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The α_1-adrenoceptor antagonist profile of doxazosin: preclinical pharmacology

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1 The antihypertensive efficacy of the new α_1-adrenoceptor antagonist doxazosin is described, and its selectivity for α_1-adrenoceptors is reported from both *in vivo* and *in vitro* studies.
2 Groups of beagle dogs with chronic perinephritic hypertension were given doxazosin orally, and systolic blood pressure was recorded indirectly from an exteriorized carotid loop. Dogs given doxazosin 0.5 mg kg^{-1} daily for 10 days showed consistent daily falls in systolic pressure in addition to a progressive reduction in daily pre-dose pressures. A clear indication of antihypertensive action in excess of 24 h post dose was evident. Heart rate changes were minimal.
3 In pentobarbitone anaesthetized dogs pretreated with desimipramine, doxazosin 10–500 μg kg^{-1} i.v. reduced responses of the nictitating membrane to electrical stimulation of the vago-sympathetic-depressor nerve trunk (an α_1-adrenoceptor response) but had no effect on the chronotropic response of the heart to electrical stimulation of the ansa subclavia. In contrast, the prejunctional α_2-adrenoceptor antagonist activity of yohimbine 10–100 μg kg^{-1} i.v. was manifest as a marked dose-related increase in both the heart rate and nictitating membrane responses.
4 The lack of effect of doxazosin on postjunctional α_2-adrenoceptors *in vivo* was demonstrated in the anaesthetized cat. Doxazosin at 50 and 100 μg kg^{-1} i.v. inhibited pressor responses to injected phenylephrine (an α_1-adrenoceptor agonist) but had no effect on pressor responses to either α-methylnoradrenaline (an α_2-adrenoceptor agonist) or angiotensin II.
5 Studies in isolated tissues, for example the rabbit pulmonary artery and the dog saphenous vein, have also shown the lack of activity of doxazosin at pre- and postjunctional α_2-adrenoceptors.
6 The high degree of selectivity of doxazosin for α_1-adrenoceptor sites was confirmed by ligand binding studies in rat brain membranes where the mean ± s.e. mean K_i values (n = 6) for displacement of [^{3}H]-prazosin, [^{3}H]-rauwolscine and [^{3}H]-clonidine were 1.1 ± 0.1 nM, 449 ± 61 nM and > 10 μM, respectively.
7 Pharmacological studies indicate therefore that the antihypertensive activity of doxazosin is a consequence of selective inhibition of postjunctional α_1-adrenoceptors.

Keywords α_1-adrenoceptor antagonists antihypertensives doxazosin pre- and post-junctional α-adrenoceptors

Introduction

Doxazosin mesylate (UK-33,274 Pfizer UK Ltd) (Figure 1) is a new antihypertensive agent which is structurally related to prazosin. This paper describes the antihypertensive efficacy of doxazosin in conscious renal hypertensive dogs and reports on pharmacological studies carried out both *in vivo* and *in vitro* to define its mechanism of action.

Methods

In vivo *studies in dogs and cats*

Male beagle dogs were surgically prepared with exteriorized carotid arteries. Chronic perinephritic hypertension was induced by wrapping both kidneys in semipermeable cellophane. A loose fitting latex capsule was placed over each kidney to retain and preserve the cellophane. Systolic blood

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MW Base 451.3

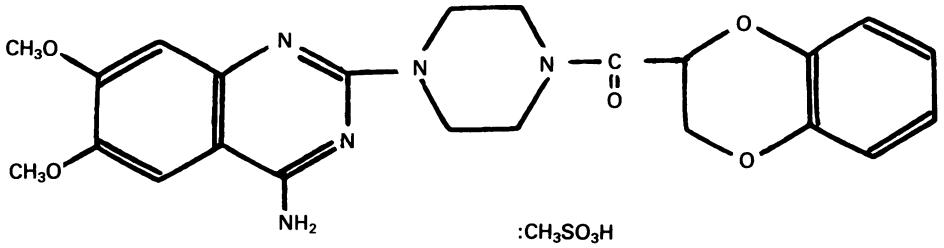

Figure 1 The chemical structure of doxazosin mesylate.

