockade.

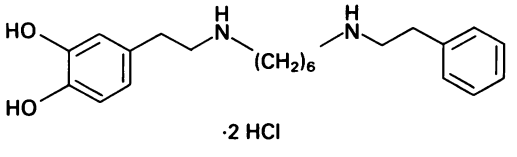

Figure 1 Structural formula of dopexamine dihydrochloride.

Isolated ear artery of the rabbit

Prejunctional dopamine (DA_2)-receptor agonist activity was detected as inhibition of neurogenic vasoconstriction of the rabbit isolated ear artery (Brown & O'Connor, 1981). The central ear artery was dissected free and mounted in an organ bath containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, KCl 5.4, $NaHCO_3$ 25.0, $CaCl_2$ 2.55, $MgSO_4$ 1.12, NaH_2PO_4 0.9, glucose 11.1 and gassed with 5% CO_2 in O_2 at 37°C. The solution, which also perfused the artery at a rate of 3 ml min^{-1}, contained propranolol (10^{-6} M) and cocaine (5×10^{-5} M) to block β-adrenoceptors and neuronal catecholamine uptake respectively. In some experiments cocaine was omitted to establish the importance of neuronal uptake. Neurogenic vasoconstriction, produced by a regular train of field stimulation (1–3 Hz, 0.5 ms pulse width at 70 V for 10 s every 2.5 min) resulted in brief periods of vasoconstriction (increase in perfusion pressure). In each experiment, 6,7-ADTN (2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene) was used as the standard DA_2-receptor agonist. Each agonist was added extraluminally to the bath 1.5 min before stimulation and the dose increased after each response, to give cumulative dose-responses. The effects of the agonists were then examined at least 20 min after pretreatment with the DA_2-receptor antagonists metoclopramide (2.5×10^{-6} M, Hope *et al.*, 1978) or sulpiride (10^{-6} M, Brown & O'Connor, 1981). The effects of dopexamine and 6,7-ADTN were re-examined in the absence of antagonist, in some experiments, to test the reproducibility of the responses.

Cardiac accelerans nerve stimulation in the cat

DA_2-receptor agonist responses were also detected as inhibition of sympathetically mediated tachycardia in the cat (Ilhan & Long, 1975; Hilditch *et al.*, 1984). The cats (2.5–3.9 kg of either sex) were anaesthetized with chloralose (80 mg kg^{-1}, i.v.) following induction by halothane/nitrous oxide and respired artificially by means of a constant stroke volume pump. Catheters were placed in a femoral vein for intravenous injection and in a carotid artery for measurement of BP and heart rate (HR). The chest was opened, the right stellate ganglion crushed and a bipolar electrode

placed on the post-ganglionic nerve. Stimulation of the nerve (1 Hz, 1 ms pulse width and supramaximal voltage of 8–12 V) produced a stable maintained tachycardia. Neuronal uptake was blocked by desmethylimipramine (0.5 mg kg^{-1} and 0.1 mg kg^{-1}, i.v. each hour after the first 2 h) and the cats were pretreated with ICI 118551 (0.2 mg kg^{-1} and 0.2 mg $kg^{-1} h^{-1}$, i.v.) to prevent stimulation of cardiac and vascular β_2-adrenoceptors. The effects of dopexamine, dopamine and 6,7-ADTN (i.v. bolus) were examined before and after administration of the selective DA_2-receptor antagonist, domperidone (5 $\mu g\,kg^{-1}$, i.v.) (Kohli *et al.*, 1983).

The isolated saphenous vein of the dog

The isolated saphenous vein strip of the dog contains post-junctional α_1- and α_2-adrenoceptors, both of which produce contraction when stimulated (Langer & Shepperson, 1981). The lateral saphenous veins were removed from beagles under pentobarbitone anaesthesia. Each vein was cut spirally to give two strips, and suspended under 2 g resting tension in Krebs-Henseleit solution (95% O_2:5% CO_2, 37°C) containing cocaine (2.5×10^{-5} M) and propranolol (10^{-6} M) to block neuronal uptake and β-adrenoceptors respectively. The ability to produce isometric contractures to dopexamine, dopamine and noradrenaline, added cumulatively, was examined. To determine if the induced contractures were due to α-adrenoceptor stimulation, the agonists were examined after the strips had been incubated for a minimum of 15 min with the α-adrenoceptor antagonist phentolamine (10^{-6} M).

Spontaneously beating atria of the guinea-pig

β_1-Adrenoceptor agonist activity was assessed as an increase in spontaneous atrial contraction rate, sensitive to antagonism by propranolol (10^{-6} M). The paired atria were removed from male guinea-pigs and allowed to beat spontaneously under 2 g diastolic tension in Krebs-Henseleit solution (95% O_2:5% CO_2 at 37°C) containing cocaine (5×10^{-5} M) to prevent uptake$_1$. The isometric contractions were recorded by a Grass transducer and used to trigger a cardiotachometer. Cumulative dose-responses were obtained with dopexamine, dopamine, salbutamol or isoprenaline in the absence and then the presence of the β-adrenoceptor antagonist propranolol (10^{-6} M) given 30 min previously to assess the involvement of β_1-adrenoceptors.

