Br. J. Pharmac. (1985), **86**, 327–333

An investigation of α-adrenoceptor responsiveness in the vas deferens of spontaneously hypertensive rats

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1 α-Adrenoceptor-mediated responses were investigated in isolated vasa deferentia from spontaneously hypertensive rats (SHR) and normotensive Wistar rats (NWR).

2 There was no significant difference between NWR and SHR in the inhibition of the isometric contraction to single pulse field stimulation by α_2-selective agonists in prostatic portions, nor by α_2-selective agonists and the α_1-selective agonist, amidephrine in epididymal portions in the presence of nifedipine to prevent postjunctional actions of α-$_1$-selective agonists.

3 There was no significant difference between NWR and SHR in the potency of amidephrine in causing a postjunctionally mediated potentiation of the isometric contraction to single pulse field stimulation in prostatic portions but the maximum potentiation was significantly reduced in SHR. However, the maximum potentiation of the isometric contraction by the calcium entry facilitator, Bay K 8644, was not significantly different between NWR and SHR. The maximum direct contraction to amidephrine, but not to Bay K 8644, was also significantly reducd in SHR.

4 The irreversible α_1-adrenoceptor antagonist, phenoxybenzamine was more potent in SHR than NWR in reducing the maximum potentiation by amidephrine of the stimulation-evoked isometric contraction and in reducing the maximum direct contraction to amidephrine.

5 It is concluded that there is a reduced postjunctional α_1-mediated responsiveness in the vas deferens of SHR due probably to a reduction in receptor number.

Introduction

Since catecholamines are involved in the physiological control of blood pressure, changes in responsiveness to catecholamines might be expected to occur in the development or in the maintenance of high blood pressure. The object of this present study was to look for changes in α-adrenoceptor-mediated responsiveness in a non-cardiovascular tissue of spontaneously hypertensive rats (SHR), namely, the isolated vas deferens. Although changes in cardiovascular responsiveness may be due to a balance between receptor changes and structural changes, changes in responsiveness of the vas deferens may more exactly reflect adaptive changes in receptors due to alterations in sympathetic activity.

In the isolated vas deferens of the rat, it is possible to demonstrate the present of inhibitory prejunctional α_2-receptors and inhibitory, presumed prejunctional, α_1-receptors (Docherty, 1984a; Docherty *et al.*, 1984a), however, postjunctionally, responses to exogenous α-agonists are mediated predominantly, if not exclusively, by α_1-receptors (Docherty *et al.*, 1979). α_1-Agonists have two postjunctional actions: they produce spontaneous contractions (MacDonald & McGrath, 1980) and they potentiate nerve stimulation-evoked contractions (MacDonald & McGrath, 1980; Docherty & O'Malley, 1983). Since the calcium entry facilitator Bay K 8644 (Schramm *et al.*, 1983) also potentiates nerve stimulation-evoked contractions (Docherty *et al.*, 1986b), changes in responsiveness beyond the level of the α-adrenoceptor can be investigated. Xylazine, clonidine and UK 14304 were chosen as α_2-selective agonists and amidephrine as an α_1-selective agonist (see Docherty, 1984a; Docherty *et al.*, 1984b).

Some of these results have been published in abstract form (Docherty, 1984b).

Methods

Young adult male spontaneously hypertensive rats (SHR, Okamoto Aoki, 2–3 months old, 250–300 g) and age-matched male normotensive Wistar rats (NWR) were obtained from Biological Laboratories, Ballina, Ireland.

Anaesthetized rats

Some animals were anaesthetized with ether and a cannula was placed in the carotid artery for recording blood pressure and heart rate.

Vas deferens

Vasa deferentia were bisected into prostatic and epididymal portions and were placed between platinum ring electrodes in 50 ml organ baths at 37°C in Krebs-Henseleit solution of the following composition (mM): NaCl 119, $NaHCO_3$ 25, D-glucose 11.1, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2 and $MgSO_4$ 1.0. Tissues were attached to myograph transducers and isometric responses to single pulse field stimulation (supramaximal voltage, 0.5 ms) were obtained at intervals of 5 min.

