

# Difference in the potency of $\alpha_2$ -adrenoceptor agonists and antagonists between the pithed rabbit and rat

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1 The subtypes of  $\alpha$ -adrenoceptors which mediate pressor responses to sympathomimetic agonists or to nerve stimulation in pithed rabbits have been classified according to the effects of 'selective' antagonists and a comparison has been made, for the  $\alpha_2$ -subtype, with corresponding responses in the rat.

2 In the rabbit the dose-response curve for phenylephrine was shifted to the right in parallel by prazosin (1 mg kg<sup>-1</sup>) and was unaffected by rauwolscine (1 mg kg<sup>-1</sup>). The dose-response curve for noradrenaline was shifted to the right by prazosin (1 mg kg<sup>-1</sup>) and was shifted to a smaller extent by rauwolscine (1 mg kg<sup>-1</sup>) or imiloxan (10 mg kg<sup>-1</sup>). After rauwolscine, prazosin produced a rightward shift larger than when given alone. After prazosin, rauwolscine produced a rightward shift larger than when given alone.

3 The responses to pressor nerve stimulation at low frequencies (< 1 Hz) could be reduced by prazosin, rauwolscine or imiloxan but those at a higher frequency could be reduced only by prazosin.

4 These results indicate that the responses to noradrenaline or to nerve stimulation are mediated by both  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors. Low doses or frequencies have a proportionately greater component which is  $\alpha_2$ .

5 Responses to noradrenaline after prazosin (1 mg kg<sup>-1</sup>), were sufficiently sensitive to rauwolscine to be considered as predominantly  $\alpha_2$ . A comparison was therefore made of such responses in the rat and rabbit. They were produced by a lower dose per unit body weight in the rat whereas this was less marked for the  $\alpha_2$ -adrenoceptor agonist guanabenz. In the rabbit they were more susceptible to blockade by rauwolscine but were less sensitive to Wy 26703 than in the rat. This demonstrates that the  $\alpha_2$ -adrenoceptors mediating pressor responses *in vivo*, like those in other tissues *in vitro*, are different in rat and rabbit, with regard to antagonists.

## Introduction

$\alpha$ -Adrenoceptors consist of two subtypes,  $\alpha_1$  and  $\alpha_2$  which can be defined in terms of agonist and antagonist selectivity (Langer, 1974; Starke, 1981; McGrath, 1982). Recently it has been suggested that the  $\alpha_2$ -adrenoceptor subtype may have different pharmacological properties in different species (Nahorski *et al.*, 1985; Waterfall *et al.*, 1985; Alabaster *et al.*, 1985; 1986). For example the prejunctional  $\alpha_2$ -adrenoceptors in vas deferens of rat and rabbit had a different antagonist potency series, yohimbine being more potent than Wy 26703 in the rabbit but less potent in the rat. It was subsequently found that the

potency of each antagonist at postjunctional  $\alpha_2$ -adrenoceptors in the rabbit saphenous vein was similar to that found at the prejunctional  $\alpha_2$ -adrenoceptors in rabbit vas deferens (Alabaster *et al.*, 1986).

We have now made a comparison of the postjunctional  $\alpha_2$ -adrenoceptors which mediate pressor responses in the pithed rat and rabbit, since this type of preparation has been used extensively in the basic classification and investigation of  $\alpha$ -adrenoceptor subtypes (Drew & Whiting, 1979; Docherty & McGrath, 1980). In order to keep conditions as similar as possible between the two species we have employed the physiological agonist noradrenaline in the presence of the  $\alpha_1$ -adrenoceptor antagonist prazosin. The effects of rauwolscine and Wy 26703 were then compared.

We first describe the pharmacological properties, in the pithed rabbit, of the vascular  $\alpha$ -adrenoceptors activated by intravenously administered agonists or

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nerve stimulation since this has been published only in short form (McGrath & McKean, 1981; 1982; McGrath *et al.*, 1982). Secondly, we compare the properties of the  $\alpha_2$ -adrenoceptors in rat and rabbit.

## Methods

Male New Zealand white rabbits (3–4 kg) were initially anaesthetized with Althesin injected via an ear vein and were pithed under halothane anaesthesia (McGrath & McKenzie, 1977), then artificially ventilated with 100% oxygen. Right and left carotid arteries were cannulated to monitor arterial blood pressure and for the addition of propranolol at 30 min intervals, respectively. All other drugs, including bolus injections of noradrenaline (NA), were administered via a cannula inserted into the right external jugular vein. The diastolic pressor effects of agonists or sympathetic nerve stimulation via the pithing rod (1 cm electrode, T8, 20 pulses, 0.1–10 Hz) were determined under control conditions and following administration of antagonists.

Male Wistar rats (250–275 g) were pithed under halothane anaesthesia (Gillespie *et al.*, 1970) and artificially ventilated with 100% oxygen. Carotid arterial pressure was monitored. Drugs, including propranolol, were injected via a jugular vein.