Isolated tracheal chain of the guinea-pig

Agonist activity at the β_2-adrenoceptor was assessed in the isolated tracheal chain of the guinea-pig suspended in a 25 ml bath containing Krebs-Henseleit solution (95% O_2:5% CO_2, 37°C). The chains were attached to Grass force transducers to record isometric tension and placed under a 2 g resting tension. The bathing fluid contained atenolol (4×10^{-6} M) and phentolamine (10^{-5} M) to block β_1- and α-adrenoceptors respectively and the inclusion of 17-β-oestradiol (5×10^{-5} M) prevented both neuronal and extraneuronal uptake mechanisms (Salt, 1972). The tissues were repeatedly dosed with a supramaximal dose of salbutamol (10^{-5} M) and then washed several times, resulting in the generation of stable spontaneous tone. Salbutamol was then added cumulatively until maximal relaxation was obtained. Following the regeneration of tone, this procedure was repeated with either dopexamine, isoprenaline or dopamine and maximal relaxation was determined by the addition of the supramaximal dose of salbutamol. The relaxation produced by the test agonist was expressed as a percentage of the salbutamol-induced maximal relaxation. Each agonist was re-examined 30 min after the addition of ICI 118551 (2×10^{-8} M) to block the β_2-adrenoceptors.

Isolated perfused heart of the guinea-pig

Arrhythmogenicity was assessed in isolated perfused guinea-pig hearts. The hearts were perfused after the method of Langendorff (1895), by retrograde perfusion of the aorta at 8 ml min^{-1}, using McEwen's solution the composition of which was (mM): NaCl

Table 1 Potency of dopexamine and dopamine in reducing the renal vascular resistance of the dog

	Dopexamine	*Dopamine*
ED_{20} (mol kg^{-1})	2.3×10^{-8} ($1.7–3.09 \times 10^{-8}$)	0.78×10^{-8} ($0.5–1.2 \times 10^{-8}$)
Equipotent molar ratio	1	0.34

ED_{20} is the dose in mol kg^{-1} (i.a.) reducing renal vascular resistance by 20% and is expressed as the geometric mean (95% C.L.). The equipotent molar ratio (dopexamine = 1) is also shown (n = 16). These dogs were pretreated with propranolol and domperidone.

130, KCl 5.6, $NaHCO_3$ 25, $CaCl_2$ 2.18, NaH_2PO_4 0.92, glucose 11.1 and sucrose 13.2 gassed with 5% CO_2 in O_2 at 37°C. Isometric contractions were recorded by means of a thread attached to the ventricle and this signal was also used to derive heart rate. Perfusion pressure was used as an index of coronary vascular resistance. A 23G needle inserted into the left ventricle apex prevented accumulation of fluid within the ventricle. Dopexamine, dopamine or salbutamol were given by bolus injection into the perfusate via an injection port proximal to the aortic cannula, using volumes of less than 0.3 ml. A dose range of each agonist was selected to give effects on both the rate and force of contraction and arrhythmias were noted as disturbances in the normal regular mechanical rhythm.

In each study, comparison of the potency of dopexamine is made with dopamine and other agonists using equipotent molar ratios, i.e. the ratio of equi-effective molar concentrations or doses. When using antagonists, dose-ratios (DR) are quoted as an estimate of the degree of antagonism. Results are expressed either as geometric mean values with 95% confidence limits (CL) or as the mean ± s.e.mean. Statistical significance was tested by Student's t test (two-tailed).

Drugs used

Dopexamine dihydrochloride and the other amines were dissolved in normal saline using ascorbic acid as the antioxidant. Dopexamine and 6,7-ADTN were synthesized in the Medicinal Chemistry Laboratories of Fisons plc and the other compounds obtained as follows: propranolol, atenolol and ICI 118551 (erythro-(±)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol) (Imperial Chemical Industries), cocaine (May & Baker), sulpiride (Delagrange), domperidone (Janssen), SCH 23390 ([R]-[+]-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine) (Schering Plough), phenoxybenzamine (Smith, Kline & French) and desmethylimipramine (Ciba-Geigy).

The following compounds were purchased: haloperidol (Searle), metoclopramide (Beecham), dopamine hydrochloride (Sigma), noradrenaline acid tartrate (Winthrop), isoprenaline hydrochloride (Pharmax) and salbutamol sulphate (Allen & Hanburys).

