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EVIDENCE FOR TWO DISTINCT TYPES OF POSTSYNAPTIC α-ADRENOCEPTOR IN VASCULAR SMOOTH MUSCLE *in vivo*

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1 The effects of the highly selective α_1-adrenoceptor antagonist, prazosin, and the relatively selective α_2-adrenoceptor antagonist, yohimbine, on the pressor responses to intravenous injections of phenylephrine and noradrenaline have been examined in anaesthetized cats and pithed rats in an attempt to determine whether α_1- and α_2-adrenoceptors are located postsynaptically on vascular smooth muscle.

2 In anaesthetized cats prazosin caused a much greater reduction in the pressor responses to phenylephrine than to noradrenaline or splanchnic nerve stimulation (after adrenalectomy). Yohimbine was of similar potency in reducing the pressor responses to each stimulus.

3 A differential blocking activity of prazosin against intra-arterial injections of phenylephrine and noradrenaline was also demonstrated in the blood-perfused cat hind limb. As in the whole animal, prazosin was more potent against phenylephrine than noradrenaline. A similar, though less marked, effect was seen in the mesenteric circulation, but not in the renal circulation, where prazosin was almost equipotent in reducing responses to phenylephrine and noradrenaline.

4 In pithed rats prazosin was a potent, competitive antagonist of phenylephrine, but had little effect against noradrenaline; only the responses to high doses of noradrenaline were reduced by prazosin. Yohimbine was approximately equipotent as an antagonist of phenylephrine and noradrenaline. In the anococcygeus muscle, prazosin was as potent an antagonist of noradrenaline as it was of phenylephrine on vascular smooth muscle.

5 The results suggest that there are two types of α-adrenoceptor in the vasculature of cats and rats. Phenylephrine produces pressor responses by stimulating one type of postsynaptic α-adrenoceptor that is blocked by prazosin and yohimbine; these are α_1-adrenoceptors. Noradrenaline exerts some of its effect via these receptors but most of its effect appears to be exerted through prazosin-insensitive receptors. The latter receptors appear to differ from α_2-adrenoceptors.

Introduction

Prazosin is a novel antihypertensive agent (Cohen, 1970; Constantine, McShane, Scriabine & Hess, 1973) that is believed to act primarily, if not exclusively, by blocking the postsynaptic α-adrenoceptors in vascular smooth muscle (Wood, Phelan & Simpson, 1975; Cavero, 1976; Brogden, Heel, Speight & Avery, 1977; Cavero, Fénard, Gomeni, Lefèvre & Roach, 1978). Despite being a potent antagonist at postsynaptic α-adrenoceptors in many tissues (Wood *et al.*, 1975; Cambridge, Davey & Massingham, 1977; Doxey, Smith & Walker, 1977) including human visceral arteries (Moulds & Jauernig, 1977; Jauernig, Moulds & Shaw, 1978) prazosin did not block the contractile responses to noradrenaline in isolated strips of human palmar digital arteries (Moulds & Jauernig, 1977; Jauernig *et al.*, 1978). In contrast, phentolamine antagonized the contractile effects of noradrenaline in both human visceral and digital artery strips, which confirms that α-adrenoceptors mediate the responses to noradrenaline in both these tissues.

A possible explanation for the differential blocking action of prazosin is that the α-adrenoceptors in human visceral and digital arteries are different. Two sub-types of α-adrenoceptor have already been described. One type has been identified on the terminals of the sympathetic nerves supplying the rabbit pulmonary artery (Starke, Endo & Taube, 1975; Cambridge *et al.*, 1977; Borowski, Starke, Ehrl & Endo, 1977) and the rat heart (Drew, 1976; Cavero, Lefèvre & Roach, 1977) and the motor nerves supplying the rat vas deferens (Drew, 1977; Doxey *et al.*, 1977). These presynaptic receptors have been subclassified, tentatively, as α_2-adrenoceptors to distinguish them from the α_1-type of adrenoceptor generally located postsynaptically on smooth muscle. The α_2-adrenoceptors differ from the α_1-adrenoceptors in their sensitivity to α-adrenoceptor agonists and antag-