Different experimental protocols were employed in epididymal and prostatic portions. In epididymal portions, experiments were carried out in the presence of the calcium entry blocker nifedipine (10 μM) or the calcium entry facilitator Bay K 8644 (10 μM). In prostatic portions concentration-response curves to the test drug were carried out in the absence of prior drug treatment or in the presence of antagonist drugs. In phenoxybenzamine (Pbz) experiments, tissues were exposed to Pbz for 15 min, washed, and the test drug was added 45 min after the end of Pbz exposure. In interaction experiments, the α_1-adrenoceptor antagonist prazosin or the α_2-adrenoceptor antagonist rauwolscine was added 45 min before beginning responses to test drug. In all experiments consistent responses (in absence or presence of prior drug treatment) were obtained before beginning cumulative concentration-response curves to α_2-selective agonists or to amidephrine or Bay K 8644, and one nerve stimulation-evoked response was obtained in the presence of a given concentration of drug before the next concentration was added (0.5 log unit increments at 5 min intervals). Evidence had first been obtained that over the period of such experiments, responses in the absence of drugs remained constant and after exposure to individual low concentrations of agonists returned to control values. Whilst cumulative additions at 5 min intervals proved suitable for α_1- and α_2-adrenoceptor agonists, it was found that Bay K 8644 differed in that maximum effect was not achieved until approximately 15 min after the highest concentration was given. To check that a true maximum had been obtained with Bay K 8644 (10 μM), some experiments were carried out in which cumulative additions of Bay K 8644 were given at 15 min intervals (see results). Agonist IC_{30} or IC_{50} values (concentration producing 30 or 50% inhibition of the contraction to a single stimulus pulse) or EC_{50} values (concentration producing 50% of maximum potentiation of the contraction to a single stimulus pulse) were obtained from each individual experiment. Direct effects of agonists on the smooth muscle were assessed in the intervals between nerve stimulation.

Drugs

The following drugs were used: acetylcholine chloride (Sigma); (±)-amidephrine hydrochloride (gift: Bristol-Myers); Bay K 8644 (methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl) pyridine-5-carboxylate; gift: Bayer); clonidine hydrochloride (gift: Boehringer); nifedipine (gift: Bayer); phenoxybenzamine hydrochloride (gift: Smith Kline & French); prazosin hydrochloride (gift: Pfizer); rauwolscine hydrochloride (Roth); UK 14304 (5-bromo-6- (2-imidazolin-2-ylamino)-quinoxaline; gift: Pfizer); xylazine hydrochloride (gift: Bayer). Drug stocks were prepared in distilled water, except for nifedipine and Bay K 8644 (100% ethanol) and phenoxybenzamine hydrochloride (tartaric acid 1 mM), and dilutions were made up with distilled water. Nifedipine solutions were kept in the dark. In control experiments, an equivalent volume of vehicle was administered. Stated concentrations refer to the base.

Statistics

Differences in IC_{30}, IC_{50} and EC_{50} values, maximum potentiations and maximum contractions were compared using Student's t test for unpaired data. When required, differences in maximum potentiation were compared using a Mann-Whitney U-test for nonparametric data. Values are arithmetic mean ± s.e.mean or geometric means ± 95% confidence limits.

Results

Anaesthetized rats

In rats anaesthetized with ether, systolic blood pressure was 168.0 ± 4.8 and 145.0 ± 5.4 mm Hg, diastolic pressure was 113.8 ± 6.7 and 86.2 ± 8.7 mm Hg and heart rate was 378 ± 18 and 382 ± 34 min^{-1} in SHR ($n = 6$) and NWR ($n = 5$), respectively (mean ± s.e.mean). Systolic and diastolic pressures were significantly higher in SHR than in NWR ($P < 0.05$).

