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# THE ROLE OF PRESYNAPTIC α-ADRENOCEPTORS IN THE REGULATION OF BLOOD PRESSURE IN THE CONSCIOUS RABBIT

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**1** Changes in mean arterial pressure, heart rate and plasma noradrenaline after α-adrenoceptor blockade with several α-adrenoceptor antagonists have been studied in the conscious rabbit in order to investigate the possible role of presynaptic α-adrenoceptors in cardiovascular regulation.

**2** Prazosin (0.05–2 mg/kg) and phentolamine (0.5–20 mg/kg) produced dose-dependent falls in mean arterial pressure and rises in plasma noradrenaline. These changes were related to the degree of postsynaptic α-adrenoceptor blockade determined by the pressor response to intravenous phenylephrine.

**3** Similar changes in mean arterial pressure and plasma noradrenaline were observed after administration of the direct vasodilators hydralazine (1–10 mg/kg) and nitroprusside ($2.5–55\ \mu g\ kg^{-1}\ min^{-1}$).

**4** After baroreceptor deafferentation by sinoaortic denervation the falls in mean arterial pressure were much greater and the rise in plasma noradrenaline was markedly attenuated.

**5** Yohimbine (1 mg/kg) increased mean arterial pressure and plasma noradrenaline but it was not possible to exclude the possibility that central nervous effects of yohimbine underlay the increased sympathetic activity.

**6** The magnitude of the baroreflex response to changes in pressure make it unlikely that the functional significance of the presynaptic α-adrenoceptor can be readily determined by measurement of plasma noradrenaline in intact animals.

## Introduction

α-Adrenoceptors have been divided into two categories on the basis of agonist and antagonist potencies (Starke, 1972; Starke, Montel, Gayk & Merker, 1974; Drew, 1976; Berthelsen & Pettinger, 1977; Doxey, Smith & Walker, 1977): classical postsynaptic $\alpha_1$-adrenoceptors which are situated on the postsynaptic membranes of smooth muscle of the effector organs and $\alpha_2$-adrenoceptors located presynaptically on noradrenergic nerve endings. These presynaptic α-adrenoceptors are involved in a negative feedback mechanism through which the neurotransmitter noradrenaline can regulate its own release (Langer, 1974; 1977; Starke, 1977; Dixon, Mosimann & Weiner, 1979).

Most investigations into the role of presynaptic α-adrenoceptors have used α-adrenoceptor agonists and antagonists and measured their effects on the release of noradrenaline from isolated tissues after electrical stimulation (Langer, 1977; Starke, 1977). However, in many cases very high frequencies of stimulation have been used and some doubt has been expressed as to the physiological significance of these presynaptic receptor mechanisms *in vivo* (Kalsner, 1979; Chan & Kalsner, 1979; Kalsner, Suleiman & Dobson, 1980).

Few investigations have been carried out in intact animals or man. Although studies in the anaesthetized dog suggest that presynaptic $\alpha_2$-adrenoceptors do have a physiological role (Yamaguchi, De Champlain & Nadeau, 1977) preliminary studies in conscious animals (Graham & Pettinger, 1979) and man (Dollery, FitzGerald & Watkins, 1979) are contradictory. Graham and Pettinger's work suggested that there was a significant physiological role for presynaptic α-adrenoceptors in conscious rats but Dollery and his colleagues were unable to confirm these findings in man.

If presynaptic $\alpha_2$-adrenoceptors do modify noradrenaline release from the sympathetic nerve terminals in the conscious animal, antagonists which act primarily on $\alpha_2$-adrenoceptors would be expected to cause a detectable rise in plasma noradrenaline while preferential blockade of the postsynaptic α-

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adrenoceptors should result in a fall in blood pressure but little change in plasma noradrenaline. Studies in intact animals are complicated by the presence of other compensatory mechanisms which may mask changes initiated at the α-adrenoceptor. In particular, changes in arterial pressure will influence the aortic and carotid baroreceptors causing changes in sympathetic nerve activity, noradrenaline release and heart rate (Bing, Thomas & Waples, 1945; De Quattro, Nagatsu, Maronde & Alexander, 1969; Alexander & De Quattro, 1974a,b).