Results

Renal vascular resistance of the dog (Table 1 and Figure 2)

In preliminary experiments ($n = 5$), in which haloperidol was used to block the DA_2-receptors, dopexamine was equipotent with dopamine in reducing RVR, but less effective at increasing RBF, due to the larger fall in BP. The RVR ED_{20} for dopexamine was 0.9×10^{-8} mol kg^{-1} (95% CL $0.5-1.5 \times 10^{-8}$ mol kg^{-1}). After infusion of ICI 118551, the renal vasodilatation produced by dopexamine was reduced

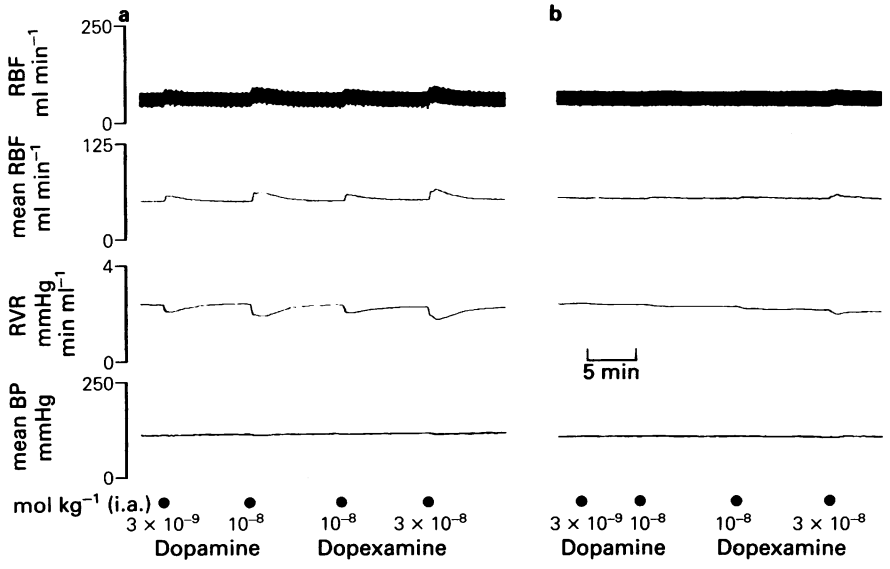

Figure 2 Pentobarbitone anaesthetized dog: effects of dopexamine and dopamine on renal blood flow (RBF), renal vascular resistance (RVR) and mean blood presure (BP) on injection into the renal artery (a) before and (b) after SCH 23390 (10 μg kg^{-1}, i.v.) to block the DA_1-receptors.

Table 2 Potency of dopexamine, dopamine and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN) in reducing neurogenic constriction of isolated ear artery of the rabbit

Compound	n	IC_{50} (M)	*Equipotent molar ratio*
Dopexamine	19	1.15×10^{-6} ($0.85-1.53 \times 10^{-6}$)	1
Dopamine	10	1.91×10^{-7} ($1.26-2.89 \times 10^{-7}$)	0.17
6,7-ADTN	19	1.05×10^{-8} ($0.68-1.62 \times 10^{-8}$)	0.008

The geometric mean IC_{50} value (95% C.L.) is calculated as the concentration reducing the neurogenic vasoconstriction by 50%. The equipotent molar ratio is shown (dopexamine = 1).

slightly so that dopexamine was therefore half as potent as dopamine in reducing RVR.

In other dogs ($n = 16$) pretreated with propranolol and domperidone to block β-adrenoceptors and DA_2-receptors respectively, dopexamine was three times less active than dopamine in reducing RVR (Table 1) and increasing RBF (Figure 2) without affecting BP. The renal vascular responses to dopexamine were antagonized by SCH 23390, producing a DR of 7 whilst the renal vasodilatation produced by dopamine was either antagonized (Figure 2) or reversed to produce vasoconstriction.

Isolated ear artery of the rabbit (Table 2)

In preparations in which neuronal uptake was blocked by cocaine, dopexamine produced a concentration-dependent reduction in neurogenic vasoconstriction over the range of $3 \times 10^{-7}-10^{-5}$M, with an IC_{50} of 1.15×10^{-6}M making it less potent than dopamine and 6,7-ADTN as shown in Table 2. Metoclopramide (2.5×10^{-6}M) antagonized both dopamine and 6,7-ADTN equally (DR of 23) but produced a smaller antagonism of dopexamine (DR of 2, $P<0.05$, $n = 19$). However, in the presence of sulpiride (10^{-6}M), the effects of dopexamine ($n = 11$) and dopamine ($n = 5$) were both equally antagonized (DR of 4) but to a smaller extent than 6,7-ADTN (DR of 23). The small degree of antagonism of dopexamine is considered significant since the omission of antagonist resulted in reproducible dopexamine and 6,7-ADTN responses ($n = 6$). In experiments in which cocaine was omitted, the sensitivity of the preparation to dopexamine remained unaffected but was reduced approximately six fold in the case of dopamine and 6,7-ADTN ($n = 5$).

Cardiac accelerans nerve stimulation in the cat (Table 3)

In five cats, cardiac accelerans nerve stimulation (1 Hz) caused a rise in heart rate of 56 ± 7 beats min^{-1} from a resting value of 152 ± 5 beats min^{-1}. Dopexamine ($10^{-8}-10^{-7}$ mol kg^{-1}, i.v.) produced a dose-related reduction in this tachycardia, but was less potent than either dopamine or 6,7-ADTN (Table 3). After DA_2-receptor block produced by domperidone (5 μg kg^{-1}, i.v.), the inhibitory effects of dopamine and 6,7-ADTN were equally antagonized (DR of about 8), whereas the effect of dopexamine was abolished, being replaced by a small further increase in heart rate.