When comparing properties of  $\alpha_2$ -adrenoceptors in the vasculature of rat and rabbit, dose-diastolic carotid arterial pressor response curves to NA were constructed. The  $\alpha_2$ -adrenoceptor-mediated response was isolated by the addition of prazosin (1 mg kg<sup>-1</sup>), which blocked the  $\alpha_1$ -adrenoceptor-mediated response of NA. The effects of two  $\alpha_2$ -adrenoceptor antagonists, rauwolscline and Wy 26703, on the  $\alpha_2$ -adrenoceptor-mediated response, were tested in each species.

## Control experiments

**Rabbit** In an earlier study of the pithed rabbit (McGrath & Mackenzie, 1977) we demonstrated that the cardiac output, heart rate, peripheral resistance and arterial blood pressure remained constant over a 6 h period during which reproducible responses to a variety of reversible agonists and sympathetic nerve stimulation were obtained. In the present study we carried out a short series of three experiments in which we repeated dose-response curves to noradrenaline 8 to 10 times over a 5 to 6 h period and found that responses were reproducible. In the protocol for the first series of experiments (results in Figures 1 and 2) we carried out four consecutive dose-response curves to noradrenaline, to ensure viability of the preparation and reproducibility, before testing the effects of the antagonists. In the second set of experiments (results in Figures 3 and 4) a single control curve was obtained

before proceeding to examine the effects of antagonists.

**Rat** In the pithed rat, four consecutive dose-response curves to noradrenaline were obtained. In contrast to the rabbit, in which the relatively small additions to plasma volume had no effect on the resting cardiovascular system, in the rat the diastolic blood pressure remained constant but the pulse pressure increased throughout the experiment. This was presumably due to an increase in plasma volume and hence an increase in cardiac output. However, this had no significant effect on the pressor responses to noradrenaline measured as increases in diastolic pressure.

On the basis of these control experiments we are confident that shifts in dose-response curves produced by antagonists reflect the action of the antagonists and not time-related decreases in sensitivity of the preparations.

Drugs used were althesin (Glaxo), angiotensin I (Sigma), angiotensin II (hypertensin) (Ciba), captopril (Squibb), enalapril (MK-421) (Merck Sharp & Dohme), guanabenz (Sigma), halothane (Fluothane) (ICI), imiloxan (RS21361) (Syntex), (–)-noradrenaline bitartrate (Sigma), (–)-phenylephrine HCl (Sigma), prazosin HCl (Pfizer), propranolol HCl (Sigma), rauwolscline (Roth), teprotide (SQ 20,881) (Squibb), UK 14304 tartrate (5-bromo-6-[2-imidazolin-2-ylamino]-quinoxaline) (Pfizer), Wy 26703 (N-methyl-N-(1,3,4,6,7,11b-hexahydro-2H-benzo[a]-quinolizin-2-yl)-i-butanedisulphonamide HCl) (Wyeth).

## Results

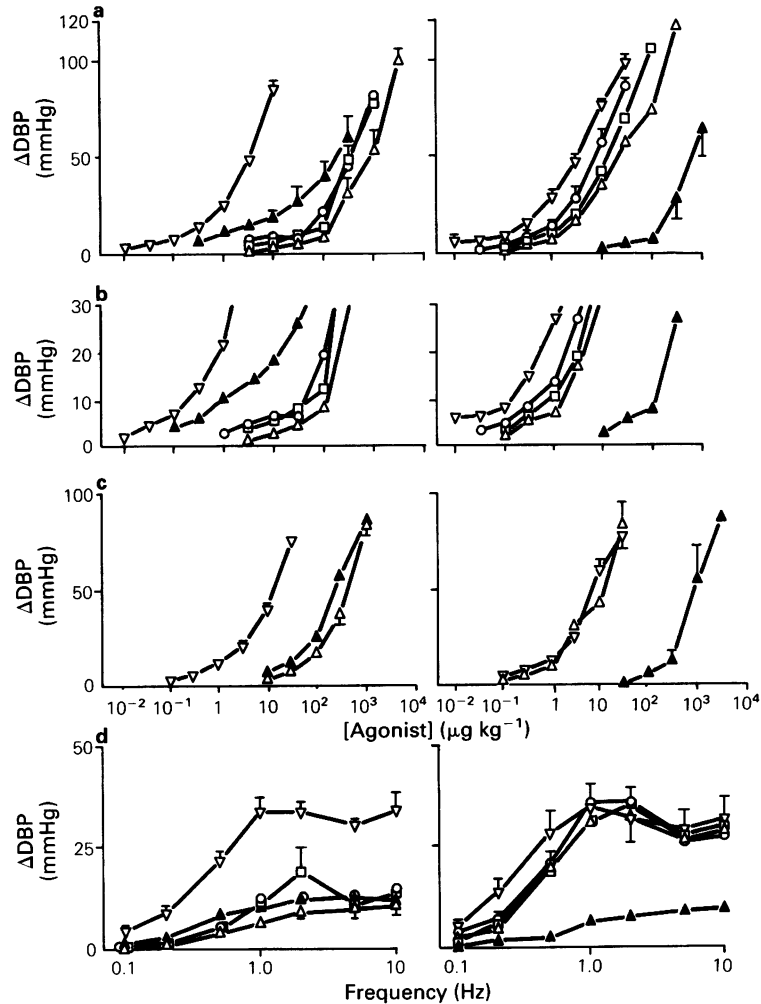
### *Pharmacological properties of vascular $\alpha$ -receptors in the pithed rabbit*

#### *Effects of antagonists on the responses to $\alpha$ -adrenoceptor agonists and to sympathetic nerve stimulation*

Noradrenaline in the range 10 ng kg<sup>-1</sup>–10  $\mu$ g kg<sup>-1</sup> produced dose-related pressor responses in the pithed rabbit (Figure 1a and b).