We have therefore attempted to determine the relative importance of the presynaptic ($\alpha_2$)-adrenoceptors in regulating noradrenaline release and thus modifying blood pressure in the conscious animal by studying the effects of a wide range of α-adrenoceptor antagonists on mean arterial pressure, heart rate and plasma noradrenaline in intact rabbits and after bilateral sinoaortic denervation to remove baroreceptor afferents.

A preliminary account of some of this work has been given to the British Pharmacological Society. (Fraser, Hamilton, Reid & Zamboulis, 1980).

## Methods

Male white New Zealand rabbits (2.2–2.8 kg) (Hylyne Commercial Rabbits, Northwich, Cheshire) were used in all studies. Three groups, of animals were examined, intact, sinoaortic denervated (SAD) and 6-hydroxydopamine (6-OHDA)-treated. The SAD animals underwent bilateral sinoaortic denervation as described by Chalmers & Wurtman (1971) at least two weeks before the cardiovascular studies. 6-Hydroxydopamine 50 mg/kg in 0.1% ascorbic acid given in two doses of 25 mg/kg 2 h apart,was administered intravenously 24–48 h before the cardiovascular studies were started. This dose has been reported to cause a relative chemical sympathectomy for 7–10 days with marked depletion of tissue noradrenaline (Yates, Bennett, Fentem & Tomlinson, 1975).

### *Cardiovascular studies*

Catheters were placed in the central artery of the ear under local anaesthesia for direct recordings of mean arterial pressure (MAP), heart rate (HR) and for removal of arterial blood for the measurement of plasma noradrenaline (NA) by the radioenzymatic method of Da Prada & Zurcher (1976).

A further catheter was introduced into the central vein of the ear, inserted 6–8 cm towards the heart and used for injection of drugs.

Basal measurements of MAP and HR were made in all animals and a 2 ml arterial blood sample was withdrawn for measurement of plasma NA. A pressor dose-response curve to the $\alpha_1$-adrenoceptor agonist, phenylephrine (10–50 μg/kg, i.v.), was constructed using at least 4 dose levels. The animals then received an intravenous injection of vehicle or one of the following α-adrenoceptor antagonists: the $\alpha_1$-antagonist, prazosin (0.05–2.0 mg/kg), the mixed $\alpha_1/\alpha_2$-antagonist, phentolamine (0.5–20 mg/kg), or yohimbine (1.0 mg/kg) which blocks $\alpha_2$-adrenoceptors preferentially (Doxey *et al.*, 1977). The animals in this group were studied on two occasions 3–5 days apart. The rabbits received different treatments on each occasion so that each animal was given two of the four drugs (prazosin, phentolamine, yohimbine or vehicle). Five animals were studied at each dose of each drug.

Measurements of MAP and HR were repeated 20 min after injection, by which time, changes in pressure had reached a maximum. A second blood sample (2 ml) was withdrawn for catecholamine measurement and another dose-response curve to intravenous phenylephrine (10–200 μg/kg) constructed. The total volume of blood removed over 3–4 h was 4 ml. This did not cause significant changes in MAP, HR or plasma NA.

In separate groups of animals ($n = 5–6$) MAP, HR and plasma NA were also measured before and 30 min after intravenous injection of hydralazine (1–10 mg/kg) or at the end of a 10 min infusion of sodium nitroprusside (2.5–55 $\mu g\,kg^{-1}\,min^{-1}$). The infusion rate was increased stepwise from 2.5–20 $\mu g\,kg^{-1}\,min^{-1}$. The 55 $\mu g\,kg^{-1}\,min^{-1}$ infusion was carried out in a separate group of rabbits ($n = 6$).

Similar studies were carried out in the SAD animals before and 20 min after administration of prazosin (0.1 and 0.5 mg/kg), phentolamine (1.0 and 5.0 mg/kg) and yohimbine (1.0 mg/kg). The effects of yohimbine (1.0 mg/kg) on MAP, HR and plasma NA were also examined in the 6-hydroxydopamine treated rabbits. Eight animals were studied at each dose of each drug.

### *Drugs*

Drugs were obtained from the following sources: prazosin (Pfizer Ltd); yohimbine hydrochloride, noradrenaline hydrochloride, phentolamine mesylate, sodium nitroprusside, phenylephrine hydrochloride, hydralazine, 6-hydroxydopamine hydrochloride, (Sigma Chemicals Co.) and were dissolved in distilled water for administration. Concentrations were such that the maximum injection volume was 0.5 ml.