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onists. In particular, although noradrenaline is similar in potency at each type of receptor, the α_2-adrenoceptors are much less sensitive than the α_1-adrenoceptors to the α-adrenoceptor agonist, phenylephrine (Starke *et al.*, 1975; Drew, 1976; 1977). Amongst the antagonists, phentolamine is approximately equipotent at both receptors (Borowski *et al.*, 1977) but prazosin shows much greater selectivity for the α_1-adrenoceptors (Cavero *et al.*, 1977; Doxey *et al.*, 1977), whilst yohimbine is about 10 to 30 times more potent an antagonist at the α_2- than at the α_1-adrenoceptors (Doxey *et al.*, 1977; Borowski *et al.*, 1977).

Thus it is possible that the postsynaptic α-adrenoceptors in human visceral arteries are of the α_1-type whilst those in the digital arteries are of the α_2-type. In an attempt to determine whether both types of α-adrenoceptor are present postsynaptically on vascular smooth muscle we have examined the relative abilities of prazosin and yohimbine to antagonize the vasopressor responses to phenylephrine and noradrenaline.

A preliminary account of some of these findings has been presented to the British Pharmacological Society (Bentley, Drew & Whiting, 1977).

Methods

Anaesthetized cats

Cats of either sex (weight range 1.75 to 4.5 kg) were anaesthetized with chloralose (80 mg/kg i.v.) after induction with halothane (3.5%) in a 3:1 nitrous oxide:oxygen mixture. Animals were bilaterally vagotomized and respired artificially with room air through a tracheal cannula. Body temperature was maintained at 38.5°C by means of a thermostatically controlled electric blanket. Arterial blood samples were taken throughout the experiments for blood gas analysis, and pH, Po_2 and Pco_2 were maintained within normal limits (i.e. 7.3 to 7.4, 70 to 110 mmHg and 24 to 32 mmHg respectively) by alteration of tidal volume and by addition of oxygen to the inspired air or administration of sodium bicarbonate when necessary. Blood pressure was measured with a Hewlett Packard pressure transducer connected to a polythene cannula in a carotid or femoral artery, and was displayed on a Hewlett Packard recorder (model 7758 A). A femoral vein was cannulated for drug injection.

Two groups of experiments were carried out. In the first, the right adrenal gland was removed and the right splanchnic nerve was sectioned. Then, approximately equal increases in aortic blood pressure were obtained to single intravenous injections of submaximal doses of phenylephrine (2 to 20 μg/kg) and noradrenaline (0.05 to 0.7 μg/kg) and to stimulation of the distal part of the right splanchnic nerve at supramaximal voltage for periods of 30 s at a frequency of 5 to 15 Hz; the pulse duration was 1 ms. When responses to phenylephrine, noradrenaline and nerve stimulation became constant, prazosin or yohimbine was injected intravenously and each of the pressor challenges was repeated 15 min later in the same sequence. Subsequent doses of the antagonist were injected using a cumulative dose-schedule, and the percentage change in the response to each challenge was calculated after each dose of antagonist.

In the second group of experiments the right adrenal gland and splanchnic nerve were left intact and the hind limb, mesenteric or renal vascular bed, was perfused with blood withdrawn at constant rate from the aorta by means of a Watson-Marlow (MHRE 200) pump. The perfusion pressure was monitored continuously. The blood flow rate was adjusted at the beginning of each experiment so that the perfusion pressure in the vascular bed under examination was similar to mean aortic pressure; thereafter flow was kept constant. The mean flow rates in the hind limb, mesenteric and renal beds were 9.0 (range 5 to 11), 17.3 (range 12 to 29) and 16.5 (range 14 to 19) ml/min respectively. Approximately equipressor doses of phenylephrine (1 to 60 μg i.a.) and noradrenaline (0.1 to 5 μg i.a.) were injected into the perfusing blood. When responses became constant prazosin was injected intravenously and the responses to intra-arterial injections of phenylephrine and noradrenaline were measured 15 min later. Subsequent doses of prazosin were administered on a cumulative dose schedule.

