FPL 63012AR: a potent D₁-receptor agonist

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- 1 FPL 63012AR is a D₁-receptor agonist in the dog kidney, 10 times as potent as dopamine, reducing renal vascular resistance by 20% with an intra-arterial dose of 0.42 nmol kg⁻¹.
- 2 No prejunctional inhibitory D₂-receptor agonist activity was detected in either the isolated ear artery of the rabbit or in the conscious dog as D₂-receptor-mediated emesis.
- 3 Unlike dopamine, FPL 63012AR had no significant agonist activity at α_1 -, α_2 -, β_1 - or β_2 -adrenoceptors.
- 4 FPL 63012AR is a potent inhibitor of [³H]-noradrenaline uptake (Uptake₁) into brain synaptosomes, with an IC₅₀ of 29.5 nM, i.e. 9.2 times more potent than dopamine.
- 5 The ability to block Uptake₁ in the anaesthetized dog was confirmed by inhibition of the tyramine-induced pressor and inotropic responses.
- 6 Intravenous infusion of FPL 63012AR in anaesthetized and conscious dogs (0.3 to 3 nmol kg⁻¹ min⁻¹) reduced vascular resistance and increased blood flow to the kidney which was accompanied by hypotension and tachycardia.
- 7 It is concluded that FPL 63012AR is an example of a novel class of potent agonists at the D₁-receptor. Such compounds may have the potential for use clinically in improving renal perfusion and reducing afterload.

Introduction

Peripheral dopamine receptors have been subclassified into prejunctional D₂- and postjunctional D₁-receptors (previously DA₂ and DA₁ respectively). Stimulation of the latter leads to clinically useful actions, namely increased renal blood flow, natriuresis and diuresis, and elevation of blood flow to other vascular beds containing D₁-receptors (Goldberg & Kohli, 1983; Lokhandwala, 1987). However, dopamine lacks selectivity, stimulating both D-receptor subtypes as well as α - and β -adrenoceptors and this limits the clinical usefulness of dopamine (Goldberg *et al.*, 1977; Makabali *et al.*, 1982). During our investigations aimed at improving the receptor profile of dopamine we have discovered and developed a D₁-receptor agonist (dopexamine hydrochloride) which lacks agonist activity at both α - and β_1 -adrenoceptors but is a more potent β_2 -adrenoceptor agonist than dopamine (Brown *et al.*, 1985a). Subsequently a group of compounds was discovered in a series of chemical analogues related to dopexamine in which potent D₁-receptor agonist resided but with no agonist activity at the D₂-receptor or at the above receptors. In this study the activities of one of these compounds, FPL 63012AR (Figure 1) is described.

Methods

The biological properties of FPL 63012AR were examined in several preparations to characterize its pharmacological and cardiovascular properties. Since most of these methods have been fully described before, only brief descriptions are given here.

D₁-receptor

D₁-receptor stimulation was studied as renal vasodilatation in pentobarbitone-anaesthetized beagle dogs (10.0–15.2 kg) of either sex (Brown *et al.*, 1985a). Left renal blood flow (RBF, electromagnetic flow probe) and arterial blood pressure (BP), were used to derive electronically renal vascular resistance

(RVR). A 23 G needle inserted into the renal artery allowed injection of drugs into the renal vascular bed and selective antagonists were given (i.v.) to block the α - (phenoxybenzamine, 10 mg kg⁻¹) and β - (propranolol, 0.5 mg kg⁻¹ and 0.25 mg kg⁻¹ h⁻¹) adrenoceptors, and D₂-receptors (domperidone, 0.1 mg kg⁻¹). Dopamine, the drug of comparison, and FPL 63012AR were administered by bolus administration into the renal artery before and after SCH 23390 (10 μ g kg⁻¹ with 5 μ g kg⁻¹ h⁻¹, i.v.) to block D₁-receptors.