### *Analysis of results*

All groups consisted of at least 5 animals. Groups were compared with the appropriate vehicle-treated

**Table 1** Changes in mean arterial pressure, heart rate and plasma noradrenaline after α-adrenoceptor blockade

| Group | Dose-ratio | *MAP* (mmHg) Baseline | Δ | *HR* (beats/min) Baseline | Δ | *Plasma NA* (nM) Baseline | Δ |
|---|---|---|---|---|---|---|---|
| Vehicle | 1.0±0.2 | 76±7 | −0.3±1.6 | 255±25 | +25±7 | 2.5±1.2 | −0.3±0.4 |
| Prazosin | | | | | | | |
| 0.05 mg/kg | 1.6±0.4 | 80±10 | −8.5±3.5 | 252±21 | +47±28 | 2.5±1.3 | −0.5±2.5 |
| 0.1 mg/kg | 4.0±1.7 | 79±12 | −6.0±4.0 | 291±19 | +51±18 | 2.7±1.0 | +1.0±2.1 |
| 0.5 mg/kg | 9.7±3.3 | 73±10 | **−12.4±5.5 | 307±29 | **+72±15 | 2.4±1.5 | *+2.2±1.2 |
| 1.0 mg/kg | 16.2±3.3 | 73±10 | **−12.0±6.4 | 311±34 | **+66±17 | 2.3±1.7 | *+4.8±3.0 |
| 2.0 mg/kg | 30.1±7.1 | 70±9 | **−15.5±5.3 | 311±35 | **+81±27 | 2.5±1.3 | **+5.9±2.6 |
| Phentolamine | | | | | | | |
| 0.5 mg/kg | 2.6±1.0 | 70±7 | −3.4±3.8 | 209±17 | −11±8 | 2.7±0.8 | −0.4±0.3 |
| 1.0 mg/kg | 4.7±0.7 | 70±12 | **−5.0±3.6 | 268±27 | +8±2 | 2.2±0.7 | +0.7±1.8 |
| 5.0 mg/kg | 9.5±3.6 | 78±14 | **−9.3±2.0 | 258±32 | +8±25 | 2.5±1.2 | *+1.3±2.0 |
| 10.0 mg/kg | 14.0±3.1 | 78±8 | *−12.0±3.9 | 241±25 | +16±42 | 3.2±1.4 | *+2.4±2.4 |
| 20.0 mg/kg | 19.5±5.0 | 73±11 | **−20.5±4.9 | 228±37 | +50±5 | 2.5±1.1 | **+5.3±0.7 |

*$P<0.05$ and **$P<0.01$ when the difference before and after treatment with vehicle are compared with drug treatment by the Wilcoxon non-parametric test. There was no significant difference between starting levels of mean arterial pressure (MAP), heart rate (HR) or plasma noradrenaline (NA).

groups using the non parametric Wilcoxon test. All results are expressed as mean±s.d. The phenylephrine dose-ratio was used to quantify the degree of postsynaptic $\alpha_1$-adrenoceptor blockade. Dose-response curves to phenylephrine were constructed in individual animals before and after administration of α-adrenoceptor antagonists and the shift in these curves expressed as dose-ratios; only the linear portion of the curves was considered when calculating dose-ratios.

## Results

### *Changes in mean arterial pressure, plasma noradrenaline and heart rate after α-adrenoceptor antagonism with prazosin and phentolamine in intact rabbits*

Increasing doses of prazosin from 0.05 to 2 mg/kg and phentolamine from 0.5 to 20 mg/kg caused a stepwise parallel shift to the right in the dose-response curve to phenylephrine. Dose-ratios are shown in Table 1.