Prazosin (10  $\mu$ g kg<sup>-1</sup>–1 mg kg<sup>-1</sup>), given on its own, produced a dose-related rightward shift in the NA dose-response curve. Figure 1a shows this for prazosin (1 mg kg<sup>-1</sup>). This shift was not parallel and resulted in a shallower gradient for the NA dose-response curve, i.e. prazosin was more effective at higher doses of NA than at the lower dose range (Figure 1a and b).

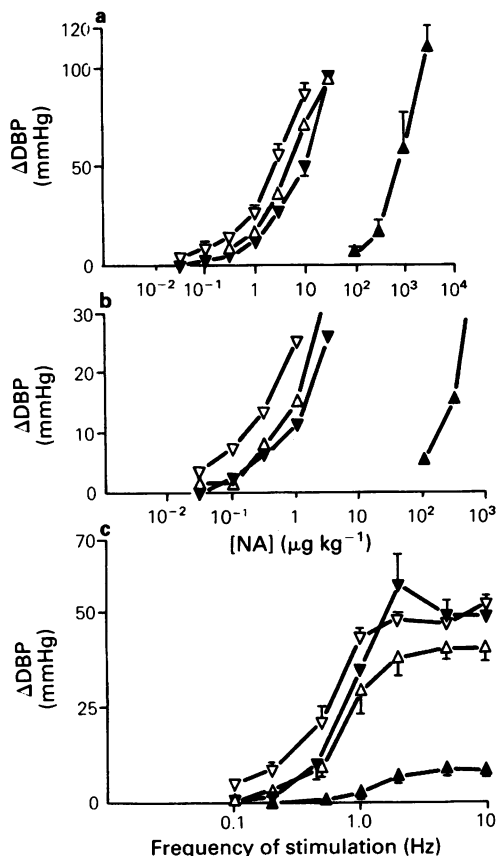
Rauwolscline (100  $\mu$ g kg<sup>-1</sup>–1 mg kg<sup>-1</sup>) (Figure 1a and b) and 10  $\mu$ g kg<sup>-1</sup>–30  $\mu$ g kg<sup>-1</sup> (not illustrated) or imiloxan (10 mg kg<sup>-1</sup>) (Figure 2a and b) and 1 mg kg<sup>-1</sup>–3 mg kg<sup>-1</sup> (not illustrated), given on their



**Figure 1** The effects of sequential administration of antagonists on pressor responses (change in diastolic blood pressure (DBP)) in the pithed rabbit to (a) noradrenaline (b) noradrenaline on an expanded scale (c) phenylephrine and (d) sympathetic nerve stimulation (T8, 20 pulses, via the pithing rod). Propranolol  $1 \text{ mg kg}^{-1}$  was present throughout. Control responses ( $\nabla$ ) were obtained and repeated after prazosin then 3 increasing doses of rauwolscine (left panels) or rauwolscine then prazosin (right panels). Symbols indicate the last drug administered: prazosin  $1 \text{ mg kg}^{-1}$  ( $\blacktriangle$ ); rauwolscine  $100 \text{ } \mu\text{g kg}^{-1}$  ( $\circ$ ); rauwolscine  $300 \text{ } \mu\text{g kg}^{-1}$  ( $\square$ ); rauwolscine  $1 \text{ mg kg}^{-1}$  ( $\triangle$ ). Responses shown are means with vertical lines indicating s.e. means (omitted where these are smaller than the symbols or, in (b), for clarity).

own, produced small rightward shifts of the NA dose-response curve. Rauwolscine was more potent than imiloxan and shifted the curve further. Given after prazosin ( $1 \text{ mg kg}^{-1}$ ) each of these  $\alpha_2$ -adrenoceptor antagonists produced a further rightward shift, greater than in the absence of prazosin. Combined  $\alpha_1$ - and  $\alpha_2$ -adrenoceptor blockade caused a parallel rightward shift in the dose-response curve.

*Phenylephrine* produced dose-related pressor responses in the range  $100 \text{ ng kg}^{-1}$ – $30 \text{ } \mu\text{g kg}^{-1}$  (Figure 1c). Prazosin shifted the dose-response curve to phenylephrine to the right. Subsequent addition of rauwolscine ( $0.1$  and  $0.3 \text{ mg kg}^{-1}$ ) had no effect and rauwolscine ( $1 \text{ mg kg}^{-1}$ ) produced only a further small shift to the right. Rauwolscine given on its own had no effect on the phenylephrine dose-response curve but