pressure was measured with a combined cuff and strain gauge system and heart rate measured from the pressure trace. A group of four dogs was given a 2 day placebo run in, and then doxazosin was administered daily for 10 days. Each day, after stable control blood pressures had been obtained, doxazosin was given at 0.5 mg kg^{-1} dissolved in acidified distilled water (pH 3) by gavage, and blood pressure measured at 1, 2, 4 and 6 h following dosing. Placebo (vehicle alone) was then administered on days 11 to 14 and finally a single oral dose of doxazosin 0.5 mg kg^{-1} was given on day 15.

Normotensive beagle dogs were anaesthetized with pentobarbitone 35 mg kg^{-1} i.v. and artificially respired. Catheters were placed in the femoral artery for blood pressure measurement, and femoral vein for administration of test substances. The chest was opened between the first and second ribs to allow isolation and section of the right ansa subclavia. A shielded, bipolar electrode (Palmer) was then attached to the nerve trunk to allow stimulation of the afferent cardiac sympathetic nerve fibres. The vagosympathetic trunk was isolated, sectioned and a shielded, bipolar electrode was attached to the nerve trunk to allow stimulation of the sympathetic fibres innervating the right nictitating membrane. The latter was attached to an isometric force transducer in order to measure tension changes, and placed under 5 g resting tension. Frequency response curves were obtained alternatively for increases in heart rate and contractions of the nictitating membrane by applying an electrical current to the stimulating electrodes (Grass S88 stimulator) for 45 s at supramaximal voltage (20 V), 1 ms duration and at frequencies of 0.25, 0.5, 1 and 2 Hz. Consistent control frequency response curves were obtained before giving either doxazosin or yohimbine. The experiments were performed in the presence of the uptake-1 blocker desimipramine 1 mg kg^{-1} i.v. as it had been found previously that the prejunctional effects of α-adrenoceptor antagonists are enhanced by uptake-1 blockade.

Male cats, 3.5–4.5 kg, were anaesthetized with chloralose 100 mg kg^{-1} intravenously after induction with a mixture of halothane, nitrous oxide and oxygen (4:32:64, by vol). Blood pressure was measured via a cannula in the left femoral artery connected through a Statham pressure transducer to a Grass polygraph. The animals were respired and arterial blood gases and pH were maintained within the physiological range. Body temperature was maintained at 38°C. Atropine (1 mg kg^{-1} plus 0.3 mg kg^{-1} h^{-1}) and propranolol (2 mg kg^{-1} plus 0.5 mg kg^{-1} h^{-1}) were given intravenously via the cephalic vein. Pressor responses were obtained to bolus injections into the femoral vein of phenylephrine 1–3 μg kg^{-1}, α-methylnoradrenaline 0.1–0.3 μg kg^{-1}, and angiotensin II 10–100 μg kg^{-1}. After consistent control responses were obtained to the agonists, doxazosin or rauwolscine (an α_2-adrenoceptor selective antagonist) was given and the dose-pressor relationship for each agonist redetermined.

In vitro *studies*

Contractions of rabbit pulmonary artery rings (2–4 mm diameter) in response to noradrenaline were recorded via isometric transducers. The tissue was bathed in Krebs solution to which uptake blockers (10 μM normetanephrine, 0.6 μM desimipramine) and the β-adrenoceptor antagonist propranolol 0.04 μM had been added. After a cumulative dose-response curve to noradrenaline had been obtained, doxazosin or prazosin was added to the bathing fluid and the responses repeated after 30 min.