D₂-receptor

Stimulation of prejunctional D₂-receptors reduces neurogenic vasoconstriction in the rabbit isolated ear artery, caused by field-stimulation (3 Hz, 10 s duration, every 2.5 min), by inhibiting noradrenaline release. FPL 63012AR was compared with the selective D₂-receptor agonist 6,7-ADTN (Brown *et al.*, 1985a). In some experiments, the stimulator was switched-off in the presence of the highest inhibitory concentrations of FPL 63012AR and 6,7-ADTN studied, to examine the effect of either drug on the vasoconstriction produced by a submaximal concentration of exogenous noradrenaline (60 or 100 nM). The inhibitory effect of both drugs on the neurogenic vasoconstriction was re-examined 20 min after addition of the selective D₂-receptor antagonist metoclopramide (2.5 μ M).

Figure 1 Chemical structure of FPL 63012AR (dihydrochloride salt, molecular weight 549.6).

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α -Adrenoceptors

Agonist activity at postjunctional α_1 - and α_2 -adrenoceptors was studied as contracture of the canine isolated saphenous vein, prepared as previously described (Brown *et al.*, 1985a) with the exception that they were cut into 3 to 5 mm long tubes. Cumulative doses of FPL 63012AR were examined after recovery from noradrenaline.

β_1 -Adrenoceptor

Spontaneously beating guinea-pig atria Increases in the rate of contraction of guinea-pig isolated right atria evoked by FPL 63012AR were expressed as a percentage of the response produced by a maximally effective concentration ($0.3 \mu\text{M}$) of isoprenaline (Brown *et al.*, 1985a). Blockade of the response by propranolol ($1 \mu\text{M}$) was used to confirm activity at the β_1 -adrenoceptor.

Paced guinea-pig papillary muscle The ability of FPL 63012AR to increase the isometric developed tension was examined in paced isolated left papillary muscles of guinea-pig (1 Hz, 0.5 ms, supramaximal voltage) bathed in Krebs-Henseleit at 37°C (95% O_2 : 5% CO_2) under 1 g resting tension.

β_2 -Adrenoceptor

Activity at this receptor was examined as relaxation of spontaneously contracted guinea-pig isolated tracheal chains (Brown *et al.*, 1985a). Cumulatively added FPL 63012AR was examined following characterization with salbutamol.

Uptake₁ block

Rabbit brain synaptosomes The ability to block the Na^+ -dependent uptake of [^3H]-noradrenaline was examined *in vitro* in rabbit cerebral cortex synaptosomes prepared either as crude or as purified fractions (Mitchell *et al.*, 1987).

Tyramine inhibition in the dog Confirmation of Uptake₁ blockade in 4 anaesthetized dogs was determined as inhibition of the pressor and positive inotropic actions of bolus tyramine injection ($60 \mu\text{g kg}^{-1}$, i.v.) during i.v. infusion of FPL 63012AR ($10^{-9} \text{ mol kg}^{-1} \text{ min}^{-1}$) as previously described (Smith & Naya, 1987).

Cardiovascular actions

Anaesthetized dog Four pentobarbitone-anaesthetized male Beagle dogs (10–15 kg) were surgically prepared as described by Brown *et al.* (1985b). Left ventricular contractility ($dP/dt.P^{-1}$) was calculated by use of a pressure-sensitive catheter (Gaeltec 5F) placed in the left ventricle. BP, HR, RBF and RVR were measured as described above. FPL 63012AR was administered as discontinuous 30 min i.v. infusions of 3×10^{-10} , 10^{-9} and $3 \times 10^{-9} \text{ mol kg}^{-1} \text{ min}^{-1}$ (0.17, 0.55 and $1.65 \mu\text{g kg}^{-1} \text{ min}^{-1}$) with 30 min between infusions to allow recovery. A 10 min infusion of the highest rate was repeated 15 min after administration of the selective D_1 -receptor antagonist SCH 23390 ($10 \mu\text{g kg}^{-1}$ and $30 \mu\text{g kg}^{-1} \text{ h}^{-1}$). Lead II ECG was also monitored.