**Figure 2** The effects of sequential administration of antagonists on pressor responses in the pithed rabbit to (a) noradrenaline (NA) (b) stimulation via the pithing rod (1 cm electrode, T8, 20 pulses). Propranolol  $1 \text{ mg kg}^{-1}$  was present throughout. Control responses ( $\nabla$ ) were obtained and repeated after a sequence of 3 increasing doses of imiloxan at concentrations of  $1 \text{ mg kg}^{-1}$  (not shown),  $3 \text{ mg kg}^{-1}$  (not shown) and finally  $10 \text{ mg kg}^{-1}$  (as shown). This was followed by the addition of rauwolscline ( $1 \text{ mg kg}^{-1}$ ) and then prazosin ( $1 \text{ mg kg}^{-1}$ ). ( $\Delta$ ) Imiloxan  $10 \text{ mg kg}^{-1}$ ; ( $\nabla$ ) rauwolscline  $1 \text{ mg kg}^{-1}$ ; ( $\blacktriangle$ ) prazosin  $1 \text{ mg kg}^{-1}$ . Responses shown are means with vertical lines indicating s.e.means, (omitted where these are smaller than the symbols or, in (b), for clarity).

slightly enhanced the effectiveness of prazosin.

**Guanabenz** ( $1 \mu\text{g kg}^{-1}$ – $300 \mu\text{g kg}^{-1}$ ) produced dose-related pressor responses but did not produce a definite maximum (Figure 5a). Rauwolscline significantly reduced responses to guanabenz but tachyphylaxis to guanabenz made accurate assessment of blockade impossible (results not shown).

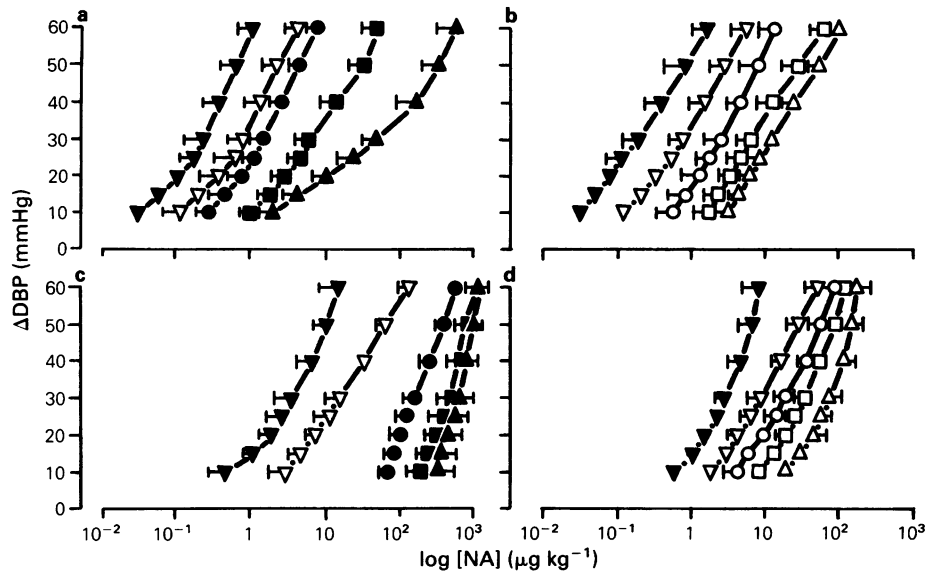
**Pressor nerve stimulation** (T8, 20 pulses, 0.1–10 Hz) produced frequency-related responses which reached a plateau at 1 Hz (Figures 1d and 2c). Prazosin, rauwolscline and imiloxan were all effective antagonists at some point on this frequency-response curve but to different degrees at different frequencies. When given first, rauwolscline and imiloxan were more effective against low frequency nerve stimulation but did not reduce responses to higher frequencies. Prazosin was effective in reducing responses at both low and high frequencies, but between 1 Hz and 10 Hz a residual component remained. The combination of prazosin and rauwolscline, or, imiloxan with rauwolscline and prazosin (each at  $1 \text{ mg kg}^{-1}$ ), produced a greater inhibition than did prazosin alone but did not produce a complete block.

**Angiotensin II (AII) and angiotensin I (AI)** at  $1 \mu\text{g kg}^{-1}$  and  $10 \mu\text{g kg}^{-1}$  produced dose-related pressor responses in the rabbit. To investigate whether endogenous AII is necessary for the production of the response mediated by  $\alpha_2$ -adrenoceptors, the effects of angiotensin converting enzyme inhibitors (ACE-inhibitors) on the pressor responses to agonists in the pithed rabbit were also studied in a small number of preparations (not illustrated). The ACE-inhibitors teprotide, captopril and enalapril (each at  $0.1 \text{ mg kg}^{-1}$ ) all reduced the pressor response to AI ( $1 \mu\text{g kg}^{-1}$ ) by approximately 80%. Peak responses to NA ( $100 \text{ ng kg}^{-1}$ – $10 \mu\text{g kg}^{-1}$ ), the  $\alpha_1$ -adrenoceptor agonist phenylephrine ( $100 \text{ ng kg}^{-1}$ – $30 \mu\text{g kg}^{-1}$ ) and to the  $\alpha_2$ -adrenoceptor agonist UK 14304 ( $1 \mu\text{g kg}^{-1}$ – $30 \mu\text{g kg}^{-1}$ ) were unaffected by any of the ACE-inhibitors, as were the late phase of these responses. In the pithed rat, peak responses to NA also were unaffected at this dose of teprotide. However, the late phase of the NA response was significantly reduced (Grant & McGrath, 1984).