The isolated saphenous vein of the dog (Figure 3)

Dopexamine ($n = 6$) failed to contract the venous strip at concentrations of up to 10^{-4}M. By contrast, dopamine ($n = 6$) was 120 times less potent than noradrenaline, with an EC_{50} (95% CL) of 1.7×10^{-5}M ($0.1-27 \times 10^{-5}$M), producing a maximal response of 85% that of noradrenaline. Phentolamine abolished the contraction produced by both of these agents.

Table 3 Potency of dopexamine, dopamine and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN) in reducing effects of cardiac accelerans nerve stimulation in the cat

Compound	ID_{20} (mol kg^{-1})	*Equipotent molar ratio*
Dopexamine	5.4×10^{-8} ($3.02-9.55 \times 10^{-8}$)	1
Dopamine	1.2×10^{-8} ($0.74-2.04 \times 10^{-8}$)	0.23
6,7-ADTN	9.6×10^{-10} ($5.4-17 \times 10^{-10}$)	0.018

ID_{20} is the inhibitory dose producing a 20% fall in tachycardia and is expressed as the geometric mean (95% CL; $n = 5$) allowing estimation of the equipotent molar ratio (dopexamine = 1). The post-ganglionic nerve was stimulated continuously at 1 Hz.

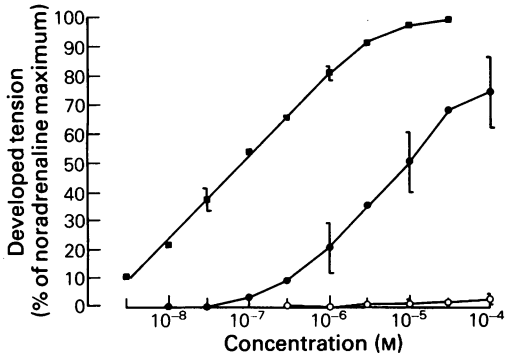

Figure 3 Canine isolated saphenous vein strip: α-adrenoceptor-mediated contractures produced by noradrenaline (■, upper curve, $n = 9$) and dopamine (●, middle curve, $n = 6$) expressed as a percentage of the maximal noradrenaline (mean ± s.e.mean) response, contrasting with the lack of effect with dopexamine (○, bottom curve, $n = 6$).

Spontaneously beating atria of the guinea-pig (Figure 4)

Dopexamine produced a small rise in rate over the concentration range of 3×10^{-7}–10^{-5} M but the maximum rise of 16 ± 3 beats min^{-1} ($n = 11$) was equivalent to an intrinsic activity of only 0.1 relative to isoprenaline (EC_{50} 0.98×10^{-8} M, $n = 6$), which increased rate by a maximum of 165 ± 12 beats min^{-1}. Above 10^{-4} M, dopexamine reduced rate. Dopamine ($n = 8$) and salbutamol ($n = 6$) were also active but were respectively 3500 and 32 times less active than isoprenaline with relative intrinsic activities of 0.60 and 0.67. The tachycardia produced by each agent was antagonized by propranolol (10^{-6} M).

Isolated tracheal chain of the guinea-pig (Figure 5)

Dopexamine was a full agonist, producing a concentration-related relaxation (IC_{50} 1.4×10^{-6} M, $n = 24$) and was 60 times more potent than dopamine, but approximately 32 and 250 times less potent than salbutamol and isoprenaline respectively. The relaxation produced by each of the above agonists was antagonized by ICI 118551 (2×10^{-8} M), producing a DR of approximately 10.

Isolated perfused heart of the guinea-pig

Dopexamine (10^{-8}–10^{-5} mol, $n = 7$) produced a transient increase in systolic tension followed by a prolonged fall with maximal effects reached at 3×10^{-6} mol. Diastolic tension was not affected. Heart rate rose by 17% at 10^{-5} mol and coronary perfusion pressure fell by 10%, but neither effect was dose-dependent above 10^{-7} mol. Even up to 10^{-5} mol, i.e. 1000 times the minimum dose having an effect on the heart, dopexamine did not produce abnormal contractions.

Dopamine (10^{-8}–10^{-5} mol, $n = 6$) also produced a rise then fall in systolic tension, but unike dopexamine, increased diastolic tension. A dose-related tachycardia occurred, reaching a maximum of 52 ± 3% at 3×10^{-6} mol and coronary perfusion pressure showed a dose-dependent rise followed by a prolonged fall. Brief periods of irregular rhythm were observed at doses as low as 3×10^{-8} mol, i.e. three times the minimum effective dose affecting the heart, and their occurrence was dose-dependent. At 10^{-7} mol, more than 50% of the hearts were arrhythmic and all displayed irregular contractions at 3×10^{-7} mol and above, lasting up to 10 min.