Pithed rats

Male albino rats (A & H Wistar derived; 200 to 400 g) were anaesthetized with halothane (3.5%) in a 3:1 nitrous oxide:oxygen mixture. The rats were then pithed and immediately artificially respired with room air (1 ml/100 g body weight at a rate of 50 strokes/min). Blood pressure was recorded from the common carotid artery with a Bell & Howell pressure transducer (type 4-442-0001 or 4-327-L221). The pressure pulse was displayed on a Devices recorder. A femoral vein was cannulated for drug injection. Animals were kept warm by a lamp positioned about 30 cm above the chest. Before experimentation all animals received atropine and (+)-tubocurarine (1 mg/kg i.v. of each) and the vagus nerves were sectioned in the neck.

Vasopressor-response curves to phenylephrine or noradrenaline were obtained before and after cumulative doses of prazosin or yohimbine. A period of 15 min was allowed to elapse after each dose of antagonist before the agonist dose-response curve was repeated. The results were plotted according to the method of Arunlakshana & Schild (1959) and for each

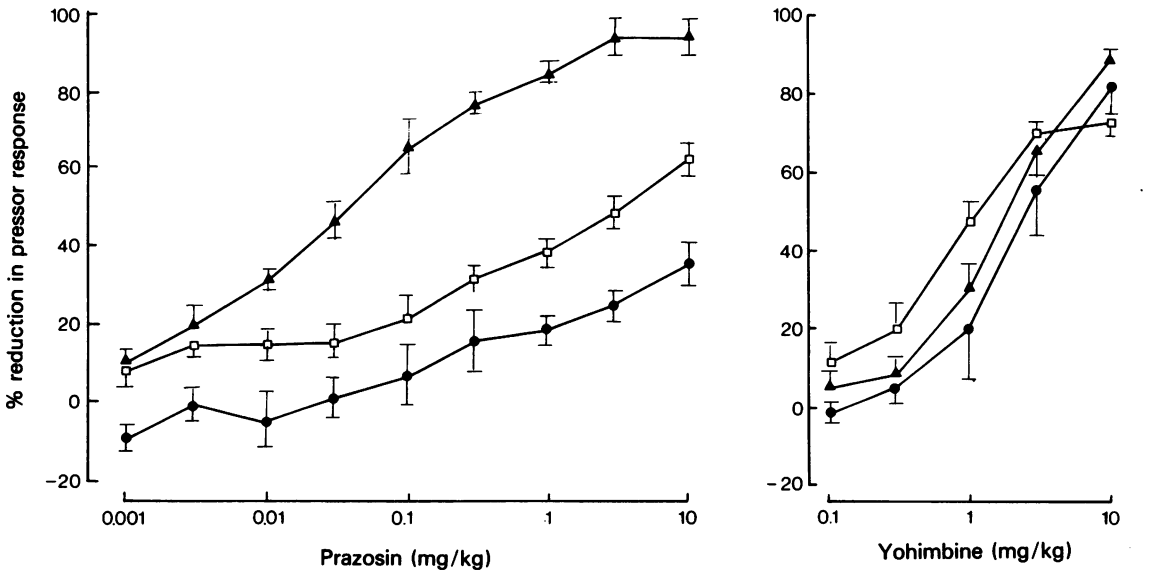

Figure 1 The effect of prazosin ($n = 6$) and yohimbine ($n = 6$) on the matched vasopressor responses to intravenous injection of phenylephrine (▲) and noradrenaline (□) and to stimulation of the right splanchnic nerve (●) in anaesthetized cats. Percentage change is expressed as the mean; vertical lines show s.e. mean.

Table 1 The α-adrenoceptor blocking potencies of prazosin and yohimbine in anaesthetized cats

		*Prazosin ED_{50} (mg/kg)**		*Yohimbine ED_{50} (mg/kg)**
	n		n	
Systemic blood pressure				
Phenylephrine	6	0.04 (0.02–0.07)	6	1.82 (0.96–3.42)
Noradrenaline	6	2.72 (1.2–6.1)	6	1.11 (0.73–1.68)
Splanchnic nerve stimulation	6	>10.0	6	2.58 (0.94–7.07)
Hind-limb perfusion pressure				
Phenylephrine	5	0.033 (0.11–0.10)		—
Noradrenaline	5	See text		—
Mesenteric perfusion pressure				
Phenylephrine	6	0.013 (0.008–0.023)		—
Noradrenaline	6	0.068 (0.014–0.34)		—
Renal perfusion pressure				
Phenylephrine	5	0.013 (0.005–0.034)		—
Noradrenaline	5	0.022 (0.004–0.12)		—

* ED_{50} = dose causing 50% reduction in pressor response; results expressed as geometric mean (and 95% confidence limits).

antagonist the dose required to cause a 10 fold shift to the right in the agonist dose-response curve (DR_{10}) and the slope of the regression were calculated.