#### *Comparison of $\alpha_2$ -adrenoceptor-mediated pressor responses to NA in the rat and rabbit*

Prazosin ( $1 \text{ mg kg}^{-1}$ ) in the rat produced a parallel rightward shift in the NA dose-response curve (Figure 3a and b). In the rabbit, prazosin ( $1 \text{ mg kg}^{-1}$ ) produced a greater inhibition against higher doses of NA than against lower doses, thus leaving a shallower dose-response curve to NA (Figure 3c and d).

In either species (Figure 3), rauwolscline and Wy26703, given after prazosin, produced a further rightward shift. For Wy 26703 the shifts were approximately parallel. In the rabbit, rauwolscline produced a greater inhibition against lower doses of NA than against higher doses. In the rat, the higher doses of rauwolscline ( $3 \text{ mg kg}^{-1}$ ) tended to reduce the slope of the curve indicating a non-specific action of rauwolscline. At these doses, no significant pressor responses



**Figure 3** The effects of sequential administration of blocking agents on the noradrenaline (NA) pressor-response curve in the pithed rat (a and b) and pithed rabbit (c and d). For this figure log dose-response curves were drawn as in Figures 1 and 2 for individual rabbits and the doses to produce responses of various sizes from 10 to 60 mmHg were interpolated. The means of the doses for each response were then plotted with their s.e. means (omitted where these are smaller than the symbols). The order of administration of the drugs was: (1) propranolol 1 mg kg<sup>-1</sup> (▼); (2) prazosin 1 mg kg<sup>-1</sup> (▽); (3) rauwolscline 300 μg kg<sup>-1</sup> (●), or Wy 26703 300 μg kg<sup>-1</sup> (○); (4) rauwolscline 1 mg kg<sup>-1</sup> (■), or Wy 26703 1 mg kg<sup>-1</sup> (□); (5) rauwolscline 3 mg kg<sup>-1</sup> (▲), or Wy 26703 3 mg kg<sup>-1</sup> (△).

were produced by the antagonists.

These shifts were expressed as dose-ratios (the dose of NA required to produce a standard response in the presence of the  $\alpha_2$ -adrenoceptor antagonist as well as prazosin, divided by the dose of NA required to produce the same response in the presence of prazosin only). Dose-ratios were measured at changes in diastolic blood pressure (DBP) of between 10 and 60 mmHg. For the illustration of  $\alpha_2$ -adrenoceptor antagonist potency the graph of dose-ratio against  $\alpha_2$ -adrenoceptor antagonist dose at a change in diastolic blood pressure of 10 mmHg showed the greatest shift, indicating that at these lower pressor changes the  $\alpha_2$ -adrenoceptor-mediated component dominates.

At a change in DBP of 10 mmHg (Figure 4a) absolute antagonist potency and order of potency were found to differ between the species. In the rat rauwolscline and Wy 26703 were equipotent. In the rabbit rauwolscline was more potent than Wy 26703. Rauwolscline was more potent in the rabbit than in the rat. Wy 26703 was more potent in the rat than in the rabbit (results were analysed by Student's paired *t* test and results with *P* > 0.05 were considered to be non-significant).

At 20 mmHg change in DBP (Figure 4b) rauwols-

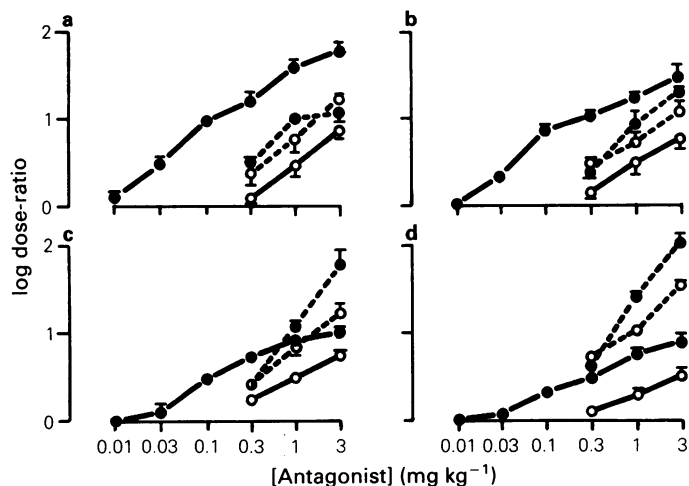
cine and Wy 26703 were still equipotent in the rat. In the rabbit rauwolscline was again more potent than Wy 26703. The order of potency of antagonists was the same as that found at a change in DBP of 10 mmHg.

At 30 mmHg change in DBP (Figure 4c) rauwolscline was more potent than Wy 26703 in both species. At lower antagonist doses rauwolscline was more potent in the rabbit than in the rat, but at higher doses rauwolscline was more potent in the rat. Wy 26703 was more potent in the rat than in the rabbit.

At 60 mmHg change in DBP (Figure 4d) rauwolscline again, was more potent than Wy 26703 in both species. Both antagonists were more potent in the rat than in the rabbit. It seems that in the rabbit high doses of NA produce responses characterized by a relatively low dose-ratio to  $\alpha_2$ -adrenoceptor antagonists.