Vas deferens; single stimulus experiments

In prostatic portions, single pulse electrical stimulation produced a monophasic isometric contraction and there was no significant difference between NWR

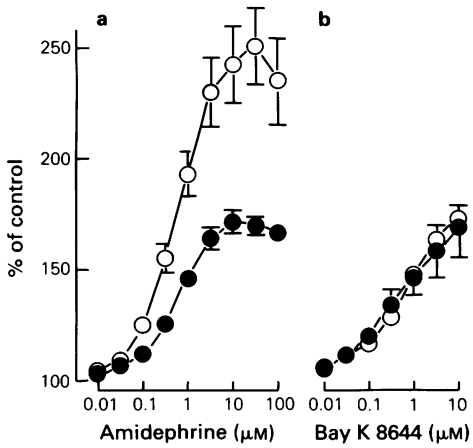

Figure 1 Concentration-response curves for the potentiation by (a) amidephrine and (b) Bay K 8644 of the isometric contraction to a single stimulus in prostatic portions of vas deferentia from NWR (○) and SHR (●). Responses are expressed as percentage of the control response to a single stimulus pulse in the absence of drug. Vertical bas represent s.e.mean. (a) NWR, $n = 15$; SHR, $n = 10$. (b) NWR, $n = 6$; SHR, $n = 7$.

and SHR in the height of the control stimulation-evoked contraction in the absence of drugs (NWR: 1.92 ± 0.16 g, $n = 18$; SHR: 1.88 ± 0.12 g, $n = 14$; mean ± s.e.mean). The α_1-adrenoceptor agonist, amidephrine, potentiated stimulation-evoked contractions and concentration-response curves were constructed for this potentiation in NWR and SHR (Figure 1). There was no significant difference between NWR and SHR in the potency of amidephrine (EC_{50} values of 6.21 ± 0.16, $n = 15$ and 6.21 ± 0.13, $n = 10$ in NWR and SHR, respectively; mean and 95% confidence limits, − log M). Prazosin (0.03 μM) did not reduce the maximum potentiation by amidephrine but reduced the potency of amidephrine to a similar extent in NWR and SHR (EC_{50} values in the presence of prazosin of 4.99 ± 0.74, $n = 3$ and 5.11 ± 0.59, $n = 4$ in NWR and SHR, respectively mean and 95% confidence limits, − log M). Rauwolscine (0.3 μM) did not significantly alter the potency or maximum effect of amidephrine in NWR or SHR. However, the maximum potentiation of stimulation-evoked contractions by amidephrine was significantly less in SHR than NWR (Figure 1 and Table 1). The calcium entry facilitator Bay K 8644 also potentiates nerve stimulation-evoked contractions and there was no difference in the potency of Bay K 8644 between NWR and SHR (Figure 1). The maximum potentiation by Bay K 8644, which was not achieved until approximately 15 min after administration of Bay K 8644 (10 μM), did not differ between NWR and SHR (Table 1). In further experiments, it was confirmed that Bay K 8644 (10 μM) produced a maximum potentiation by comparing effects of increasing concentrations 15 min after administration: the stimulation-evoked response was potentiated to 197.7 ± 23.2, 212.1 ± 34.5 and 211.1 ± 38.9% of control by Bay K 8644 1, 3 and 10 μM, respectively, data combined from NWR and SHR, $n = 4$.

Table 1 Maximum potentiations by amidephrine and Bay K 8644 of the isometric contraction to a single stimulus pulse in prostatic portions from NWR and SHR

	Prior Pbz (μM)	*NWR*	*SHR*
Distilled water	/	113.5 ± 8.4% (4)	103.4 ± 4.5% (6)
Amidephrine	/	249.4 ± 18.4% (15)	172.6 ± 3.0%** (11)
Amidephrine	0.1	180.1 ± 20.5% (5)	127.1 ± 5.8%* (4)
Amidephrine	0.1	164.8 ± 9.5% (5)	118.8 ± 4.9%** (5)
Amidephrine	0.2	128.4 ± 3.4% (4)	/
Amidephrine	1.0	118.6 ± 7.1% (4)	100.1 ± 3.8% (4)
Bay K 8644	/	200.6 ± 8.2% (9)	195.5 ± 18.4% (7)
Bay K 8644	1.0	229.7 ± 28.2% (4)	/

Some tissues were pre-exposed to various concentrations of phenoxybenzamine (Pbz). Values are mean percentage of pre-drug contraction and s.e.mean with number of experiments in parentheses. Asterisks denote significant differences between SHR and NWR (Student's t test: $^*P < 0.05$; $^{**}P < 0.01$).