Salbutamol ($n = 10$) produced a transient rise then fall in systolic tension between 10^{-9} and 3×10^{-5} mol but without affecting diastolic tension. Heart rate

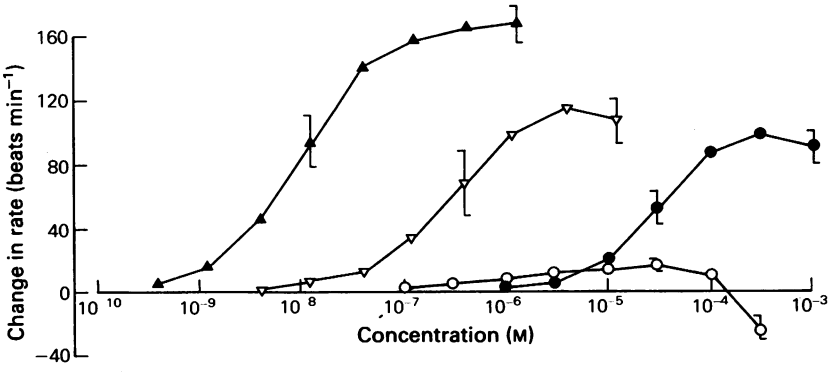

Figure 4 Spontaneously beating atria of the guinea-pig: β_1-adrenoceptor-mediated tachycardia (beats min^{-1}) produced by isoprenaline (▲, $n = 6$), salbutamol (▽, $n = 5$), dopamine (●, $n = 8$) and dopexamine (○, $n = 11$). Values are mean with s.e.mean indicated by bars.

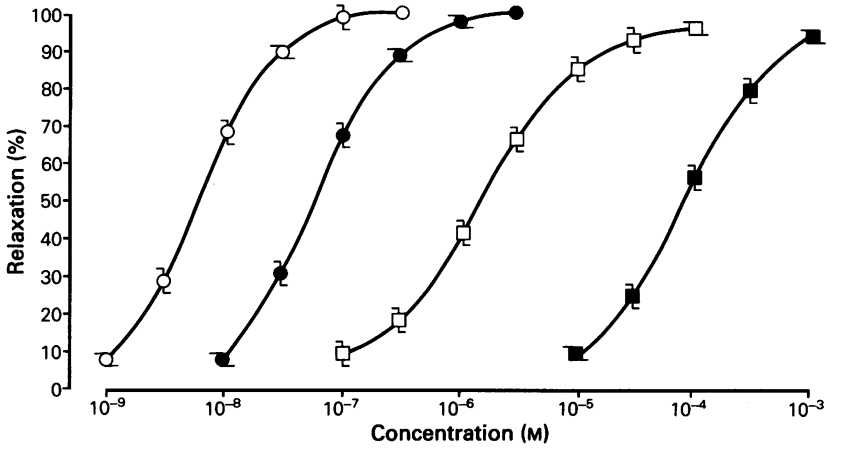

Figure 5 Isolated tracheal chain of the guinea-pig: β_2-adrenoceptor-mediated inhibition of spontaneous contracture (mean with s.e.mean shown by bars), produced by isoprenaline (○, $n = 28$), salbutamol (●, $n = 28$), dopexamine (□, $n = 24$) and dopamine (■, $n = 16$): α- and β_1-adrenoceptors were blocked by phentolamine (10^{-5}M) and atenolol (4×10^{-6}M) respectively.

rose, reaching a maximum of 30 ± 4% at 3×10^{-7} mol accompanied by a dose-related fall in coronary perfusion pressure. Between 10^{-8} mol (ten times the minimum effective dose on the heart) and 10^{-6} mol two of the ten hearts showed brief periods of arrhythmias.

Discussion

Dopexamine produces renal vasodilatation in the canine kidney resulting in a rise in renal blood flow. The mechanism involved is two fold, involving stimulation of both vascular β_2-adrenoceptors and DA_1-receptors since β_2-adrenoceptor block produced by ICI 118551 (Bilski *et al.*, 1983) partially reduced the response leaving a renal vasodilatation sensitive to antagonism by the specific DA_1-receptor antagonist, SCH 23390 (Hilditch *et al.*, 1984). Dopexamine thus differs from dopamine, which is slightly more potent as a DA_1-receptor agonist but does not display β_2-adrenoceptor-mediated renal vasodilatation.

Dopexamine is also active in stimulating the DA_2-receptor found prejunctionally on sympathetic nerve endings. Like other DA_2-receptor agonists such as dopamine and 6,7-ADTN, this property results in a reduction in the effect of sympathetic activity, i.e. inhibition of neurogenic vasoconstriction and sympathetically-mediated tachycardia, with a potency slightly less than that of dopamine. The relative potency of dopamine compared with 6,7-ADTN in this study is consistent with our previous finding in the rabbit ear artery (Brown *et al.*, 1983) and with those of Drew *et al.* (1982) in the cat heart. In the rabbit ear artery, the response to dopexamine was poorly antagonized by the DA_2-receptor antagonist, metoclopramide (Hope *et al.*, 1978), yet was antagonized to the same extent as the response to dopamine by sulpiride, another established antagonist at this receptor (Brown & O'Connor, 1981). The reason for the inconsistency remains unexplained. The degree of antagonism of dopexamine by metoclopramide and sulpiride, although small, was experimentally significant since the response produced by dopexamine in the absence of antagonist was reproducible. The inhibitory effect of dopexamine is unlikely to be due to prejunctional α_2-adrenoceptor stimulation since dopexamine was not active in stimulating postjunctional α_2-adrenoceptors of the canine saphenous vein. In addition, sulpiride does not affect the α_2-adrenoceptor-mediated inhibition caused by clonidine in the rabbit ear artery (Brown & O'Connor, 1981). It is also unlikely that dopexamine blocks postjunctional α-adrenoceptors since at concentrations of up to 3×10^{-6}M dopexamine produces only slight attentuation of the vasconstriction induced by exogenous noradrenaline (unpublished observation).