Prazosin and phentolamine also caused a fall in MAP (Figure 1). After phentolamine the fall in MAP was related to the dose of drug administered and also correlated with the degree of $\alpha_1$-adrenoceptor blockade ($r=0.97$, $P<0.01$). Although prazosin 0.05–2.0 mg/kg caused a dose-related shift to the right in phenylephrine dose-response curves ($r=0.96$, $P<0.01$) and low doses of prazosin (0.05–0.5 mg/kg) caused substantial falls in MAP, increasing the dose from 0.5–2.0 mg/kg produced little further lowering of blood pressure. Plasma NA increased after α-adrenoceptor blockade. The rise in plasma NA was dependent on the dose of α-adrenoceptor antagonist given (Figure 2) but did not reach significance ($P<0.05$) until doses of prazosin of 0.5 mg/kg or greater or doses of phentolamine of 5.0 mg/kg or above were administered (Table 1). The rise in plasma NA, like the fall in MAP, was related to the degree of postsynaptic $\alpha_1$-adrenoceptor blockade, $r=0.90$ ($P<0.01$) for prazosin and 0.99 ($P<0.001$) for phentolamine (Figure 3). The changes in MAP, plasma NA and HR are summarized in Table 1.

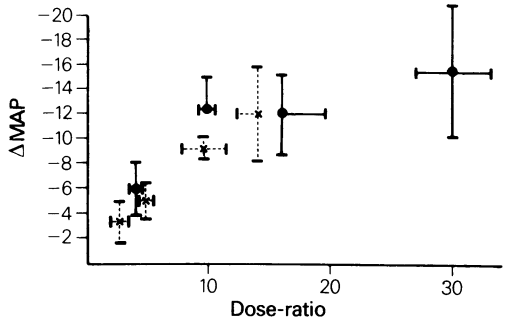


**Figure 1** Changes in mean arterial pressure after prazosin or phentolamine related to postsynaptic α-adrenoceptor blockade, expressed as phenylephrine dose-ratio: (●) prazosin; (×) phentolamine. Bars indicate s.d.

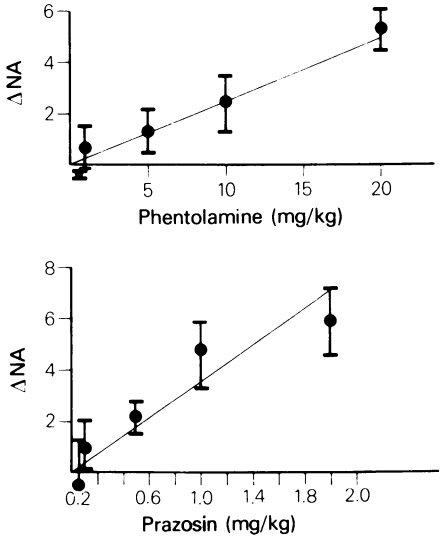


**Figure 2** Changes in plasma noradrenaline (nM) 20 min after intravenous administration of phentolamine or prazosin; bars indicate s.d.

When the changes in plasma NA and MAP were studied in individual rabbits treated with 0.1 mg/kg prazosin a negative correlation between the fall in MAP and the rise in plasma NA was observed (Figure 4).

Heart rate increased during the day in most groups of animals, including the vehicle-treated group, despite the 1 h rest period allowed before any basal measurements were made. This increase in heart rate could not be related to removal of blood for catecholamine measurements, injection of phenylephrine or vehicle and only reached significance in animals given doses of prazosin of 0.5 mg/kg or greater.

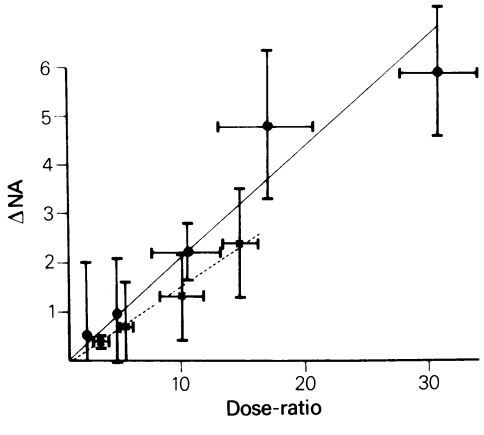


**Figure 3** Changes in plasma noradrenaline (nM) after prazosin related to postsynaptic α-adrenoceptor blockade, expressed as phenylephrine dose-ratio: (●) prazosin; (×) phentolamine. Bars indicate s.d.