Since it might be expected that maximum potentiation of stimulation-evoked contractions would be dependent on, or restricted by, the absolute amplitude (g) of the control contraction, graphs were constructed relating these two parameters (Figure 2). For Bay K 8644 there was a significant negative correlation between control stimulation-evoked response and maximum potentiation in both NWR and SHR, but there was no significant difference in slope between NWR and SHR so that data were combined (Figure 2b). However, although there was also a significant negative correlation for amidephrine in both NWR and SHR, there was a significant difference in the slope of the regression lines: the slope was much shallower in SHR (comparison of slopes: $F = 8.25$, $P < 0.01$). The maximum potentiation produced by amidephrine in SHR was significantly less than that produced in NWR when re-assessed using a Mann-

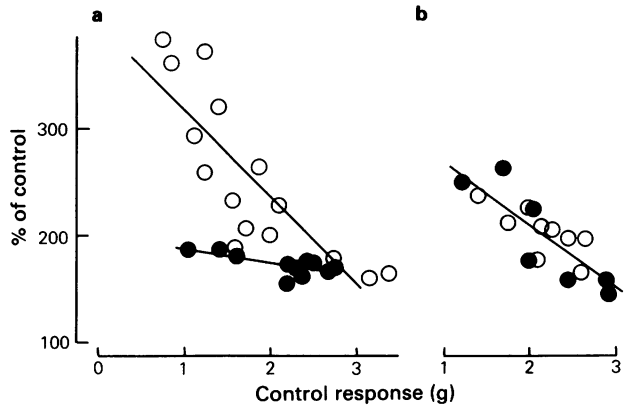

Figure 2 Correlation between height of pre-drug response to a single stimulus pulse and maximum potentiation by (a) amidephrine and (b) Bay K 8644. (a) NWR: slope = -79.5, $r = 0.82$, $n = 15$, $P < 0.01$; SHR: slope = -12.5, $r = 0.68$, $n = 11$, $P < 0.05$; comparison of slopes: F = 8.25, $P < 0.01$. (b) data for NWR and SHR combined: slope = -60.5, $r = 0.82$, $n = 16$, $P < 0.001$. Symbols: NWR (○); SHR (●).

Whitney U-test ($P < 0.01$) (Table 1), as the large differences in variance make a t test unsuitable.

In some experiments, prostatic portions were pre-exposed to Pbz, which did not significantly alter the isometric contraction to a single pulse (Pbz 0.1 μM: NWR 1.99 ± 0.28 g, $n = 8$; SHR 1.89 ± 0.30 g, $n = 6$). Pbz (0.01 μM) significantly reduced the maximum potentiation of stimulation-evoked contractions by amidephrine in SHR but not in NWR (Table 1). Pbz (0.1 μM) almost abolished the potentiation of responses by amidephrine in SHR, and significantly reduced the potentiation in NWR. A concentration of 0.2–1.0 μM Pbz was required to abolish potentiation by amidephrine almost completely in NWR (Table 1). Since Pbz (0.1 μM) significantly reduced the maximum potentiation of stimulation-evoked responses by amidephrine in NWR without significantly altering the EC_{50} (after Pbz: 6.05 ± 0.12, $n = 5$; $-\log$ M), and the same was true for Pbz (0.01 μM) in SHR, there are no spare post-synaptic α_1-receptors in prostatic portions. The maximum potentiation of stimulation-evoked contractions by Bay K 8644 was not altered by Pbz (1 μM) (Table 1).