Conscious dog Under aseptic conditions, 5 male beagle dogs (11.6–13.7 kg) were catheterized with Tygon tubing placed in a femoral artery (BP) and in a femoral vein (drug administration). The catheters were exteriorized between the scapulae by means of titanium skin buttons with teflon valves (Omnifit) as previously described (O'Connor *et al.*, 1982). In 3 of these dogs, left renal artery Doppler flow probes (Crystal Biotech, USA) were implanted through a flank retroperitoneal incision to measure RBF. The dogs were allowed a minimum of 2 weeks recovery prior to dosing studies. FPL 63012AR

was given as 10 min stepwise infusions of 3×10^{-10} to $10^{-7} \text{ mol kg}^{-1} \text{ min}^{-1}$.

Drugs

FPL 63012AR prepared as the dihydrochloride salt and 6,7-ADTN (2-amino-6,7-dihydroxy 1,2,3,4-tetrahydro-naphthalene hydrobromide) were made in the Department of Medicinal Chemistry of Fisons plc and dissolved in ascorbic isotonic saline (0.02% w/v). SCH 23390 ((R)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-benzazepine-7-ol) (Schering Plough), domperidone (Janssen), cocaine hydrochloride (May & Baker), (–)-propranolol hydrochloride (ICI) and phenoxybenzamine (SK & F) were gifts. Other drugs obtained from commercial sources were: sodium pentobarbitone (May & Baker), metoclopramide hydrochloride (Beecham), dopamine hydrochloride (Sigma), noradrenaline hydrogen tartrate (Winthrop), (–)-isoprenaline hydrochloride (Pharmax), phentolamine mesylate (Ciba-Geigy) and (–)-salbutamol sulphate (Allen & Hanbury).

Statistical analysis

Results are expressed either in terms of mean $\pm$ s.e. mean or of geometric mean with 95% confidence limits (95% CL). Student's paired *t* test was used to assess statistical significance ($P < 0.05$).

Results

D_1 -receptor

The basal RVR and RBF values in the 13 dogs were $1.57 \pm 0.12 \text{ mmHg min ml}^{-1}$ and $71 \pm 7 \text{ ml min}^{-1}$ respectively. Both FPL 63012AR and dopamine, given as arterial bolus injections, produced dose-related renal vasodilatation resulting in increased RBF as shown in Figure 2. The geometric mean dose reducing RVR by 20%, the EC_{20} (95% CL), was $0.42 \text{ nmol kg}^{-1}$ (0.31–0.55, $n = 13$) for FPL 63012AR and $3.63 \text{ nmol kg}^{-1}$ (2.51–5.25, $n = 13$) for dopamine. FPL 63012AR was therefore 10 (9–12) times more potent than dopamine. The renal vasodilatation produced by both drugs was antagonized to the same degree by SCH 23390 ($10 \mu\text{g kg}^{-1}$ with $5 \mu\text{g kg}^{-1} \text{ min}^{-1}$, i.v.) producing rightward

Figure 2 Anaesthetized dog: percentage increase in renal blood flow (RBF) and fall in renal vascular resistance (RVR) in response to intra-arterial injection of FPL 63012AR (●) and dopamine (■). Values are the mean (13 dogs) with s.e. mean shown by vertical bars.

shifts of 19.4 ± 2.4 and 22.2 ± 3.6 fold respectively. These results confirmed that FPL 63012AR, like dopamine, owes its renal action to D₁-receptor stimulation.