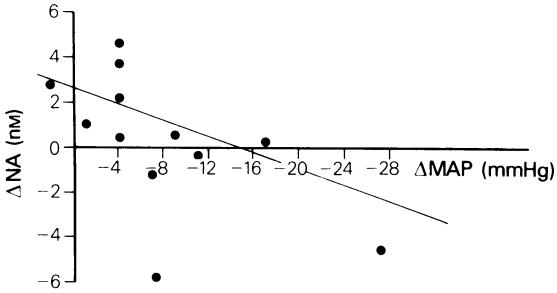


**Figure 4** Changes in mean arterial pressure (MAP) and plasma noradrenaline in individual rabbits 20 min after administration of intravenous prazosin (0.1 mg/kg) $r = 0.783$, $P < 0.01$.

*The effects of vasodilator drugs on mean arterial pressure, heart rate and plasma noradrenaline*

The direct vasodilators hydralazine (1 mg/kg–10 mg/kg) and sodium nitroprusside (2.5–55 $\mu g\,kg^{-1}\,min^{-1}$) produced falls in MAP ranging from $6.8 \pm 8.7$ to $16.5 \pm 5.1$ and $3.6 \pm 4.3$ to $24.0 \pm 10.4$ respectively. These falls in pressure were accompanied by rises in plasma NA which were comparable with the rises achieved after α-adrenoceptor blockade with prazosin and phentolamine, (Table 2).

The increase in heart rate after administration of the vasodilators was greater than that observed after α-adrenoceptor blockade. This was most marked after administration of hydralazine; falls in MAP ranging from 6.8–16.8 mmHg were accompanied by increases in HR ranging from 112–141 beats/min.

*Changes in mean arterial pressure, plasma noradrenaline and heart rate after α-adrenoceptor antagonism in sinoaortic denervated rabbits*

After sinoaortic denervation the rabbits showed a greater lability in MAP and the average readings obtained were higher than in intact animals. The falls in MAP after α-adrenoceptor blockade with either prazosin or phentolamine were much greater in the SAD animals, (Table 3) and could not be related to the basal pressure in individual animals. Prazosin (0.1 mg/kg) and phentolamine (1.0 mg/kg) caused falls in pressure of $30.0 \pm 5.2$ mmHg and $24.1 \pm 5.3$ mmHg respectively.

There was no significant difference between basal levels of plasma NA in intact and SAD rabbits. However, plasma NA was not significantly increased

**Table 2** Changes in mean arterial pressure, heart rate and plasma noradrenaline after treatment with vasodilators

| Group | | *MAP* (mmHg) Baseline | Δ | *Heart rate* (beats/min) Baseline | Δ | *Plasma NA* (nM) Baseline | Δ |
|---|---|---|---|---|---|---|---|
| Vehicle | | 71±10 | +2.0±2.0 | 220±27 | +32±20 | 2.2±1.0 | −0.1±0.2 |
| Hydralazine | 1 mg/kg | 73±12 | −6.8±8.7 | 175±46 | +112±73 | 1.5±1.0 | +1.7±1.5 |
| | 2 mg/kg | 72±8 | −9.3±9.6 | 201±35 | +119±68 | 2.2±1.2 | +3.9±2.7 |
| | 5 mg/kg | 72±10 | −16.8±11.1 | 187±39 | +120±44 | 2.8±1.5 | +4.5±3.6 |
| | 10 mg/kg | 71±10 | −16.5±5.1 | 165±41 | +141±37 | 2.2±0.9 | +4.4±2.8 |
| Vehicle | | 63±9 | −0.5±1.3 | 225±24 | +21±19 | 2.8±0.6 | +0.2±0.4 |
| Nitroprusside | 2.5 μg kg$^{-1}$ min$^{-1}$ | 64±7 | −3.6±4.3 | 230±23 | +24±33 | 2.9±0.9 | +0.4±0.5 |
| | 5 μg kg$^{-1}$ min$^{-1}$ | – | −6.2±4.3 | – | +32±45 | – | +2.2±2.1 |
| | 10 μg kg$^{-1}$ min$^{-1}$ | – | −10.6±8.4 | – | +58±54 | – | +1.6±0.7 |
| | 20 μg kg$^{-1}$ min$^{-1}$ | – | −16.4±10.8 | – | +83±33 | – | +4.0±3.0 |
| | 55 μg kg$^{-1}$ min$^{-1}$ | 72±13 | −24.0±10.4 | 223±29 | +120±52 | 1.4±1.7 | +2.6±1.2 |