The affinity of antagonists for prejunctional

α_2-adrenoceptors was measured using the superfused rabbit pulmonary artery preparation labelled with [^{3}H]-noradrenaline (Su & Bevan, 1970; Starke *et al.*, 1975). Stimulation of sympathetic nerve endings was elicited by transmural electrical stimulation (3 Hz for 3 min) and the outflow collected and the ^{3}H-overflow measured by liquid scintillation counting methods. Tension changes were measured by an isometric transducer.

Rabbit aortic rings were suspended in Krebs solution at 37°C under a resting tension of 5 g. Contractions were obtained under conditions as described for the pulmonary artery. The effect of doxazosin on contractions induced by submaximal concentrations of phenylephrine 10 μM, 5-hydroxytryptamine 10 μM, noradrenaline 3 μM and potassium chloride 80 mM was determined.

Rings of dog saphenous vein were prepared and used according to the method described by Shepperson & Langer (1981). Contractions were obtained twice to cumulative increasing concentrations of UK-14,304 (a selective α_2-adrenoceptor antagonist), and once 30 min after addition of either doxazosin or rauwolscine.

Radioligand binding studies were carried out using preparations of brain tissue (minus cerebellum) from male Sprague Dawley rats. The membranes were incubated with 0.2 nM [^{3}H]-prazosin of specific activity 33 Ci mmol^{-1} for 30 min at 25°C (Greengrass & Bremner, 1979) or 2 nM [^{3}H]-clonidine of specific activity 22 Ci mmol^{-1} for 30 min at 25°C (U'Prichard *et al.*, 1976) or [^{3}H]-rauwolscine of specific activity 75 Ci mmol^{-1} for 60 min at 4°C (Perry & U'Prichard, 1981). Specific binding for each ligand was defined as that displaced by 10 μM phentolamine and averaged 90%, 70% and 75% of the total binding for [^{3}H]-prazosin, [^{3}H]-clonidine and [^{3}H]-rauwolscine respectively.

Results

Antihypertensive activity in conscious renal hypertensive dogs

Single daily doses of doxazosin 0.5 mg kg^{-1} given orally to conscious renal hypertensive dogs produced falls in systolic pressure 20–35 mmHg (Figure 2). A clear indication of antihypertensive action in excess of 24 h post-dose was evident and although the measured maximum daily falls in blood pressure occurred between 4 and 6 h, the possibility remains that further falls in systolic pressures occurred after the 6 h recording period. After the 4 day placebo period (days 11–15), whilst the blood pressures did not return to those recorded during the initial pre-drug period, a further dose of doxazosin 0.5 mg kg^{-1} produced a clear antihypertensive effect.

Heart rate changes were minimal throughout the administration period, and although variable, showed a tendency towards bradycardia.

Effect on responses of the heart and nictitating membrane induced by electrical stimulation in anaesthetized dogs

The effect of doxazosin at postjunctional α_1-adrenoceptors was assessed by its ability to inhibit the contractile response of the nictitating membrane to stimulation of the vagal/sympathetic

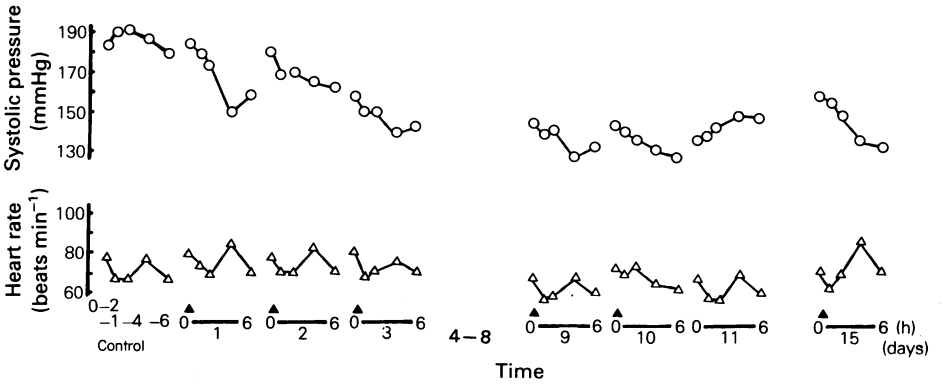

Figure 2 The effect of repeated doses of doxazosin in conscious renal hypertensive dogs (n = 4). Blood pressure (○) and heart rate (△) were measured at 1, 2, 4 and 6 h after oral administration of doxazosin 0.5 mg kg^{-1} (▲).