In prostatic portions, the α_2-adrenoceptor agonists, xylazine, clonidine and UK 14304, produced concentration-dependent inhibitions of the isometric contraction of a single stimulus pulse and virtually abolished the response but there was no significant difference between NWR and SHR in agonist IC_{50} values: xylazine, NWR 7.00 ± 0.15 ($n = 4$), SHR

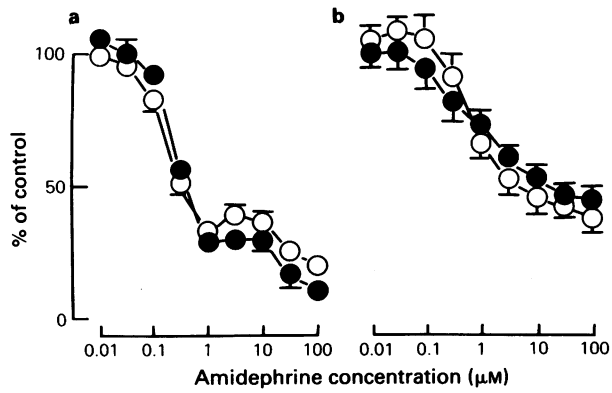

Figure 3 Concentration-response curves for the inhibition by amidephrine of the isometric contraction to a single stimulus pulse in epididymal portions in the presence of (a) nifedipine or (b) Bay K 8644. Symbols: NWR (○); SHR (●). Responses are expressed as percentage inhibition of the response to a single stimulus in the absence of amidephrine but in the presence of nifedipine or Bay K 8644. Vertical bars represent s.e.mean. Results are the mean of at least 4 experiments.

Table 2 Maximum height of spontaneous contractions produced by amidephrine and Bay K 8644 in prostatic portions from NWR and SHR

	Prior Pbz (μM)	*NWR*	*SHR*
Distilled water	/	0.05 ± 0.05 g (4)	0.0 ± 0.0 g (6)
Amidephrine	/	1.45 ± 0.11 g (15)	0.94 ± 0.16 g* (8)
Amidephrine	0.01	0.87 ± 0.06 g (5)	0.32 ± 0.22 g* (4)
Amidephrine	0.1	0.69 ± 0.15 g (5)	0.04 ± 0.04 g** (5)
Amidephrine	0.2	0.22 ± 0.13 g (4)	/
Amidephrine	1.0	0.03 ± 0.02 g (4)	0.04 ± 0.04 g (4)
Bay K 8644	/	0.62 ± 0.24 g (5)	0.72 ± 0.24 g (8)
Amidephrine and Bay K 8644	/	1.80 ± 0.11 g (4)	1.44 ± 0.12 g (6)
Xylazine	/	0.05 ± 0.05 g (3)	0.0 ± 0.0 g (3)
Xylazine and Bay K 8644	/	1.27 ± 0.17 g (3)	1.10 ± 0.30 g (5)

Some tissues were pre-exposed to various concentrations of phenoxybenzamine (Pbz). Values are mean and s.e.mean with number of experiments in parentheses. Asterisks denote significant differences between SHR and NWR (Student's t test: $^*P<0.05$; $^{**}P<0.01$).

7.09 ± 0.09 ($n = 7$); clonidine, NWR 8.28 ± 0.25 ($n = 5$), SHR 8.07 ± 0.28 ($n = 4$); UK 14304, NWR 8.10 ± 0.32 ($n = 5$), SHR 8.01 ± 0.17 ($n = 4$); mean and 95% confidence limits, −log M.