All results are expressed as mean ± s.d. for groups of 5 animals.
$^{*}P<0.05$ and $^{**}P<0.01$ when the difference before and after treatment with vehicle are compared with drug treatment by the Wilcoxon test. There was no significant difference between baseline levels of mean arterial pressure (MAP), heart rate (HR) or plasma noradrenaline (NA).

by prazosin (0.1 mg/kg) or phentolamine (1.0 mg/kg) in spite of the substantial falls in pressure. At higher doses of prazosin and phentolamine there was a modest increase ($P<0.05$) in plasma NA (Table 3). Similarly basal heart rate was not affected by sinoaortic denervation and the increase in HR observed after α-adrenoceptor blockade in intact animals was diminished and never reached significance in the sinoaortic denervated animals.

Similar changes in the response to the vasodilator, nitroprusside, were observed in the SAD rabbits. The falls in MAP were much larger, 30 μg kg$^{-1}$ min$^{-1}$ caused a fall in MAP of 39.0 ± 8.5 mmHg in the SAD animals whereas in intact animals 55 μg kg$^{-1}$ min$^{-1}$ only resulted in a fall of 24.0 ± 10.4 mmHg, and the increase in HR and plasma NA was reduced and did not reach significance.

*Effect of yohimbine on mean arterial pressure, heart rate and plasma noradrenaline*

Increasing doses of yohimbine, like prazosin and phentolamine, caused a progressive shift to the right in dose-response curves to phenylephrine, (Table 4). However, dose levels of yohimbine greater than 1 mg/kg also caused central effects; the rabbits were restless and agitated. Detailed studies were therefore only performed at the lower dose level of yohimbine. Yohimbine (1 mg/kg) caused a significant increase in both MAP and plasma NA when compared to vehicle-treated controls. Mean arterial pressure was increased by 10.9 ± 2.6 mmHg and plasma NA by 2.2 ± 1.9 nM. Heart rate did not increase significantly. This rise in MAP and plasma NA was not altered by sinoaortic denervation. However, destruction of

**Table 3** Changes in mean arterial pressure, heart rate and plasma noradrenaline after α-adrenoceptor blockade in sinoaortic denervated animals

| Group | *MAP* (mmHg) Baseline | Δ | *HR* (beats/min) Baseline | Δ | *Plasma NA* (nM) Baseline | Δ |
|---|---|---|---|---|---|---|
| Vehicle | 95±10 | +0.2± 5.8 | 234±28 | +16±14 | 2.1±1.6 | +0.2±1.0 |
| Prazosin 0.1 mg/kg | 98±12 | −30.0± 5.2 | 228±30 | +47±10 | 2.0±0.8 | +0.3±0.4 |
| Prazosin 0.5 mg/kg | 98±10 | −31.0± 5.3 | 240±24 | +27±48 | 2.2±1.2 | +1.4±0.7 |
| Phentolamine 1.0 mg/kg | 94±14 | −24.1± 6.8 | 250±22 | −7±10 | 2.2±1.4 | +1.2±1.2 |
| Phentolamine 5.0 mg/kg | 95±11 | −38.8±10.5 | 244±21 | +45±25 | 2.3±1.0 | +1.6±1.2 |
| Sodium nitroprusside 30 μg kg$^{-1}$ min$^{-1}$ | 89±12 | −39.0± 8.5 | 238±27 | +25±15 | 2.0±1.0 | +0.7±0.5 |

All results expressed as mean ± s.d. for groups of 8 rabbits.
$^{*}P<0.05$ and $^{**}P<0.01$ when the difference before and after treatment with vehicle are compared with drug treatment by the Wilcoxon test. There was no significant difference between baseline levels of mean arterial pressure (MAP), heart rate (HR) or plasma noradrenaline (NA).

**Table 4** Degree of postsynaptic $\alpha_1$-adrenoceptor blockade produced by yohimbine

| *Yohimbine* (mg/kg) | *Dose-ratio* |
|---|---|
| 1.0 | 1.0±0.5 |
| 1.5 | 2.1±1.6 |
| 3.0 | 3.5±1.6 |

Results expressed as mean ± s.d.

sympathetic nerve endings with intravenous 6-OHDA abolished the yohimbine-induced rise in plasma NA (Table 5).