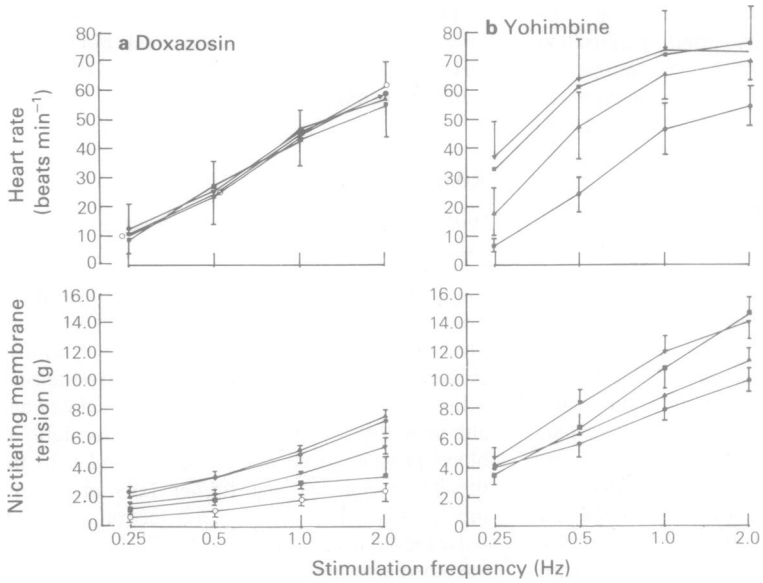

Figure 3 The effect of (a) doxazosin and (b) yohimbine on chronotropic responses of heart and contractions of the nictitating membrane to sympathetic nerve stimulation in anaesthetized dogs: control responses (●); panel a on left, doxazosin 10 μg kg^{-1} (▲), 50 μg kg^{-1} (▼), 100 μg kg^{-1} (■), 500 μg kg^{-1} (○); panel b on right, yohimbine 10 μg kg^{-1} (▲), 50 μg kg^{-1} (▼), 100 μg kg^{-1} (■). Values represent means (n = 3) with s.e. means shown as vertical bars.

nerve fibres. The effect at prejunctional α_2-adrenoceptors was assessed by its ability to increase the chronotropic response of the myocardium (mediated postjunctionally by β-adrenoceptors) to stimulation of the ansa subclavia/sympathetic nerve fibres.

Doxazosin 10 to 500 μg kg^{-1} given i.v. had no effect on the chronotropic response to sympathetic stimulation. These doses markedly reduced the contractile response of the nictitating membrane. In contrast, the prejunctional α_2-adrenoceptor antagonist activity of yohimbine was manifest as a marked and dose-related increase in the chronotropic response, and a similar increase in the contractile response of the nictitating membrane. The data from three preparations are shown in Figure 3.

Effect on pressor responses induced by α_1- and α_2-adrenoceptor agonists and by angiotensin II in anaesthetized cats

Doxazosin 25 to 100 μg kg^{-1} given i.v. inhibited pressor responses induced by bolus injections of phenylephrine and produced parallel rightward shifts in the dose-response curves (Figure 4). However, doxazosin had no effect or slightly potentiated responses to α-methylnoradrenaline and angiotensin II. In contrast, rauwolscine 50 μg kg^{-1} i.v. selectively inhibited responses to α-methylnoradrenaline although higher doses (100 μg kg^{-1}) caused some inhibition of the phenylephrine responses.