In epididymal portions, single pulse electrical stimulation produced a biphasic isometric contraction but nifedipine (10 μM) abolished the early non-adrenergic compotent to the response, leaving only the second adrenergic component (see Docherty & O'Malley, 1983). There was no significant difference between NWR and SHR in the height of the control stimulation-evoked contraction in the presence of nifedipine (NWR: 1.20 ± 0.14 g; SHR: 1.09 ± 0.12 g, $n = 14–15$). In the presence of nifedipine, the α_2-agonists, xylazine, clonidine and UK 14304, produced concentration-dependent inhibitions of nerve stimulation-evoked contractions and virtually abolished the response, but there was no significant difference between NWR and SHR in agonist IC_{50} values: xylazine, NWR 7.62 ± 0.17 ($n = 10$), SHR 7.41 ± 0.12 ($n = 6$); clonidine, NWR 8.54 ± 0.14 ($n = 5$), SHR 8.48 ± 0.43 ($n = 4$); UK 14304, 8.40 ± 0.13 ($n = 4$); SHR 8.54 ± 0.22 ($n = 4$); mean and 95% confidence limits, −log M.

In epididymal portions in the presence of nifedipine (10 μM), which prevents the postsynaptic actions of α_1-agonists, amidephrine produced concentration-dependent inhibition of stimulation-evoked contractions, but there was no significant difference between NWR and SHR in the inhibitory potency of amidephrine (Figure 3). In the presence of Bay K 8644 (10 μM), which produces a marked potentiation of nerve stimulation-evoked contractions, amidephrine produced only inhibition of stimulation evoked contractions, but again, there was no significant difference between NWR and SHR in inhibitory potency of amidephrine (Figure 3).

Agonist-induced contractions

In the absence of nerve stimulation, amidephrine produced direct contractions of the smooth muscle, consisting of spontaneous intermittent spikes. The maximum height of spontaneous contractions was quantified in prostatic portions, which do not exhibit spontaneous activity in the absence of drugs (see effects of distilled water vehicle in Table 2). The maximum contraction to amidephrine was significantly larger in NWR than SHR, and, in tissues pre-exposed to PBA, the contraction to amidephrine was almost abolished by Pbz (0.1 μM) in SHR but Pbz at a concentration of 0.2–1 μM was required in NWR to produce a similar effect (Table 2). Bay K 8644 produced a relatively small contraction which was not significantly different in NWR and SHR and the combination of Bay K 8644 and amidephrine produced a contraction, which was also not significantly different betwen NWR and SHR (Table 2). The α_2-agonist, xylazine, normally produced no significant contraction in NWR or SHR but in the presence of Bay K 8644, xylazine produced a maximum contraction that was not significantly different in NWR and SHR (Table 2).

Discussion

The object of this investigation was to look for differences between SHR and NWR in the α-adrenoceptor responsiveness of vas deferens, examining the inhibitory prejunctional effects of α_2-agonists, the inhibitory (presumed prejunctional) effects of α_1-agonists and the excitatory postjunctional effects of α_1-agonists. There were no significant differences between NWR and SHR in the inhibitory potencies of the α_2-selective agonists, xylazine, clonidine and UK 14304, whether in prostatic or epididymal portions. Inhibitory actions of α_1-agonists can be demonstrated only when the postjunctionally mediated potentiation

of stimulation-evoked contractions was prevented by the calcium entry-blocker, nifedipine (see Docherty, 1984a) or maximized by the calcium entry facilitator, Bay K 8644 (Docherty *et al.*, 1984a): there were no differences between NWR and SHR in the inhibitory potency of the α_1-selective agonist, amidephrine, in the presence of either of the above drugs. Although we have found no significant alteration in prejunctional α_1-or α_2-adrenoceptors of SHR, there are conflicting reports of supersensitive and subsensitive prejunctional α_2-adrenoceptors in SHR (see Lokhandwala & Eikenburg, 1983). Part of the confusion may be due to the presence of endogenous noradrenaline at the prejunctional receptors: in our study we have the advantage when using single pulse stimulation of examining presynaptic receptors in the absence of endogenous feedback.