D₂-receptor

FPL 63012AR and 6,7-ADTN both produced concentration-dependent inhibition of the neurogenic vasoconstriction of the field-stimulated rabbit ear artery as shown in Table 1. FPL 63012AR was 140 times weaker than 6,7-ADTN in inhibiting the vasoconstriction but its response was not prevented by metoclopramide, indicating that its action does not involve stimulation of D₂-receptors. By contrast, the inhibitory response of 6, 7-ADTN was shifted 38 fold to the right (Table 1). In 6 experiments, in which the effect of the maximum inhibitory concentration of either drug was examined against a submaximal concentration of noradrenaline (60 or 100 nM), FPL 63012AR produced $83.3 \pm 7.1\%$ inhibition of the exogenous noradrenaline contracture at a concentration of 3 and 10 μM which inhibited the neurogenic contraction to a similar degree ($73.7 \pm 5.7\%$). By contrast, 6,7-ADTN (0.1 μM) did not significantly affect the response to noradrenaline ($14.8 \pm 6.3\%$, NS) despite reducing the neurogenic response by $87.0 \pm 4.9\%$.

α -Adrenoceptors

Noradrenaline caused a concentration-dependent contracture (EC_{50} of 80 nM, $n = 7$) of canine isolated saphenous vein tubes. By contrast, FPL 63012AR was inactive at up to 10 μM .

β_1 -Adrenoceptor

Spontaneously beating guinea-pig atria A maximally effective concentration of isoprenaline (0.3 μM) increased rate by 110 ± 10 beats min^{-1} from a resting value of 182 ± 5 beats min^{-1} . FPL 63012AR produced an increase no greater than 10% of the maximal increase in rate caused by isoprenaline at concentrations of 0.1 to 1 μM but reduced rate at a concentration above 10 μM ($24.6 \pm 4.3\%$ at 30 μM , $n = 7$). Propranolol (1 μM) abolished the small rise but did not prevent the fall in rate ($14.9 \pm 4.3\%$ at 30 μM , $n = 4$) produced by FPL 63012AR.

Paced guinea-pig papillary muscle Isoprenaline (10 nM–0.3 μM) produced a concentration-related increase in tension (EC_{50} 30 nM, $n = 6$) but FPL 63012AR was inactive at up to 100 μM .

β_2 -Adrenoceptor

Salbutamol (10 nM–3 μM) caused a concentration-dependent relaxation (EC_{50} of 61 nM, $n = 9$) of tracheal chains under spontaneous tone. FPL 63012AR was virtually inactive in this preparation reaching only $9.8 \pm 2.4\%$ of the maximum salbutamol response at 100 μM .

Uptake₁ block

Rabbit brain synaptosomes FPL 63012AR inhibited the sequestration of [³H]-noradrenaline into rabbit brain syn-

Table 1 Rabbit ear artery: inhibition of sympathetically mediated vasoconstriction and antagonism by metoclopramide 2.5 μM

Drug	IC ₅₀ (μM)	Metoclopramide dose-ratio
FPL 63012AR	1.65 (1.12–2.42)	1.3 (0.8–2.0)
6,7-ADTN	0.0117 (0.0083–0.0167)	38 (28–52)

Values are the geometric mean (95% CL) of 16 experiments.

Table 2 Anaesthetized dog: prevention of the tyramine-induced responses by FPL 63012AR infusion

Treatment		HR	BP	dP/dt.P ⁻¹
Control	a	150 $\pm$ 7	135 $\pm$ 12	48 $\pm$ 3
	b	-12 $\pm$ 4*	+12 $\pm$ 2*	+48 $\pm$ 5*
FPL	a	149 $\pm$ 7	127 $\pm$ 12	51 $\pm$ 2
	b	0 $\pm$ 3	+5 $\pm$ 2	+9 $\pm$ 9

Response to i.v. bolus tyramine (60 $\mu\text{g kg}^{-1}$) as mean $\pm$ s.e.mean in 4 anaesthetized dogs before (control) and during infusion of 10^{-9} mol kg^{-1} min⁻¹ FPL 63012AR (FPL). Basal absolute (a) values are shown for HR (beats min⁻¹), BP (mmHg) and dP/dt.P⁻¹ (s⁻¹) as well as percentage changes over baseline (b) produced by tyramine. * indicates significant changes (Student's two tailed *t* test, *P* < 0.05).

aptosomes, with a geometric mean IC₅₀ of 29.5 nM (20.4–42.6, $n = 12$). The results were similar in the crude and the purified fractions.