Selectivity of doxazosin for postjunctional α_1-adrenoceptors in rabbit vascular preparations

Rabbit pulmonary artery Both doxazosin and prazosin shifted the cumulative noradrenaline dose-response curves to the right in a parallel fashion without affecting the maximum contraction obtained. The pA_2 values calculated graphically according to the method of Arunlakshana & Schild (1959) were 7.31 (slope 0.94) for doxazosin and 8.30 (slope 1.00) for prazosin.

The affinity of doxazosin, prazosin and phentolamine for prejunctional α_2- and postjunctional α_1-adrenoceptors was compared in a superfused rabbit pulmonary artery prelabelled with [^{3}H]-noradrenaline. The percentage changes in nerve stimulation induced tritium overflow and tension produced by increasing doses of doxazosin and prazosin are shown in Figure 5. The EC_{40} values for each antagonist are given in Table 1 where EC_{40}-pre is defined as the concentration producing 40% increase in overflow to nerve

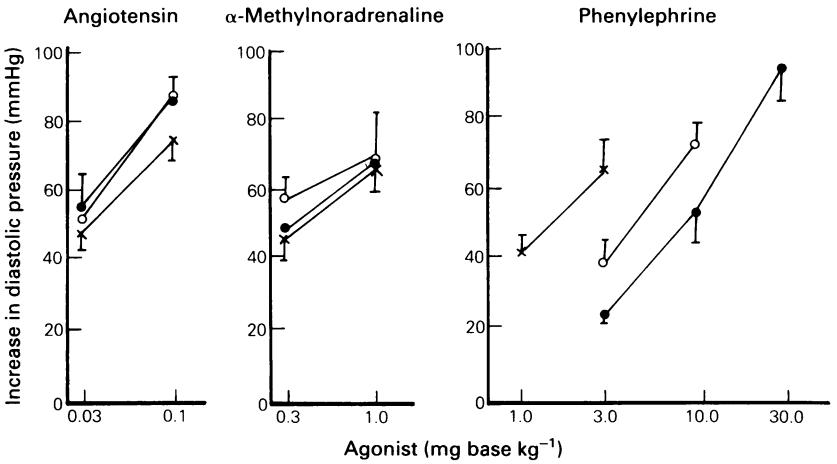

Figure 4 The effect of doxazosin on pressor responses to bolus intravenous injections of angiotensin, α-methylnoradrenaline and phenylephrine in anaesthetized cats. Values represent mean increases in diastolic pressure (n = 4) with s.e. means shown as vertical bars; control values (X), doxazosin 50 μg kg^{-1} (○), after doxazosin 100 μg kg^{-1} (●).

Table 1 Effects of antagonists at pre- and postjunctional α-adrenoceptors in superfused strips of rabbit pulmonary artery

Compound	*Prejunctional activity EC_{40}-pre (nM)*	*Postjunctional activity EC_{40}-post (nM)*	*Selectivity ratio pre/post*
Doxazosin	>30,000	50	>600
Prazosin	1,300	4.5	289
Phentolamine	120	1000	0.12

EC_{40} values were calculated from mean data (n = 4 or 6) where EC_{40}-pre is the concentration (nM) of antagonist which produced a 40% increase in ^{3}H-efflux and EC_{40}-post the concentration producing 40% inhibition of contractile response induced by nervous stimulation.

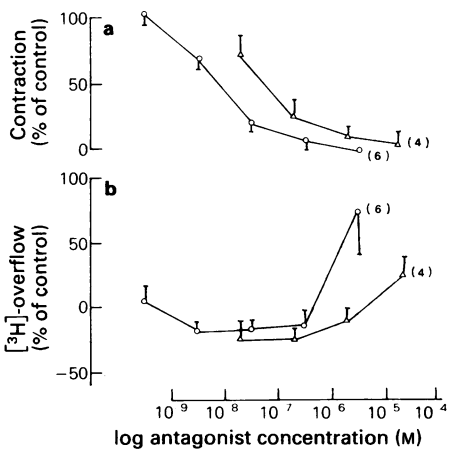

Figure 5 The effect of prazosin (○) and doxazosin (△) on (a) contraction and (b) [^{3}H]-overflow in response to nerve stimulation of rabbit pulmonary artery strips. Figures in parentheses refer to number of tissues used.

stimulation with EC_{40}-post being the concentration producing 40% reduction of the contractile response. In this preparation, the selectivity of doxazosin for postjunctional α_1- as opposed to prejunctional α_2-adrenoceptors is greater than that of prazosin.