#### *Comparing pressor responses mediated by $\alpha_1$ -adrenoceptors and $\alpha_2$ -adrenoceptors to 'selective' agonists in two species*

**$\alpha_1$ -Adrenoceptors** In the rabbit, the  $\alpha_1$ -adrenoceptor agonist phenylephrine (Figure 1c) produced dose-related but short lived pressor responses in the range 100 ng kg<sup>-1</sup>–30 μg kg<sup>-1</sup> giving peak responses com-



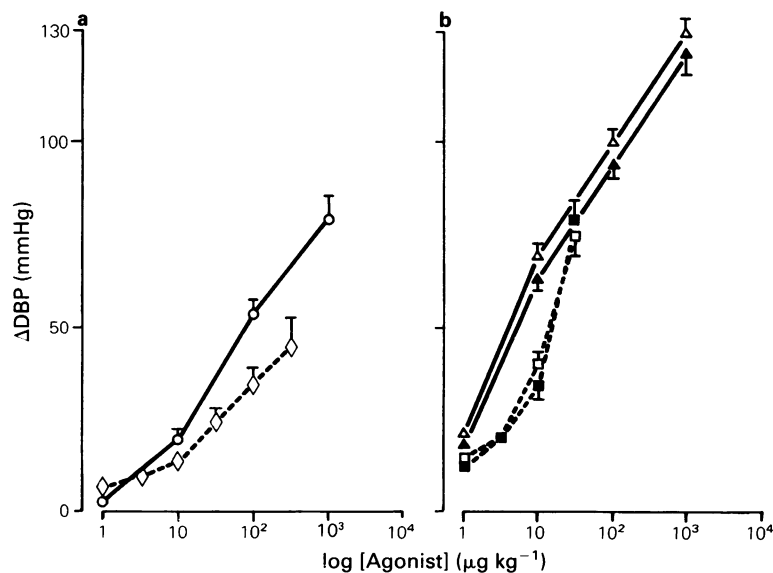
**Figure 4** Log (dose-ratio) was plotted against antagonist dose (log scale) to illustrate the antagonist potency at changes in diastolic blood pressure of (a) 10 mmHg, (b) 20 mmHg, (c) 30 mmHg and (d) 60 mmHg. Experiments as in Figure 3: rauwolscline in rat (●---●) or rabbit (●—●); Wy 26703 in rat (○---○) or rabbit (○—○).

parable to those found with NA as the agonist (Figure 1a), although the NA response was longer lasting.

In the rat (Figure 5), the pressor effects of phenylephrine were found to be very short lived in comparison with those of NA, but were of a comparable size. In

both species prazosin ( $1 \text{ mg kg}^{-1}$ ) produced a large shift in the phenylephrine dose-response curve while the  $\alpha_2$ -adrenoceptor antagonist, rauwolscline ( $1 \text{ mg kg}^{-1}$ ) left the responses virtually unaltered.

Phenylephrine was 3 times more potent in the rat



**Figure 5** Pressor responses to (a) guanabenz and (b) phenylephrine in the pithed rat and rabbit in the presence of propranolol ( $1 \text{ mg kg}^{-1}$ ). (a) (○) Guanabenz in the rat; (◇) guanabenz in the rabbit. (b) (△) Phenylephrine in the rat (with rauwolscline  $1 \text{ mg kg}^{-1}$  (▲)); (□) phenylephrine in the rabbit (with rauwolscline  $1 \text{ mg kg}^{-1}$  (■)).

**Table 1** A comparison of the potencies of  $\alpha$ -adrenoceptor agonists in the pithed rat and rabbit

	Rat	Rabbit	Ratio rabbit/rat
ED <sub>20</sub> NA ( $\alpha_1$ )	0.3 $\mu\text{g kg}^{-1}$	7.0 $\mu\text{g kg}^{-1}$	23.8
ED <sub>20</sub> PE	1.0 $\mu\text{g kg}^{-1}$	3.0 $\mu\text{g kg}^{-1}$	3.0
Molar ratio of ED <sub>20</sub> NA/PE	0.47	3.6	
ED <sub>20</sub> NA ( $\alpha_2$ )	0.3 $\mu\text{g kg}^{-1}$	7.0 $\mu\text{g kg}^{-1}$	25.0
ED <sub>20</sub> guanabenz	10.0 $\mu\text{g kg}^{-1}$	20.0 $\mu\text{g kg}^{-1}$	2.0
Molar ratio of ED <sub>20</sub> NA/G	0.04	0.5	
Molar ratio of ED <sub>20</sub> NA ( $\alpha_1$ )/NA ( $\alpha_2$ )	1.0	1.0	

The potency of  $\alpha$ -adrenoceptor agonists (phenylephrine (PE), guanabenz (G), noradrenaline (NA)) in the presence of either prazosin (NA ( $\alpha_2$ )) or rauwolscine (NA ( $\alpha_1$ )) in the pithed rat and rabbit was measured in the presence of propranolol (1 mg kg<sup>-1</sup>). ED<sub>20</sub> values are the doses of the agonist required to produce changes in diastolic blood pressure of 20 mmHg.

than in the rabbit when measuring control peak pressor responses. This ratio was less than that of NA after  $\alpha_2$ -adrenoceptor blockade (23.8 times) (Table 1).