In the anaesthetized cat, the tachycardia mediated by ansa subclavia stimulation was inhibited by dopexamine, dopamine and 6,7-ADTN, and the inhibition produced by each of these was antagonized by the selective DA_2-receptor antagonist, domperidone (Kohli *et al.*, 1983). The degree of antagonism of the dopexamine response could not be estimated due to the unmasked tachycardia, the mechanism of which was not examined.

The agonist potency of dopexamine was similar to that of dopamine at the peripheral dopamine receptors

but the activities at adrenoceptors are in marked contrast. Dopexamine is considerably more potent than dopamine in stimulating β_2-adrenoceptors and this was evident as part of the mechanism producing renal vasodilatation. By contrast, the weak activity of dopamine at vascular β_2-adrenoceptors can only be demonstrated under certain conditions (McNay & Goldberg, 1966) and is therefore unlikely to be of clinical significance. Dopexamine, unlike dopamine, does not stimulate postjunctional α_1- or α_2-adrenoceptors. Studies in the dog have shown that the vasoconstrictor effect of dopamine is predominantly due to α_2-adrenoceptor stimulation (Shepperson *et al.*, 1982) with α_1-adrenoceptor activity at higher doses (Duval *et al.*, 1984). Dopexamine is therefore unlikely to produce vasoconstriction or pressor effects as reported with dopamine in the clinic (Goldberg *et al.*, 1977; Makabali *et al.*, 1982).

Although dopexamine is active at the same concentrations as dopamine in stimulating cardiac β_1-adrenoceptors, its low intrinsic activity makes it only a very weak agonist in comparison. Dopamine is known to stimulate β_1-adrenoceptors (Goldberg, 1972), but it is a partial agonist (Tsai *et al.*, 1967) as confirmed in this study. This property gives rise to useful inotropic stimulation, but is associated with excessive tachycardia and arrhythmias (Goldberg *et al.*, 1977; Makabali *et al.*, 1982). Tachycardia arises during the administration of β_2-adrenoceptor agonists, principally as a result of the baroreceptor reflex (Alabaster & Henderson, 1982). In the conscious dog the tachycardia produced by dopexamine (Brown *et al.*, 1985) is reflexly mediated since it is almost completely prevented by ganglion block (unpublished observations). However, since baroreceptor reflex tachycardia is depressed in patients with heart failure (Cohn & Franciosa, 1977), dopexamine is unlikely to produce significant tachycardia when used in patients. In the cat, arrhythmias produced by dopamine have been shown to result from β-adrenoceptor stimulation, although the precise mechanism was not elucidated (Katz *et al.*, 1967). The lack of arrhythmogenic activity with dopexamine in this study may therefore be due to the absence of pronounced β_1-adrenoceptor agonist activity.

Both dopexamine and dopamine produced transient positive inotropic effects when given by bolus injection to the isolated perfused heart of the guinea-pig, followed by prolonged secondary depression of force. Similar observations have been made with isoprenaline (Rothaul & Broadley, 1981); the mechanism appears to be an ill-defined effect upon the excitation-contraction coupling (Ohba *et al.*, 1980). By contrast, salbutamol did not demonstrate the secondary phase, possibly due to its relatively longer duration of action.

Many other dopamine receptor agonist analogues have been developed, which also differ pharmacologically from dopamine, such as the selective DA_2-receptor agonists, N,N-dipropyl dopamine (Kohli *et al.*, 1980), 6,7-ADTN (see Woodruff, 1982) and various ergolines (Lokhandwala & Barrett, 1982). Highly selective DA_1-receptor agonist activity is found in some benzazepines, the most potent of which, fenoldopam (SKF 82526), is ten times more potent than dopamine (Hahn *et al.*, 1982). Another N-alkylated dopamine analogue, dobutamine, developed as an inotropic agent (Tuttle & Mills, 1975) is inactive as an agonist at vascular DA_1-receptors (Robie *et al.*, 1974) and at prejunctional DA_2-receptors of the rabbit ear artery (unpublished observations), but is active in stimulating α_1-, β_1- and β_2-adrenoceptors (Maccarone *et al.*, 1984).

The structural requirements for agonist activity at each of the adrenoceptors and the dopamine receptors appear to be separable. None of the dopamine receptor or adrenoceptor agonists described above, however, completely resemble the pharmacological profile of dopexamine which must therefore be considered unique. The great majority of β_2-adrenoceptor agonists are phenylethanolamine derivatives with few exceptions, such as the 1-substituted tetrahydroisoquinolines (Brittain *et al.*, 1981) and dobutamine (Maccarone *et al.*, 1984). The N-phenylethylaminohexyl structure of dopexamine therefore represents another departure from the classic β_2-adrenoceptor agonist structure.