Tyramine inhibition in the dog Intravenous infusion of FPL 63012AR (10^{-9} mol kg^{-1} min⁻¹) abolished the tyramine-induced pressor, positive inotropic effects and reflex bradycardia (Table 2).

Cardiovascular actions

Anaesthetized dog Basal cardiovascular parameters at the start of the experiment are shown in Table 3. Intravenous infusion of FPL 63012AR at 3×10^{-10} to 3×10^{-9} mol kg^{-1} min⁻¹ resulted in rapid cardiovascular changes which were quick to recover (within 10 min) following termination of the infusion (Figure 3). RBF was elevated, despite a fall in BP, due to renal vasodilatation, as shown by the fall in calculated RVR. The fall in diastolic BP was slightly greater than the systolic fall e.g. 16 ± 3 mmHg compared with 10 ± 2 mmHg at the highest infusion rate and was accompanied by small, though dose-related, increases in HR (maximum 18 ± 2 beats min⁻¹, $12 \pm 1\%$) and contractility (maximum 8.3 ± 2.0 s⁻¹, $16 \pm 4\%$). No change was seen in the ECG. The effect of the highest infusion of FPL 63012AR was completely blocked during infusion of the selective D₁-receptor antagonist SCH 23390 (10 $\mu\text{g kg}^{-1}$ with 30 $\mu\text{g kg}^{-1}$ h⁻¹, i.v.) as shown in Table 4.

Conscious dog Prior to infusing FPL 63012AR into the conscious dogs, the basal parameters were mean BP 96 ± 7 mmHg, HR 73 ± 9 beats min⁻¹, RBF 3.07 ± 0.60 kHz and RVR 31.5 ± 5.4 mmHg kHz⁻¹. Following infusion of isotonic saline, which was ineffective in changing these parameters, stepwise infusion of FPL 63012AR produced a dose-related fall in RVR and a rise in RBF with maximal effects at approximately 10^{-8} mol kg^{-1} min⁻¹ of $46 \pm 9\%$ and $76 \pm 17\%$ respectively in the 3 dogs examined (Figure 4). At and below this infusion rate, the HR response was variable, one dog showing a small bradycardia and there was no significant change in BP. At the higher infusion rates, tachycardia occurred in each dog with a small fall in BP. The compound was well tolerated and no behavioural changes or emesis were seen.

Table 3 Anaesthetized dog: basal parameters at start of experiment

RBF (ml min ⁻¹)	RVR (mmHg min ml ⁻¹)	BP (mmHg)	HR (bpm)	dP/dt.P ⁻¹ (s ⁻¹)
106 $\pm$ 15	1.18 $\pm$ 0.33	126 $\pm$ 7	144 $\pm$ 4	49 $\pm$ 3

Values are the mean $\pm$ s.e.mean of 4 dogs prior to FPL 63012AR infusion.

Figure 3 Anaesthetized dog: effect of 30 min intravenous infusions of FPL 63012AR at 3×10^{-10} (●), 10^{-9} (▲) and 3×10^{-9} (■) $\text{mol kg}^{-1} \text{min}^{-1}$ ($0.17\text{--}1.65 \mu\text{g kg}^{-1} \text{min}^{-1}$), as indicated by the horizontal bar, on renal blood flow (RBF) and vascular resistance (RVR), heart rate (HR), contractility ($dP/dt.P^{-1}$) and mean blood pressure (BP). Values are percentage changes, (mean with s.e.mean shown by vertical bars) in 4 dogs. * and ** indicate $P < 0.05$ and 0.01 respectively (Student's paired t test).