Prazosin caused an increase in ^{3}H-efflux from unstimulated strips at concentrations greater than 10^{-6}M. This action is consistent with data indicating intraneuronal disruption of noradrenaline storage at high concentrations of prazosin (Anderson *et al.*, 1979). In contrast, doxazosin had no effect on basal efflux at concentrations up to 10^{-4}M.

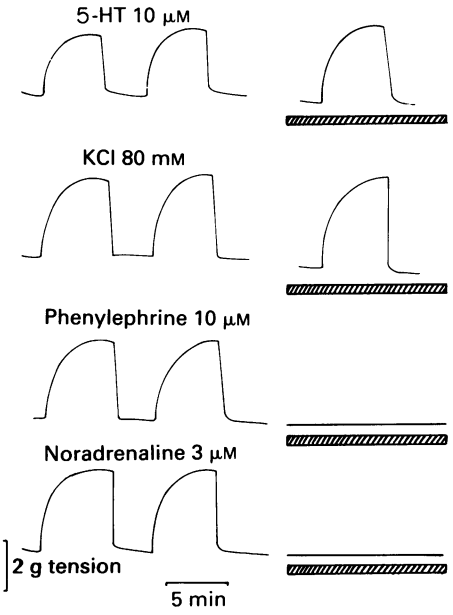

Figure 6 The effect of doxazosin on contractions of rabbit aortic rings to submaximal concentrations of 5-hydroxytryptamine (5-HT), potassium chloride (KCl), phenylephrine and noradrenaline. The control responses are shown in the left hand panel and contractions in the presence of doxazosin 10^{-7}M for 30 min (▨) on the right.

Rabbit aorta Rings of rabbit aorta were contracted with submaximal concentrations of phenylephrine, noradrenaline, 5-hydroxytryptamine and potassium chloride. Doxazosin 10^{-7}M totally abolished responses to phenylephrine and noradrenaline but had no effect on responses to 5-hydroxytryptamine or potassium chloride (n = 4 for each agonist). A representative experiment is shown in Figure 6.

Lack of activity at postjunctional α_2-adrenoceptors in dog saphenous vein

Doxazosin in concentrations up to 6 x 10^{-6}M had no effect or slightly potentiated contractions of a dog saphenous vein to UK-14,304, a selective α_2-adrenoceptor agonist. In contrast, rauwolscine was a competitive antagonist with a pA_2 of 8.56.

Radioligand binding studies

The α-adrenoceptor selectivity of doxazosin was compared with other α-adrenoceptor antagonists by determining their ability to displace tritiated prazosin, clonidine and rauwolscine from rat brain membranes. The data are shown in Table 2 and representative experiments comparing displacement of [^{3}H]-prazosin and [^{3}H]-rauwolscine are illustrated in Figure 7. Doxazosin showed a high degree of selectivity for α_1- as opposed to α_2-binding sites.

Discussion

The antihypertensive activity of doxazosin has been attributed to α_1-adrenoceptor blockade, since studies in man (Singleton *et al.*, 1982) and in cats (Timmermans *et al.*, 1980) showed that doxazosin competitively antagonized pressor responses to phenylephrine. The high degree of selectivity of doxazosin for α_1-adrenoceptors has now been demonstrated in experiments both *in vivo* and *in vitro*.