The significant change found in this study was a reduced maximum postjunctional responsiveness to amidephrine in SHR. Both the maximum direct contraction to amidephrine and the maximum potentiation of the contraction to a single stimulus pulse were significantly reduced in prostatic portions of the vas deferens of SHR. These actions of amidephrine are α_1-adrenoceptor mediated since: (a) other α_1-agonists have similar actions (cirazoline, Docherty & McGrath, 1982; phenylephrine, MacDonald & McGrath, 1980), whereas α_2-selective agonists, such as xylazine, do not normally have these actions (Hyland *et al.*, 1984); (b) prazosin antagonizes the potentiation in a competitive manner (Docherty & McGrath, 1982); (c) Pbz antagonizes the potentiation in a non-competitive manner; (d) rauwolscine did not antagonize the potentiation in concentrations that produce α_2-adrenoceptor blockade (Docherty, 1984a and present results). The potentiation of stimulation-evoked contractions by α_1-adrenoceptor agonists is postjunctionally mediated since: (a) potentiation occurs in the concentration range in which these agonists produce intermittent direct contractions of the smooth muscle (MacDonald & McGrath, 1980; and present results); (b) the calcium entry blocker, nifedipine, attenuates and the calcium entry facilitator, Bay K 8644, mimics the potentiation (Hyland *et al.*, 1984, and present results).

The reduced maximum responsiveness to amidephrine in SHR is not due to a loss of tissue responsiveness since the maximum potentiation by Bay K 8644 of stimulation-evoked contractions was not reduced in SHR. Bay K 8644 acts at the level of the calcium channel whereas activation of α_1-adrenoceptors probably opens voltage-sensitive calcium channels by causing a depolarization of the membrane. Several pieces of evidence suggest that there is a loss of postjunctional α_1-adrenoceptors in SHR. The reduction in the maximum potentiation of stimulation-evoked contractions occurred in SHR without change in the potency of amidephrine. There is a marked inverse relationship between size of the contraction to a single stimulus and the maximum potentiation by amidephrine in NWR (suggesting that the limiting factor is the maximum contractile ability of the tissue) but there is not a close relationship in SHR, so that some other factor has intervened, presumably loss of α_1-adrenoceptors. The irreversible α_1-adrenoceptor antagonist, Pbz (see Constantine & Lebel, 1980), had greater potency in SHR in reducing the maximum potentiation of stimulation-evoked contractions by amidephrine. Even in NWR there are no spare postjunctional α_1-adrenoceptors since Pbz reduced the maximum potentiation by amidephrine without altering its potency. Data obtained for direct smooth muscle contractions to amidephrine also suggest that the reduced maximum contraction in SHR is due to loss of α_1-adrenoceptors: in the presence of Bay K 8644 there was no difference between NWR and SHR in the maximum contraction to amidephrine. Bay K 8644 potentiates the actions of even a weak partial agonist such as xylazine: xylazine had virtually no contractile action in the absence by Bay K 8644.

A reduction in number of postjunctional α_1-adrenoceptors in vas deferens of SHR is in agreement with reports of reduced α_1-binding site numbers in cardiac membranes in various rat models of hypertension (Yamada *et al.*, 1980; Woodcock & Johnson, 1980), although not in SHR (Hicks *et al.*, 1983). Whilst changes in responsiveness found in our non-cardiovascular tissue generally agree with receptor binding data, all these are at variance with various reports of increased pressor responsiveness to α-adrenoceptor agonists in hypertensive rats (Kubo, 1979; Yamaguchi & Kopin, 1980; Hicks *et al.*, 1983; Walsh, 1983). However, the increased pressor responsiveness can be explained, in part, in terms of structural changes in blood vessels (Folkow *et al.*, 1977); a reduced receptor number would be of minor importance in tissues with a large receptor reserve. The reduction in α_1-adrenoceptor number seen in hypertensive rats may reflect an adaptational change in postjunctional α_1-adrenoceptors to increased sympathetic activity or increased circulating adrenaline.

In conclusion, the present results demonstrate a reduced α_1-adrenoceptor-mediated postjunctional responsiveness in vas deferens of SHR, presumably due to a reduction in receptor number.

This study was supported by research funds of the Royal College of Surgeons in Ireland and by the Irish Heart Foundation.

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(Received October 26, 1984.
Revised April 30, 1985.
Accepted May 24, 1985.)