## Discussion

Although it has been unequivocally demonstrated *in vitro* that noradrenaline exerts presynaptic effects to decrease transmitter output while phenoxybenzamine enhances output, the functional role of the inhibitory system mediated by adrenoceptors has been questioned, particularly by Kalsner and his colleagues (1979, 1980). In our studies it was not possible to differentiate clearly between the effects of the adrenoceptor antagonist, prazosin, which is believed to be relatively specific for the $\alpha_1$-adrenoceptor and the mixed $\alpha_1/\alpha_2$-antagonist, phentolamine, on mean arterial pressure and plasma noradrenaline of intact animals.

In contrast, in conscious rats in which Graham and his colleagues (Graham & Pettinger, 1979; Graham, Stephenson & Pettinger, 1980) examined the effects of prazosin and phentolamine on arterial pressure, heart rate, plasma noradrenaline and serum renin activity, effects consistent with different degrees of antagonism at a functionally significant presynaptic α-adrenoceptor were observed. For a given fall in mean arterial pressure a greater rise in plasma noradrenaline was observed after administration of the mixed $\alpha_1/\alpha_2$-adrenoceptor antagonist, phentolamine, than after the more specific $\alpha_1$-adrenoceptor antagonist, prazosin, and it was suggested that this was a consequence of the actions of phentolamine on the presynaptic $\alpha_2$-adrenoceptor. In our experiments low doses of prazosin (0.05–0.5 mg/kg) and phentolamine (0.5–5.0 mg/kg) showed a similar linear relationship between the fall in mean arterial pressure and the rise in plasma noradrenaline. In both cases these changes were related to the degree of postsynaptic $\alpha_1$-adrenoceptor blockade. Thus we were unable to show any effects of phentolamine on the presynaptic $\alpha_2$-adrenoceptor. In fact after administration of higher doses of prazosin the increase in plasma noradrenaline and heart rate was greater than after administration of phentolamine in doses which produced similar falls in pressure.

Baroreceptor reflexes will modify efferent sympathetic outflow in response to changes in pressure (Alexander & De Quattro, 1974a,b) and in individual animals there was a negative correlation ($r = -0.78$) between the fall in mean arterial pressure and the rise in plasma noradrenaline in rabbits treated with prazosin (0.1 mg/kg) and it is possible that the changes in plasma noradrenaline and heart rate observed after α-adrenoceptor blockade were a result of the reflex response to the fall in pressure.

The reduction in mean arterial pressure after prazosin and phentolamine was significantly greater in sinoaortic denervated animals while the plasma noradrenaline and heart rate increase was completely or substantially abolished.

The fall in mean arterial pressure was not related to the basal pressure in the sinoaortic denervated animals and in work with rabbits with perinephritis hypertension (mean arterial pressure 127±14) prazosin 0.1 mg/kg and 0.5 mg/kg produced falls in pressure similar to those observed in the uninephrectomised controls (mean arterial pressure 82 ± 3).

After sinoaortic denervation, animals are unable to compensate for the fall in mean arterial pressure by increasing sympathetic activity which leads to increased release and overflow of the neurotransmit-

**Table 5** Changes in mean arterial pressure, heart rate and plasma noradrenaline 20 min after administration of yohimbine 1 mg/kg

| | *MAP* (mmHg) | | *HR* (beats/min) | | *Plasma NA* (nM) | |
|---|---|---|---|---|---|---|
| *Groups* | *Baseline* | Δ | *Baseline* | Δ | *Baseline* | Δ |
| Intact | 71±6 | *+10.9±1.1 | 244±16 | +15± 9 | 1.3±0.4 | *+2.2±0.9 |
| SAD | Δ99±8 | *+13.9±5.1 | 243±11 | +9± 9 | 2.2±1.2 | +3.4±1.6 |
| 6-OHDA | 68±8 | −1.5±2.5 | 220±23 | +28±10 | Δ0.5±0.3 | +0.1±0.3 |

All results are expressed as mean ± s.d. for groups of 5–8 animals

*$P < 0.05$ when the difference before and after treatment with vehicle are compared with drug treatment by the Wilcoxon test