**$\alpha_2$ -Adrenoceptors** In the rabbit, the  $\alpha_2$ -adrenoceptor agonist guanabenz (Figure 5a) produced dose-related diastolic pressor responses in the range 1  $\mu\text{g kg}^{-1}$ –300  $\mu\text{g kg}^{-1}$ . Another  $\alpha_2$ -adrenoceptor agonist, UK 14304, produced dose-related pressor effects which reached a similar plateau of 60 mmHg at 10  $\mu\text{g kg}^{-1}$ –100  $\mu\text{g kg}^{-1}$ .

Guanabenz was twice as potent in the rat than in the rabbit (Table 1). The  $\alpha_2$ -adrenoceptor potency of NA was assessed as responses after 1 mg kg<sup>-1</sup> prazosin, as illustrated in Table 1, and was 25 times more potent in the rat.

## Discussion

The rabbit, like the rat, has  $\alpha_1$ - and  $\alpha_2$ -adrenoceptors both of which can mediate pressor responses to noradrenaline and can be classified according to antagonist potencies. The 'selectivity' of each antagonist for the  $\alpha$ -adrenoceptor subtypes in the rabbit, was established by its effects against phenylephrine. This is similarly shown in the rat. The effects of the more 'selective' imiloxan (RS 21361) (Michel & Whiting, 1981) confirmed the  $\alpha_2$ -adrenoceptor selectivity of rauwolscine and showed that the higher doses of rauwolscine had some  $\alpha_1$ -adrenoceptor antagonism.

However, against low doses of NA, rauwolscine is more potent in the rabbit than in the rat, whereas Wy 26703 is not (Table 2). This is consistent with the hypothesis that  $\alpha_2$ -adrenoceptors in rabbit are different from those in rat with regard to relative antagonist potency and shows that this applies to resistance vessels *in vivo*. We have not analysed the  $\alpha_1$ -adrenoceptors in the two species in the same way here.

The potency of prazosin against phenylephrine in the rabbit (Figure 1c) was slightly less than was found in the rat under similar conditions (in the presence of rauwolscine and propranolol, both at 1 mg kg<sup>-1</sup>) (Flavahan, 1983).

NA was more potent in the rat than in the rabbit at either  $\alpha_1$ - or  $\alpha_2$ -adrenoceptors but this was not reflected in the potency of the 'selective' agonists phenylephrine and guanabenz (Table 1). This could be interpreted as a difference in metabolism or disposition of NA between the two species, or this may represent another difference between  $\alpha$ -adrenoceptors in the two species so that both agonist and antagonist potencies differ. Together with the small difference in potency of prazosin mentioned above this might extend the difference to  $\alpha_1$ -adrenoceptors as well as  $\alpha_2$ -adrenoceptors. This has previously been suggested in isolated aorta by Ruffolo & Waddell (1982). However, caution

**Table 2** A comparison of the potencies of  $\alpha_2$ -adrenoceptor antagonists, rauwolscine and Wy 26703 in the pithed rat and rabbit

	Rat	Rabbit	Ratio rabbit/rat
Rauw	0.3	0.03	0.1
Wy 26703	0.4	1.2	3
Ratio Wy/Rauw	1.3	40	

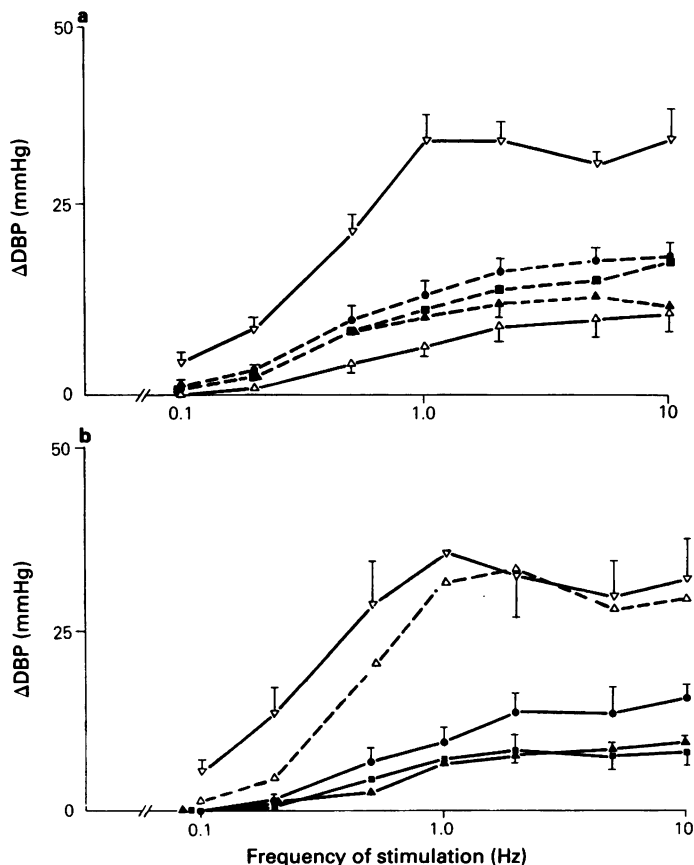
The potency of the  $\alpha_2$ -adrenoceptor antagonists rauwolscine (Rauw) and Wy 26703 was measured at a change in diastolic blood pressure of 10 mmHg, where potency is taken as the dose of antagonist (mg kg<sup>-1</sup>) required to give a 5 fold shift in the noradrenaline dose-response curve. In the rabbit rauwolscine was 10 times more potent than in the rat, whereas in the rat Wy 26703 was 3 times more potent than in the rabbit.