The presence of prejunctional α-adrenoceptors has been confirmed in all tissues so far examined in which there is a functional noradrenergic innervation. Although the degree of involvement of these receptors in physiological responses is not fully

Table 2 Inhibition of selective α-adrenoceptor ligand binding in rat brain membranes by α-adrenoceptor antagonists

	K_i (nM)		
α-adrenoceptor antagonist	*[^{3}H]-prazosin*	*[^{3}H]-rauwolscine*	*[^{3}H]-clonidine*
Doxazosin	1.11±0.1	449±61	>10,000
Prazosin	0.19±0.02	45.0±5.2	4830±1280
Phentolamine	5.40±0.47	21.4±2.6	4.0±0.24
Rauwolscine	1950±210	3.10±0.4	170±10
Idazoxan	1031±122	3.37±0.5[a]	19.1±4.6

K_i values are the mean ± s.e. mean of at least three experiments in which a range of concentrations were evaluated using triplicate incubations. All slope factors were within the range 0.80 to 1.16 except [a] which was 0.6.

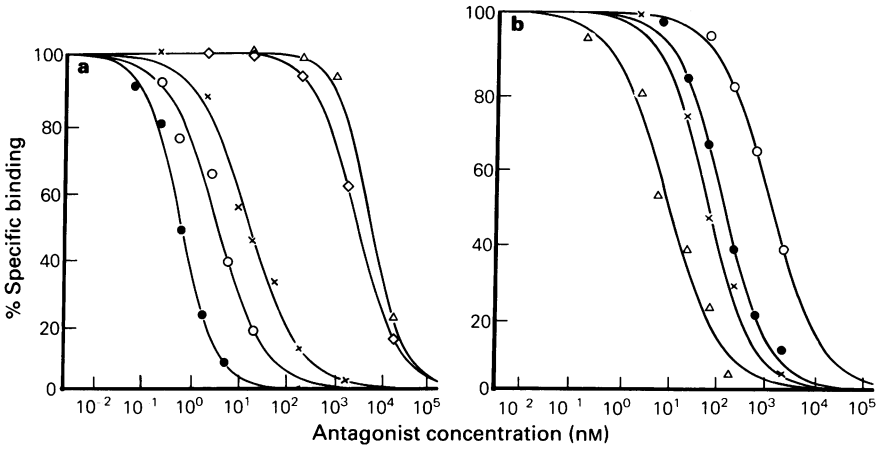

Figure 7 Selectivity of doxazosin for α_1-adrenoceptor binding sites as shown by computer-fitted curves for inhibition of (a) [^{3}H]-prazosin and (b) [^{3}H]-rauwolscine binding to rat brain membranes compared with other α-adrenoceptor antagonists: doxazosin (○), prazosin (●), phentolamine (X), idazoxan (◇), rauwolscine (△). The data points are from typical experiments where points represent the mean of triplicate determinations.

defined, the importance of maintaining an intact feedback regulation inhibiting further release from adrenergic nerves in therapy with α-adrenoceptor antagonists is well documented (Davey, 1980). The lack of effect of doxazosin at prejunctional α_2-adrenoceptors on sympathetic nerves supplying the heart was shown in the anaesthetized dog. Chronotropic responses to sympathetic stimulation were unaffected by doses of doxazosin which markedly inhibited the α_1-mediated contractile responses of the nictitating membrane. Similarly *in vitro*, doxazosin had no effect on overflow of tritium induced by nerve stimulation in [^{3}H]-noradrenaline prelabelled pulmonary artery preparations at concentrations which abolished postjunctional α_1-mediated contractions. These results confirm previous observations in the guinea-pig ileum where doxazosin had no effect on the clonidine-induced reductions of responses to nerve stimulation (Cambridge & Davey, 1980).

This selectivity of doxazosin should preclude effects such as tolerance, tachycardia and diarrhoea seen with non-selective α-adrenoceptor antagonists and attributed to interruption of local feedback control of transmitter release.