Δ$P < 0.05$ when sinoaortic denervated (SAD) and 6-hydroxydopamine (6-OHDA) groups are compared with intact group

ter noradrenaline. The lack of baroreflex compensation accounts for the large pressure falls in these animals. These experiments confirm that an important component of the changes in plasma noradrenaline after α-adrenoceptor blockade is mediated via the arterial baroreceptor reflex (De Quattro *et al.*, 1969; De Quattro & Alexander, 1974). Thus the rise in plasma noradrenaline after α-adrenoceptor blockade with both prazosin and phentolamine is a result of increased sympathetic activity following arterial baroreceptor activation and is directly related to the fall in pressure. The magnitude of this baroreceptor response could mask small changes in plasma noradrenaline due to blockade of the presynaptic $\alpha_2$-adrenoceptor and in our experiments it was not possible to distinguish between the changes in plasma noradrenaline mediated via the $\alpha_1$-adrenoceptor antagonist, prazosin, and the mixed $\alpha_1$,$\alpha_2$-adrenoceptor antagonist, phentolamine, in intact animals. However, some differences in the cardiovascular effects of prazosin and phentolamine were observed. Prazosin at 1 mg/kg caused a much greater degree of postsynaptic $\alpha_1$-adrenoceptor blockade than 0.5 mg/kg but the fall in mean arterial pressure was similar in both groups of animals, and increasing the dose of prazosin to 2.0 mg/kg resulted in only a small further fall in pressure. In contrast, there was a linear relationship between fall in mean arterial pressure and postsynaptic $\alpha_1$-adrenoceptor blockade for all doses of phentolamine. Prazosin and phentolamine also had different effects on heart rate and it is likely that the changes in heart rate, plasma noradrenaline and mean arterial pressure observed after α-adrenoceptor blockade with prazosin and phentolamine are complicated by additional actions of the drugs either on pre- or post-junctional α-adrenoceptors, β-adrenoceptors (Bertin, Guidicelli & Boissier, 1971) or different direct effects on arteriolar and venous capacitance vessels (Constantine, 1974). The relationship between changes in mean arterial pressure and plasma noradrenaline found after administration of the α-adrenoceptor antagonists prazosin and phentolamine was similar to that obtained after giving the direct vasodilators, hydralazine and sodium nitroprusside, although there were differences in the heart rate response to the vasodilators. In particular the increase in heart rate was much greater after hydralazine and did not show the same dose-effect relationship. In sinoaortic denervated rabbits the heart rate and plasma noradrenaline increases observed during nitroprusside infusion were diminished and did not reach significance despite the large fall in mean arterial pressure thus once again emphasising the importance of baroreflexes in regulating blood pressure.

Graham & Pettinger (1979) did not examine the contribution of baroreceptor reflexes in their study nor did they relate the changes in mean arterial pressure, heart rate, plasma noradrenaline or renin to the effects of the drugs on the $\alpha_1$-adrenoceptor. However, it is not possible to explain fully the differences in the findings of their study in rats and the present study in rabbits.

Perhaps in the rabbit, small changes in noradrenaline release resulting from presynaptic α-adrenoceptor antagonism may not lead to detectable changes in overall noradrenaline overflow and thus arterial plasma noradrenaline in the presence of intact catecholamine uptake mechanisms and the enzymes catechol-*O*-methyl transferase and monoamine oxidase.

In man, Dollery *et al.* (1979) were unable to demonstrate a reduction in sympathetic activity by peripheral presynaptic antagonism and as in our present studies it is possible that small changes in noradrenaline release from nerve endings may be obscured by other factors determining transmitter overflow from the synapse *in vivo*.

The rise in plasma noradrenaline after yohimbine could be due to antagonism of the inhibitory presynaptic $\alpha_2$-adrenoceptor thus facilitating transmitter release and causing a rise in blood pressure. However, it was not possible to exclude additional non specific central nervous effects of yohimbine increasing sympathetic activity.

Thus while there is evidence from *in vitro* studies for a role for presynaptic α-adrenoceptors in regulating peripheral sympathetic vasoconstrictor activity, arterial baroreflex responses to blood pressure changes make it unlikely that the functional significance of the presynaptic α-adrenoceptor can be readily determined by measurement of plasma noradrenaline in intact animals.

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