Table 4 Anaesthetized dog: antagonism of FPL 63012AR by SCH 23390

Treatment		mBP	HR	dP/dt.P ⁻¹	RBF	RVR
Control	a	125 ± 8	156 ± 7	53 ± 3	110 ± 17	1.09 ± 0.23
	b	-12 ± 3*	+5 ± 2	+14 ± 4*	+20 ± 2*	-26 ± 3*
SCH	a	110 ± 10	146 ± 7	48 ± 5	94 ± 14	1.12 ± 0.24
	b	-1 ± 2	-1 ± 1	+3 ± 3	-4 ± 1*	+2 ± 3

Values are mean ± s.e.mean ($n = 4$) of basal absolute values (a) for parameters as described in Table 2 as well as for RBF (ml min^{-1}) and RVR (mmHg min ml^{-1}) and percentage changes (b) induced by FPL 63012AR infusion ($3 \times 10^{-9} \text{ mol kg}^{-1} \text{min}^{-1}$, after 10 min) both before (control) and during infusion of SCH 23390 (SCH). *indicates significant changes (Student's two-tailed t test, $P < 0.05$).

Figure 4 Conscious dog: effect of stepwise 10 min infusions of FPL 63012AR of 3×10^{-10} to $10^{-7} \text{ mol kg}^{-1} \text{min}^{-1}$ ($0.17\text{--}55 \mu\text{g kg}^{-1} \text{min}^{-1}$) on blood pressure (BP) (○) and heart rate (HR) (▲) in 5 dogs and on renal blood flow (RBF) (●) and renal vascular resistance (RVR) (■) in 3 of these dogs. Values are percentage changes, mean with s.e.mean shown by vertical bars. * and ** indicate $P < 0.05$ and 0.01 respectively (Student's paired t test).

Discussion

The action of FPL 63012AR in the dog kidney is clearly due to the stimulation of vascular D_1 -receptors, since it is abolished by the selective antagonist SCH 23390 (Goldberg *et al.*, 1984). Moreover it is 10 times more potent than dopamine. FPL 63012AR has been shown to be an agonist at the central D_1 dopamine receptor, approximately 11.4 times as potent as dopamine in the D384 human astrocyte cell line (E. Wells, personal communication).

No agonist activity could be detected at the prejunctional D_2 -receptor of the field-stimulated perfused ear artery since metoclopramide was ineffective against the inhibitory action of FPL 63012AR. The lack of stimulant activity at the D_2 -receptor (or more correctly the central D_2 -receptor, which is regarded as similar in character) was confirmed in the conscious dog by the absence of emesis at infusion rates 30 to 300 times greater than that required to produce D_1 -receptor mediated renal vasodilatation.

FPL 63012AR was also inactive in stimulating postjunctional α_1 - and α_2 -adrenoceptors of the dog saphenous vein and therefore should be devoid of vasoconstrictor activity. Although a small degree of agonist activity was seen at the

atrial β_1 -adrenoceptor, this could not be confirmed in ventricular muscle and the reason for this disparity is unclear. Above 10 μ M, FPL 63012AR depressed the sino-atrial node by an unknown mechanism. In addition only a small degree of β_2 -adrenoceptor agonist activity could be detected, with an intrinsic activity of less than 0.1. In the anaesthetized dog, only weak cardiac stimulation was observed and since this was abolished by SCH 23390, this implies that the cardiac stimulation was a consequence of the baroreflex secondary to D₁-receptor stimulation and not due to the direct stimulation of either cardiac β_1 - or β_2 -adrenoceptors.

In addition to showing selective agonism for the D₁-receptor, FPL 63012AR is also a potent blocker of noradrenaline uptake (Uptake₁) into rabbit brain synaptosomes. Using previously published data obtained from this preparation (Mitchell *et al.*, 1987), FPL 63012AR is calculated to be 9.2 times as potent as dopamine (IC₅₀ 270 nM) and 3.7 times more potent than cocaine (IC₅₀ 108 nM). Blockade of Uptake₁ by FPL 63012AR was confirmed in the anaesthetized dog by the abolition of the response to tyramine. The actions of tyramine, an indirect sympathomimetic, rely on its ability to enter the sympathetic neurone via Uptake₁ to displace noradrenaline. Dopexamine hydrochloride, which is of similar potency to FPL 63012AR as an Uptake₁ blocker (Mitchell *et al.*, 1987), also prevented the action of tyramine in the anaesthetized dog and in addition potentiated the cardiac effects of exogenous noradrenaline and sympathetic nerve stimulation in the dog (Smith & Naya, 1987; Bass *et al.*, 1987).