In addition to prejunctional α_2-adrenoceptors on neurones, an α_2-subtype is present postjunctionally in some vascular tissues e.g. dog saphenous vein (Shepperson & Langer, 1981). Doxazosin had no effect on contractions induced by the selective α_2-adrenoceptor agonist UK-14,304 in this preparation in concentrations up to three orders of magnitude greater than those required to inhibit α_1-induced responses to noradrenaline in the rabbit pulmonary artery. α_2-Adrenoceptors mediating vasoconstriction have also been demonstrated *in vivo* (Timmermans & van Zwieten, 1981; Alabaster & Davey, 1984). In normal volunteers, the selective α_2-adrenoceptor antagonist idazoxan had little effect on pressor dose-response curves to phenylephrine but produced a substantial shift to the right of the pressor dose-response curves to α-methylnoradrenaline, which is relatively selective for α_2-adrenoceptors (Elliott *et al.*, 1983). Using a similar protocol in anaesthetized cats, the *in vivo* selectivity of doxazosin for postjunctional α_1- as opposed to postjunctional α_2-adrenoceptors was demonstrated. Doxazosin antagonized pressor responses to phenylephrine at doses which had no effect on pressor responses to α-methylnoradrenaline.

The selectivity of doxazosin was confirmed in radioligand binding studies. Doxazosin showed some 400 times greater affinity for α_1-binding sites compared to α_2-sites labelled with [^{3}H]-rauwolscine, and more than 10,000 times greater affinity compared to α_2-sites labelled with [^{3}H]-clonidine. The difference in affinity of doxazosin at the α_2-binding sites can be attributed to the binding of clonidine (agonist) and rauwolscine (antagonist) to different affinity states of the α_2-adrenoceptor. Most antagonists, with phentolamine being a notable exception, show greater affinity for the low affinity state labelled by [^{3}H]-rauwolscine (Hoffman *et al.*, 1980). It is likely therefore that doxazosin will have less

affinity for the α_2-site in the presence of nerve traffic when the receptor is in the active conformation.

Thus doxazosin shares with prazosin marked selectivity for α_1-adrenoceptors. Data from ligand binding studies and experiments in the rabbit pulmonary artery show that doxazosin is, if anything, more selective than prazosin for α_1- as opposed to α_2-adrenoceptors. In addition, in contrast to prazosin at concentrations of greater than 10^{-6}M, doxazosin did not interfere with the binding of noradrenaline in intraneuronal storage granules. However these differences are probably not clinically relevant since they are observed only at concentrations of prazosin several orders of magnitude higher than those achieved clinically.

The *in vitro* α-adrenoceptor antagonist profile of doxazosin translated to the intact animal at doses which were antihypertensive. Doxazosin therefore exerts its peripheral vasodilator activity via selective inhibition of postjunctional α_1-adrenoceptors in vasculature. No evidence was obtained that doxazosin had any direct effect on vascular smooth muscle. Thus doxazosin had no effect on pressor responses to angiotensin II in anaesthetized cats, and had no effect on contractions induced by potassium chloride in isolated rabbit aorta. 5-Hydroxytryptamine-induced contractions of the aorta were also unaffected by doxazosin. Lack of affinity of doxazosin for 5-hydroxytryptamine ([^{3}H]-ketanserin) and dopamine ([^{3}H]-domperidone) binding sites have also been shown using radioligand binding techniques (M. G. Wyllie, unpublished data).

A central mechanism is unlikely to underlie the acute hypotensive effect of doxazosin since Timmermans *et al.* (1980) showed that comparable amounts injected intravenously or into the vertebral artery produced similar effects on blood pressure.

In conscious hypertensive dogs, repeated daily doses of doxazosin produced falls in blood pressure in excess of 24 h duration indicating the potential for once-daily dosing in man. Of importance, this antihypertensive effect was obtained without accompanying tachycardia. In man, the onset of activity and the mean elimination half-life of doxazosin is longer than that of prazosin (Elliott *et al.*, 1982), and studies in hypertensive patients have confirmed that doxazosin is an effective antihypertensive agent on once-daily administration (Frick *et al.*, 1986).

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