The potential usefulness of dopexamine as a renal vasodilator, leading to increased renal blood flow combined with a reduction of afterload, has been confirmed in the anaesthetized and conscious dog and will be discussed in greater detail in the following paper (Brown *et al.*, 1985).

We appreciate the excellent technical assistance of Mrs L. Kasprzak, Mr G. Williams, Miss A. Young and Mrs M. Wade.

References

ALABASTER, C.T. & HENDERSON, C.G. (1982). The cardiac stimulant effects of isoprenaline in the conscious dog: Studies on the role of β_1- and β_2-adrenoceptors. *Br. J. Pharmac.*, **76**, 251P.

BILSKI, A.J., HALLIDAY, S.E., FITZGERALD, J.D. & WALE, J.L. (1983). The pharmacology of a β_2-selective adrenoceptor antagonist (ICI 118,551). *J. Cardiovasc. Pharmac.*, **5**, 430–437.

BRITTAIN, R.T., DEAN, C.M. & JACK, D. (1981). Sympathomimetic bronchodilator drugs. In *Respiratory Phar-*

macology. International Encyclopaedia of Pharmacology and Therapeutics. ed. Widdicombe, J.G. Oxford: Pergamon Press.

BROWN, R.A. & O'CONNOR, S.E. (1981). Stereoselective antagonism of prejunctional dopamine receptors in the rabbit ear artery by sulpiride. *Br. J. Pharmac.*, **73**, 189P.

BROWN, R.A., HALL, J.C., HUMPHRIES, R.G., O'CONNOR, S.E., SMITH, G.W. & VERITY, A. (1983). Peripheral dopamine receptors: Agonist potencies in different models. *Acta Pharmaceutica Suecica*, Suppl. 2, 195–197.

BROWN, R.A., FARMER, J.B., HALL, J.C., KASPRZAK, L., O'CONNOR, S.E., SMITH, G.W. & YOUNG, A. (1984a). FPL 60278 (Dopexamine): Actions at pre- and postjunctional dopamine receptors and at α- and β-adrenoceptors. *Br. J. Pharmac.*, **81**, 120P.

BROWN, R.A., FARMER, J.B., HALL, J.C., HUMPHRIES, R.G., O'CONNOR, S.E. & SMITH, G.W. (1984b). FPL 60278, a novel agonist at peripheral dopamine receptors and β_2-adrenoceptors: Cardiovascular effects in the dog. *Br. J. Pharmac.*, **81**, 10P.

BROWN, R.A., FARMER, J.B., HALL, J.C., HUMPHRIES, R.G., O'CONNOR, S.E. & SMITH, G.W. (1985). The effects of dopexamine on the cardiovascular system of the dog. *Br. J. Pharmac.*, **85**, 609–619.

COHN, J.N. & FRANCIOSA, J.A. (1977). Vasodilator therapy of cardiac failure (second of two parts). *New Engl. J. Med.*, **297**, 254–258.

CHATTERJEE, K. & PARMLEY, W.W. (1980). Vasodilator therapy for chronic heart failure. *A. Rev. Pharmac. Tox.*, **20**, 475–512.

DREW, G.M., GOWER, A.J., HILDITCH, A. & MARRIOTT, A.S. (1982). A pharmacological comparison of dopamine receptors in the cat heart and those mediating emesis in the dog. *Br. J. Pharmac.*, **75**, 145P.

DUVAL, N., HICKS, P.E. & LANGER, S.Z. (1984). Dopamine stimulates postsynaptic α_2-adrenoceptors in the femoral but not the renal vascular bed of the anaesthetised dog. *Br. J. Pharmac.*, **81**, 150P.

FARMER, J.B. (1966). Indirect sympathomimetic actions of dopamine. *J. Pharm. Pharmac.*, **18**, 261–262.

GOLDBERG, L.I. (1972). Cardovascular and renal actions of dopamine: Potential clinical applications. *Pharmac. Rev.*, **24**, 1–29.

GOLDBERG, L.I., HSIEH, Y.Y. & RESNEKOV, L. (1977). Newer catecholamines for the treatment of heart failure and shock: An update of dopamine and a first look at dobutamine. *Prog. Cardiovasc. Dis.*, **19**, 327–340.

HAHN, R.A., WARDELL, J.R., SARAU, H.M. & RIDLEY, P.T. (1982). Characterisation of the peripheral and central effects of SK & F 82526, a novel dopamine receptor agonist. *J. Pharmac. exp. Ther.*, **223**, 305–313.

HILDITCH, A., DREW, G.M. & NAYLOR, R.J. (1984). SCH 23390 is a very potent and selective antagonist at vascular dopamine receptors. *Eur. J. Pharmac.*, **97**, 333–334.

HOPE, W., McCULLOCH, M.W., RAND, M.J. & STORY, D.F. (1978). Modulation of noradrenergic transmission in the rabbit ear artery by dopamine. *Br. J. Pharmac.*, **64**, 527–537.

ILHAN, M. & LONG, J.P. (1975). Inhibition of the sympathetic nervous system by dopamine. *Archs Int. Pharmacodyn.*, **216**, 4–10.