In other experiments the effects of noradrenaline on blood pressure and on the anococcygeus muscle tension were recorded simultaneously. The ventral bar joining the two muscles was exposed as described by Gillespie & McGrath (1973) and attached under an initial tension of 1 g to an Ether 2 oz strain gauge. The resting tension declined progressively to about 0.5 g over the next 15 to 30 min before the experiment was started. Thereafter it remained fairly steady, exhibiting only small and irregular spontaneous contractions.

Drugs

The following drugs were used: atropine sulphate (BDH); cocaine hydrochloride (Macfarlan Smith); (−)-noradrenaline bitartrate (Koch-Light); (−)-phenylephrine hydrochloride (Koch-Light); prazosin hydrochloride (Pfizer); propranolol hydrochloride (ICI); tubocurarine hydrochloride (Burroughs Wellcome) and yohimbine hydrochloride (Sigma). Except for prazosin, drugs were made up freshly before use in 0.9% w/v NaCl solution (saline) or distilled water. Prazosin was dissolved in 2% 1,3-dioxolan (Merck-Darmstadt) to give a 1 mg/ml solution; subsequent dilutions were made in distilled water. Preliminary experiments demonstrated that, at concentrations used in the present work, this solvent did not affect responses to noradrenaline or phenylephrine.

Results

Anaesthetized cats

Systemic blood pressure. In the first group of experiments the mean resting blood pressure of cats anaesthetized with chloralose ($n = 12$) before experimentation was systolic 119 ± 3, diastolic 80 ± 3 mmHg. Matching increases in diastolic pressure (62 to 101 mmHg) were produced by phenylephrine (2 to 20 μg/kg i.v.), noradrenaline (0.05 to 0.7 μg/kg i.v.) and by stimulation of the distal portion of the right splanchnic nerve (5 to 15 Hz for 30 s).

Low doses of prazosin (0.001 to 0.3 mg/kg i.v.) or yohimbine (0.1 to 3.0 mg/kg i.v.) reduced blood pressure, the maximum fall of 20 to 25 mmHg occurring with 0.1 and 3 mg/kg respectively. Higher doses of each drug, up to 10 mg/kg, often caused small pressor responses that sometimes recovered incompletely. Large doses of many other α-adrenoceptor blocking drugs have been reported to produce pressor responses in cats (Benfey & Varma, 1962).

Phenylephrine-induced pressor responses were reduced by prazosin; maximum reduction or abolition occurred after 3 to 10 mg/kg. Responses to noradrenaline and splanchnic nerve stimulation were not so readily antagonized; indeed 10 mg/kg prazosin reduced the responses to splanchnic nerve stimulation by less than 50% (Figure 1). The mean ED_{50} values for prazosin against phenylephrine, noradrenaline and splanchnic nerve stimulation are shown in Table 1. In contrast, yohimbine reduced responses to phenylephrine, noradrenaline and splanchnic nerve stimulation to a similar extent (Figure 1). The mean ED_{50} values for yohimbine are shown in Table 1, the only statistically significant difference being between those against noradrenaline and phenylephrine ($P < 0.02$, paired t test).

Perfusion pressure in hind limb, mesenteric and renal vascular beds. Intra-arterial doses were chosen from the range 0.1 to 5 μg for noradrenaline and 1 to 60 μg for phenylephrine to give matching pressor responses of between 56 and 127 mmHg in the perfused hind limb, mesenteric and renal vascular beds. Prazosin (0.003 to 1 mg/kg i.v.) reduced the perfusion pressure by 3 to 30% in the mesenteric and renal circulations and caused a similar *increase* in the hind limb. In each bed prazosin caused a dose-related reduction in the responses to phenylephrine; a narrow range of ED_{50} values was found. In contrast, the reduction in noradrenaline responses was much more variable (see Table 1). A mean ED_{50} for prazosin against noradrenaline in the hind limb could not be calculated because the individual values ranged from 0.049 to >1 mg/kg in a total of 5 experiments. Marked variation was also seen in the mesenteric bed, although in this case an ED_{50} value was determined. Nonetheless, the clear finding emerged that in both of these beds prazosin was more effective against phenylephrine than noradrenaline in each experiment.