The weak inhibitory action of FPL 63012AR against neurogenic vasoconstriction in the rabbit ear artery was due to prevention of the postjunctional action of noradrenaline since the effect of exogenously applied noradrenaline was reduced to the same degree as the neurogenic vasoconstriction. This property was not apparent in the anaesthetized dog at the infusion rates examined, since the cardiovascular actions of FPL 63012AR were completely prevented by SCH 23390 and therefore solely attributable to D₁-receptor stimulation. Inhibition of the postjunctional actions of noradrenaline may well, however, occur at higher infusion rates than are necessary to stimulate D₁-receptors.

We have previously confirmed the moderately potent actions of dopamine *in vitro* at vascular postjunctional α - and cardiac β_1 -adrenoceptors (Brown *et al.*, 1985a), properties which limit the clinical usefulness of dopamine by producing intense vasoconstriction, arrhythmias and tachycardia. Moreover the D₂-receptor-stimulant action of dopamine can lead to nausea and emesis (Goldberg *et al.*, 1977; Makabali *et al.*, 1982). The lack of these properties in a more potent D₁-receptor agonist as displayed by FPL 63012AR potentially represents a clinical advantage over dopamine.

Compared with dopexamine hydrochloride (Brown *et al.*, 1985a) the introduction of the 2-[3-hydroxyphenyl]ethyl group in FPL 63012AR leads to a dramatic alteration in the pharmacological profile by way of suppression of agonist activity at both the β_2 -adrenoceptor and D₂-receptor with a 30 fold increase in the D₁-receptor potency.

Fenoldopam, is the most potent and selective D₁-receptor agonist of a series of benzazepines which are chemically dissimilar to FPL 63012AR. It is reported to be approximately 10 times more potent than dopamine (Hahn *et al.*, 1982) and therefore of similar potency to FPL 63012AR. It possesses a similar pharmacological profile to FPL 63012AR in that it also prevents the postjunctional effect of noradrenaline, by antagonizing α_2 -adrenoceptors (Ohlstein *et al.*, 1985) but this is only seen at intravenous doses exceeding those necessary for D₁-receptor stimulation (Goldberg *et al.*, 1986).

There is now good evidence that endogenous renal dopamine plays a physiological role in the handling of sodium by the kidney. For example in saline-loaded rats, SCH 23390 prevents the subsequent natriuresis and diuresis (Hegde *et al.*, 1989) and in conscious dogs, intra-renal arterial infusion of SCH 23390 reduces sodium and urine output without affecting renal haemodynamics (Siragy *et al.*, 1988). Moreover these effects of endogenous dopamine can be reproduced by infusion of either dopamine (Frederickson *et al.*, 1984) or fenoldopam (Hilditch *et al.*, 1988) into the dog renal artery and are prevented by SCH 23390. Evidence in the rabbit suggests that dopamine acts on the proximal tubule to reduce sodium and water reabsorption (Bello-Reuss *et al.*, 1982). These findings strengthen the case for the use of selective D₁-receptor agonists in the treatment of acute renal failure (Goldberg, 1972; Hahn, 1984). A recent report demonstrated beneficial effects of fenoldopam in patients with advanced chronic renal failure (Garcia Robles *et al.*, 1989).

Selective D₁-receptor agonists have also been advocated for the acute treatment of heart failure, by reducing afterload and improving renal perfusion. Fenoldopam produces beneficial haemodynamic changes in rabbits with experimental congestive heart failure (Jover & McGrath, 1988) and favourable findings have also been reported with i.v. fenoldopam in heart failure patients (Young *et al.*, 1988).

In conclusion, FPL 63012AR is an example of a novel class of potent D₁-receptor agonists which may have potential in the treatment of renal and cardiovascular diseases.

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