KATZ, R.L., LORD, C.O. & EAKINS, K.E. (1967). Anaesthetic-dopamine cardiac arrhythmias and their prevention by beta adrenergic blockade. *J. Pharmac. exp. Ther.*, **158**, 40–45.

KOHLI, J.D., WEDER, A.B., GOLDBERG, L.I. & GINOS, J.Z. (1980). Structure activity relationships of N-substituted dopamine derivatives as agonists of the dopamine vascular and other cardiovascular receptors. *J. Pharmac. exp. Ther.*, **213**, 370–374.

KOHLI, J.D., GLOCK, D. & GOLDBERG, L.I. (1983). Selective DA_2 versus DA_1 antagonist activity of domperidone in the periphery. *Eur. J. Pharmac.*, **89**, 137–141.

LANGENDORFF, O. (1895). Untersuchungen am uberlebenden Saugetierherzen. *Pflugers Arch.*, **61**, 291–296.

LANGER, S.Z. & SHEPPERSON, N.B. (1981). Evaluation of the selectivity of M7 for α_1 and α_2-adrenoceptors in vitro. *Br. J. Pharmac.*, **74**, 841P.

LOKHANDWALA, M.F. & BARRETT, R.J. (1982). Review. Cardiovascular dopamine receptors: Physiological, pharmacological and therapeutic implications. *J. Auton. Pharmac.*, **3**, 189–215.

MACCARONE, C., MALTA, E. & RAPER, C. (1984). β-Adrenoceptor selectivity of dobutamine: *In vivo* and *in vitro* studies. *J. cardiovasc. Pharmac.*, **6**, 132–141.

MAKABALI, C., WEIL, M.H. & HENNING, R.J. (1982). Dobutamine and other sympathomimetic drugs for the treatment of low cardiac output failure. *Sem. Anaesth.*, **1**, 63–69.

MEYER, M.B., McNAY, J.L. & GOLDBERG, L.I. (1967). Effects of dopamine on renal function and haemodynamics in the dog. *J. Pharmac. exp. Ther.*, **156**, 186–192.

McDONALD, R.H., GOLDBERG, L.I., McNAY, J.L. & TUTTLE, E.P. (1964). Effects of dopamine in man: Augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. *J. clin. Invest.*, **43**, 1116–1124.

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

OHBA, M., SAKAMOTO, Y. & TOMITA, T. (1980). Negative inotropic effect of β-blockers in the guinea-pig atrium after pre-incubation with isoprenaline. *Eur. J. Pharmac.*, **65**, 257–266.

RAJFER, S.I. & GOLDBERG, L.I. (1982). Dopamine in the treatment of heart failure. *Eur. Heart J.*, **3** (Suppl. D), 103–106.

ROBIE, N.W., NUTTER, D.O., MOODY, C. & McNAY, J.L. (1974). *In vivo* analysis of adrenergic receptor activity of dobutamine. *Circulation Res.*, **34**, 663–671.

ROTHAUL, A.L. & BROADLEY, K.J. (1981). Use of hexobendine to examine whether the coronary vasodilator metabolite released from guinea-pig isolated hearts is adenosine. *Cardiovasc. Res.*, **15**, 599–610.

SALT, P.J. (1972). Inhibition of noradrenaline uptake 2 in the isolated rat heart by steroids, clonidine and methoxylated phenylethylamines. *Eur. J. Pharmac.*, **20**, 329–340.

SHARMA, B. & GOODWIN, J.F. (1978). Beneficial effect of salbutamol on cardiac function in severe congestive cardiomyopathy. *Circulation Res.*, **58**, 449–460.

SHEPPERSON, N.B., DUVAL, N. & LANGER, S.Z. (1982). Dopamine decreases mesenteric blood flow in the anaesthetised dog through the stimulation of postsynaptic α_2-adrenoceptors. *Eur. J. Pharmac.*, **81**, 627–635.

SHEPPERSON, N.B., DUVAL, N., MASSINGHAM, R. & LAN-

GER, S.Z. (1982). Differential blocking effects of several dopamine receptor antagonists for peripheral pre- and post-synaptic dopamine receptors in the anaesthetised dog. *J. Pharmac. exp. Ther.*, **221**, 753–761.

TSAI, T.H., LANGER, S.Z. & TRENDELENBURG, U. (1967). Effects of dopamine and α-methyl-dopamine on smooth muscle and on the cardiac pacemaker. *J. Pharmac exp. Ther.*, **156**, 310–324.

TUTTLE, R.R. & MILLS, J. (1975). Dobutamine: Development of a new catecholamine to selectively increase cardiac contractility. *Circulation Res.*, **36**, 185–196.

WEBER, K.T., ANDREWS, V., JANICKI, J.S., KILOFF, M. & REICHEK, N. (1982). Pirbuterol, an oral beta-adrenergic receptor agonist, in the treatment of chronic heart failure. *Circulation.*, **66**, 1262–1266.

WOODRUFF, G.N. (1982). ADTN – A potent dopamine receptor agonist. *Trends Pharmac. Sci.*, **3**, 59–61.

(Received November 7, 1984.
Revised January 29, 1985.
Accepted February 22, 1985.)