Such variability did not occur in the renal bed. With one exception prazosin was almost equipotent in reducing responses to phenylephrine and noradrenaline. The effects of prazosin on responses to phenylephrine and noradrenaline in these vascular beds are shown in Figure 2.

Pithed rats

Systemic blood pressure. The resting blood pressure of pithed rats before experimentation was systolic 76 ± 2, diastolic 43 ± 2, ($n = 33$), and was unaltered by intravenous injection of prazosin (10 to 100 μg/kg) or yohimbine (0.3 to 10 mg/kg). Prazosin was a potent, competitive antagonist of the vasopressor responses to phenylephrine, but in marked contrast had little or no effect on the pressor responses to low doses of noradrenaline (30 to 300 ng/kg i.v.). However, there was some reduction in the response to

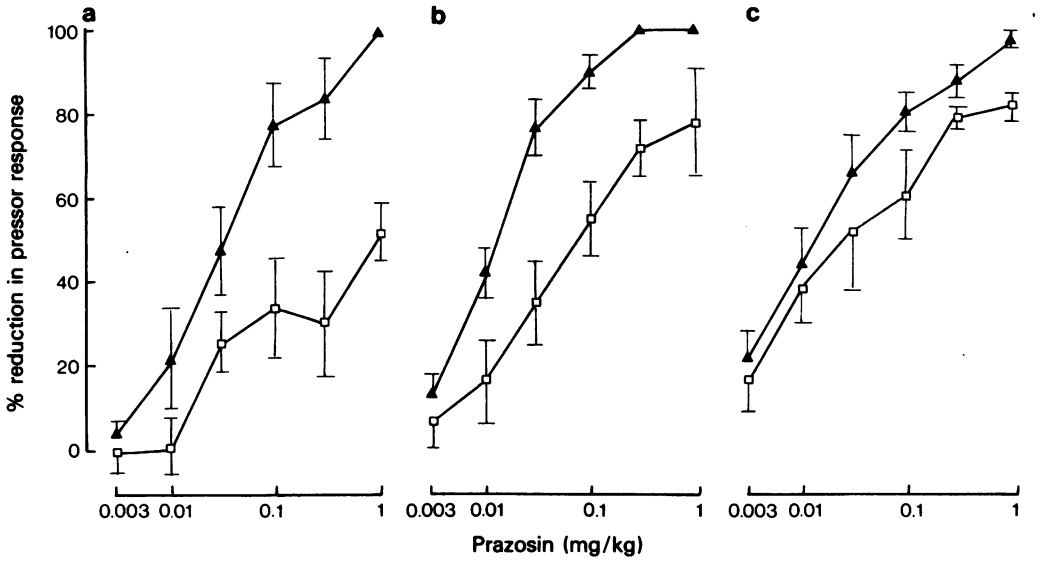

Figure 2 The effect of prazosin on the matched vasopressor responses to intra-arterial injections of phenylephrine (▲) and noradrenaline (□) into (a) the cat hind limb (n = 5), (b) mesenteric (n = 6) and (c) renal (n = 5) vascular beds during perfusion with blood at constant flow. Vertical lines show s.e. mean.