is necessary in interpreting absolute potency differences under non-equilibrium *in vivo* conditions (see Docherty & Hyland, 1985), particularly since some of the newer synthetic  $\alpha_2$ -adrenoceptor antagonists have partial agonist activity which varies between species (Paciorek & Shepperson, 1983; authors unpublished observations).

Responses to NA in rabbit have a higher proportion mediated by  $\alpha_2$ -adrenoceptors at low doses compared with high doses at which  $\alpha_1$ -adrenoceptors become dominant. A similar phenomenon occurs with pressor nerve-induced responses which have a relatively greater  $\alpha_2$ -adrenoceptor-mediated component at low frequencies of stimulation. This conclusion can be reached using either rauwolscline or imiloxan as  $\alpha_2$ -adrenoceptor antagonist.

It is conceivable that other factors, such as differences in the way that the two species metabolize the agonists or antagonists, could contribute to the apparent differences in antagonist potencies encountered in this study. However, no simple model of such factors occurs to us at present.

Recent work by Schumann & Lues (1983) proposes a role for AII in the vascular postsynaptic  $\alpha_2$ -adrenoceptor-mediated response by showing that AII, acting postsynaptically, potentiates the contractile response of  $\alpha_2$ -adrenoceptor agonists in the saphenous vein of the rabbit. However, the addition of teprotide, captopril and enalapril in the rabbit did not affect the responses to NA, UK 14304 or phenylephrine, but did reduce the response to AI by 80%. Therefore this proposal is not supported by the present study.



**Figure 6** The effects of sequential administration of antagonists on pressor responses in the pithed rabbit to sympathetic nerve stimulation (T8, 20 pulses, via the pithing rod). Propranolol  $1 \text{ mg kg}^{-1}$  was present throughout. Control responses ( $\nabla$ ) were obtained and repeated after 3 increasing doses of prazosin followed by rauwolscline (a) or rauwolscline then 3 increasing doses of prazosin (b). Symbols indicate the last drug administered: prazosin  $100 \mu\text{g kg}^{-1}$  ( $\bullet$ ); prazosin  $300 \mu\text{g kg}^{-1}$  ( $\blacksquare$ ); prazosin  $1 \text{ mg kg}^{-1}$  ( $\blacktriangle$ ); rauwolscline  $1 \text{ mg kg}^{-1}$  ( $\Delta$ ). Responses shown are means with vertical lines indicating s.e. means (omitted where these are smaller than the symbols).



The present results show that components of the response to vasopressor nerve stimulation can be partly blocked by  $\alpha$ -adrenoceptor antagonists but that a resistant component remains. This indicates both  $\alpha$ -adrenergic and non- $\alpha$ -adrenergic (possibly non-adrenergic) components of the vascular excitatory transmission process. We have already demonstrated in a separate study in the rat that there is an  $\alpha$ -blocker-resistant vasopressor response susceptible to the purinergic blocker  $\alpha$ ,  $\beta$ -methylene ATP (Flavahan *et al.*, 1985; Bulloch & McGrath, 1986). It has even been suggested that in some preparations the  $\alpha$ -adrenergic component is the minor one and that our interpretation, which is based on prazosin's effects, overestimates the role of  $\alpha_1$ -adrenoceptors because the high doses of prazosin, which we employ, are not selective (Hirst & Lew, 1987). However, the present study in the rabbit, together with the earlier data from the rat, refutes this.

Against pressor responses to stimulation of the spinal outflow, low doses of prazosin (0.1 and 0.3 mg kg<sup>-1</sup>), in the rabbit (Figure 6) and in the rat (Docherty & McGrath, 1980; Flavahan *et al.*, 1985), produced the same degree of blockade as did the

higher dose of 1 mg kg<sup>-1</sup>. Another  $\alpha_1$ -adrenoceptor antagonist, corynanthine, was also effective from 0.5 mg kg<sup>-1</sup> (Demichel *et al.*, 1982). This shows that responses are susceptible to low doses of  $\alpha_1$ -blockers and provides no evidence that the higher dose of prazosin (1 mg kg<sup>-1</sup>) produces non-specific effects, as suggested by Hirst *et al.* (1985). Nevertheless there is a substantial component of the vasopressor response, particularly at higher frequencies, which in the rabbit, as in the rat, is resistant to  $\alpha$ -adrenoceptor blockers. In contrast the  $\alpha_2$ -adrenoceptor-mediated component can be most easily demonstrated at low frequencies of stimulation.

In conclusion, the results are consistent with the characteristics of the vascular postjunctional  $\alpha_2$ -adrenoceptor being species-dependent. Both  $\alpha$  subtypes contribute to pressor responses to catecholamines and sympathetic nerves.

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