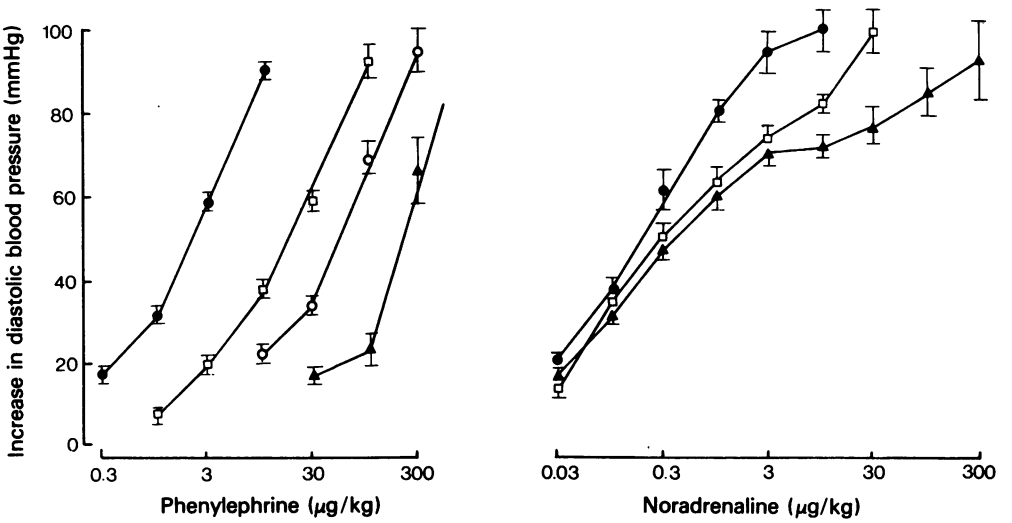

Figure 3 The effects of intravenous prazosin, 10 (□), 30 (○) and 100 (▲) μg/kg on the vasopressor responses to intravenous injections of phenylephrine (n = 6) and noradrenaline (n = 5) in pithed rats. Control responses are shown (●). Vertical lines show s.e. mean.

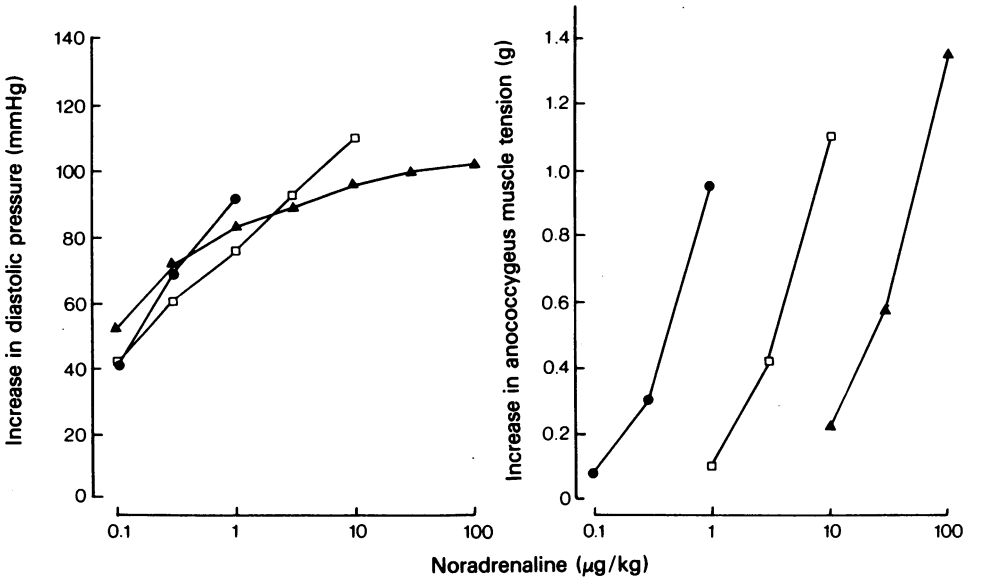

Figure 4 The effect of intravenous prazosin, 10 (□) and 100 (▲) μg/kg on the noradrenaline-induced increases in diastolic blood pressure and anococcygeus muscle tension in a pithed rat. Control responses are shown (●).

a higher dose of noradrenaline (1 μg/kg) and prazosin clearly reduced the pressor responses to 3 μg/kg and more of noradrenaline. Thus prazosin appeared to separate the noradrenaline dose-response curve into two components (Figure 3). Although this separation was distinct in only four out of six experiments it was noted that the displacements caused by prazosin in the upper portion of the noradrenaline dose-response curves were similar to those undergone by the entire dose-response curves to phenylephrine.

The interaction between prazosin and noradrenaline was unaltered by inhibition of uptake$_1$ (cocaine 5 mg/kg i.v. pretreatment and 1 mg/kg i.v. between subsequent noradrenaline dose-response curves; $n = 5$) or β-adrenoceptor blockade (propranolol 0.5 mg/kg i.v. pretreatment and 0.1 mg/kg i.v. between noradrenaline dose-response curves; $n = 5$).

In contrast to prazosin, yohimbine competitively antagonized the pressor responses to both phenylephrine and noradrenaline. The DR_{10} values for prazosin and yohimbine against phenylephrine and noradrenaline are shown in Table 2.

Anococcygeus muscle. Noradrenaline (0.1 to 3 μg/kg i.v.) caused contraction of the anococcygeus muscle. The tension developed ranged between 0.06 and 0.95 g and, although sensitivity between preparations varied, responses in individual preparations remained steady. In contrast to its effects on the pressor responses to noradrenaline, prazosin (10 and 100 μg/kg i.v.) was as potent an antagonist of noradrenaline on the anococcygeus muscle as it was of phenylephrine on vascular smooth muscle (Table 2). An example of one such experiment is shown in Figure 4. These results are important because they demonstrate that prazosin can antagonize one type of response to noradrenaline whilst having little or no effect on another, in the same animal and at the same time. The effects of yohimbine on the responses of the anococcygeus muscle to noradrenaline were not examined.

Discussion

The results of the experiments described here demonstrate that prazosin is a potent antagonist of phenylephrine on vascular smooth muscle in anaesthetized cats and pithed rats. It was equally potent in antagonizing the contractile effects of noradrenaline on the anococcygeus muscle in rats, but was a much weaker antagonist of the vascular effects of noradrenaline in both cats and rats. The latter finding is in agreement with the observation that prazosin does not antagonize the contractile responses to noradrenaline in isolated strips of human palmar digital arteries (Moulds & Jauernig, 1977; Jauernig *et al.*, 1978) but contrasts sharply with the reports that prazosin is a very potent antagonist of noradrenali .e in the rat isolated mesentery (Wood *et al.*, 1975), human visceral artery strip (Moulds & Jauernig, 1977; Jauernig

et al., 1978), the rabbit aortic strip (Cavero *et al.*, 1978) and in the autoperfused rat hind limb *in vivo* (Wood *et al.*, 1975).

It is difficult to interpret the present findings in terms of the generally held belief that phenylephrine and noradrenaline exert their pressor effects via a single type of postsynaptic α-adrenoceptor and some alternative explanations are also untenable. For example, cocaine did not modify the interaction between prazosin and noradrenaline in pithed rats, so the failure of prazosin to block responses to noradrenaline in untreated preparations cannot be ascribed to an inhibitory action of prazosin on uptake$_1$, as is the case with labetalol in anaesthetized dogs (Farmer, Kennedy, Levy & Marshall, 1972). Furthermore, prazosin was no more effective in antagonizing noradrenaline after pretreatment with propranolol. Thus, it is unlikely that the prazosin-insensitive component of the pressor response to noradrenaline is attributable to a β-adrenoceptor mediated increase in cardiac output. In addition, pressor responses to noradrenaline in anaesthetized cats are mediated via increases in resistance rather than cardiac output (Karim, 1966) and the differential blocking activity of prazosin was still seen during perfusion of the cat hind limb or mesenteric vascular beds at constant flow.

It might be argued that there is only one type of vascular α-adrenoceptor but that low doses of noradrenaline exert their effects through a population of these receptors that, for some reason, are inaccessible to prazosin, whilst higher doses stimulate not only these receptors but also those to which prazosin can gain access. However, it seems unlikely that low doses of noradrenaline would gain access to only those receptors inaccessible to prazosin. The simplest explanation for the differential blocking action of prazosin is that two different types of postsynaptic vascular α-adrenoceptors are involved in mediating the pressor responses to phenylephrine and noradrenaline. One type is stimulated by phenylephrine and noradrenaline, and is blocked by prazosin; this type of receptor clearly resembles the α_1-adrenoceptor. Presumably the α-adrenoceptors in the rat anococcygeus muscle are of the same type. The second type of receptor is stimulated by lower doses of noradrenaline than are required to stimulate the α_1-adrenoceptors, is not stimulated by phenylephrine and is not blocked by prazosin. The question that arises is whether this type of receptor corresponds to the α_2-adrenoceptor.

There are already precedents for α_2-adrenoceptors located postsynaptically. For example, the α_2-adrenoceptors in the guinea-pig ileum (Drew, 1978) are generally considered to be presynaptic with respect to the cholinergic synapse, but they are postsynaptic with respect to the noradrenergic nerves which innervate them. Furthermore, in radioligand binding experiments, a mixed population of differing proportions of receptors with characteristics similar to α_1- and α_2-adrenoceptors has been identified postsynaptically in the rat brain (U'Prichard, Greenberg & Snyder, 1977; Miach, Dausse & Meyer, 1978) and rat kidney (U'Prichard, Charness, Robertson & Snyder, 1978). The two populations have generally been characterized by their different affinities for α-agonists and for antagonists, particularly prazosin and yohimbine.

However, a mixed population of α_1- and α_2-adrenoceptors has not yet been identified in vascular smooth muscle, and the present results with yohimbine do not further clarify the picture. If the prazosin-insensitive component of the pressor response to noradrenaline is mediated via vascular α_2-adrenoceptors it might be anticipated that yohimbine would be a more potent

Table 2 The α-adrenoceptor blocking potencies of prazosin and yohimbine in pithed rats

	Prazosin			*Yohimbine*		
	n	DR_{10} (mg/kg)*	Slope†	n	DR_{10} (mg/kg)*	Slope†
Systemic blood pressure						
Phenylephrine	6	0.013 (0.009–0.17)	1.12 (0.91–1.38)	4	3.36 (2.38–4.72)	1.22 (1.03–1.44)
Noradrenaline	5	⩾0.1	—	4	1.84 (0.77–4.42)	0.90 (0.61–1.33)
Anococcygeus muscle						
Noradrenaline	4	0.015 (0.009–0.027)	0.99 (0.84–1.17)		—	—

* DR_{10} = dose of antagonist required to cause a 10 fold shift to the right in the agonist dose-response curve; results expressed as geometric mean (and 95% confidence limits).
† Slope of the regression of the Schild plot—results expressed as geometric mean (and 95% confidence limits).

antagonist of the responses to noradrenaline than to phenylephrine. Just how much more potent would depend upon the relative contributions of the α_1- and α_2-adrenoceptors to the overall responses to noradrenaline and upon the relative selectivity of yohimbine for the α_2-adrenoceptors (see Introduction). However, there was no convincing evidence in the present experiments that yohimbine was much more potent in reducing the responses to noradrenaline than those to phenylephrine. This may be because yohimbine is not sufficiently selective for α_2-adrenoceptors, or because the prazosin-insensitive component of the noradrenaline responses is mediated via a receptor different from both the α_1- and α_2-types. This problem will only be resolved when an antagonist with a greater selectivity than yohimbine for α_2-adrenoceptors is available.

Whatever the nature of the prazosin-insensitive α-adrenoceptors, their presence prompts a number of questions: for example, what is their distribution in different vascular beds throughout the cardiovascular system, where are they localized within any individual bed and what purpose do they serve? These questions must remain largely unanswered until more isolated tissue preparations containing these receptors can be developed, but the present experiments provide some clues. In contrast to the responses to nerve stimulation in other tissues, (see Constantine *et al.*, 1973; Wood *et al.*, 1975 Cambridge *et al.*, 1977; Doxey & Easingwood, 1978) which were blocked by low doses of prazosin, those to stimulation of the cat splanchnic nerve were not. This shows that at least some prazosin-insensitive receptors are innervated. If prazosin-insensitive α-adrenoceptors that receive a noradrenergic innervation are widespread in vascular smooth muscle they may be responsible for mediating such reflex phenomena as the increase in hind limb resistance seen in the present experiments and the compensatory adjustments made to vertical tilt in anaesthetized dogs (Constantine *et al.*, 1973). In conclusion, it seems that in the vasculature of cats and rats there are two distinct types of α-adrenoceptors, separable by their sensitivities to prazosin, both of which may receive a noradrenergic innervation.

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