Br. J. Pharmac. (1983), **80**, 429–437

The effect of bilateral adrenal demedullation on vascular reactivity and blood pressure in spontaneously hypertensive rats

K.R. Borkowski & P. Quinn

Department of Physiology, University of Leicester, Leicester, LE1 7RH

1 Bilateral adrenal demedullation of juvenile spontaneously hypertensive rats attenuated, but did not prevent, the development of hypertension. Neither did it affect the subsequent vascular reactivity to phenylephrine though it significantly reduced the vascular effects of sympathetic nerve stimulation.

2 Demedullation of adult spontaneously hypertensive rats did not alter blood pressure, but did attenuate the pressor responses to both α-adrenoceptor agonists and sympathetic nerve stimulation.

3 In acutely demedullated adult rats, vascular reactivity to sympathetic nerve stimulation, but not to exogenous amines, could be restored by slow i.v. infusion of adrenaline in a dose-dependent manner.

4 The results support a possible facilitatory role for adrenaline in sympathetic neurotransmitter release, both during the development of genetic hypertension and in vascular responses to sympathetic nerve stimulation.

Introduction

Suggestions that circulating adrenaline might facilitate the release of sympathetic neurotransmitter by stimulating prejunctional β-adrenoceptors are supported by observations that both adrenaline and isoprenaline can facilitate electrically induced release of [^{3}H]-noradrenaline from human omental arteries; an effect which is inhibited by the β-adrenoceptor antagonist propranolol (Stjarne & Brundin, 1975). More recently, Majewski, Tung & Rand (1981) have shown that rats, implanted with a slow release depot preparation of adrenaline, develop an elevated blood pressure which can be prevented by the concomitant administration of metoprolol, suggesting a possible role for circulating adrenaline in the development of hypertension. Such an involvement might explain the prevention of development of a raised blood pressure in spontaneously hypertensive (SHR) rats by chronic treatment with propranolol, as observed by Kubo, Esumi & Ennyu (1977).

The removal of circulating adrenaline by adrenal demedullation might prevent the development of genetic hypertension or lower the blood pressure in hypertensive animals and the experiments described here were performed to test these hypotheses.

Methods

Animals

Male spontaneously hypertensive (SHR) rats, originating as a hypertensive mutant of the Wistar-Kyoto Japanese strain (Okamoto & Aoki, 1963), were obtained just after weaning (i.e. 3 weeks old). Some animals were operated on one week later (body weight 50–60 g) while others were used when adult (body weight 250–325 g).

Blood pressure measurement

(a) *Indirect* To assess the development of hypertension in young rats, systolic blood pressures (SBP) were monitored twice weekly using a non-invasive tail-cuff method in animals anaesthetized with ether. Pressures were recorded at room temperature (~20°C) without preheating the rats. The tail cuff was inflated and deflated using a manual sphygmomanometer and the tail arterial pulse, detected using a photoelectric pulse sensor (Medical Physics Lab., Leicester Royal Infirmary) placed distal to the cuff, was displayed on an oscilloscope (Tektronix 5103N). The end points used to determine SBP were

cessation of blood flow during cuff inflation and its resumption during deflation and the average of the two values was recorded.

Initial control SBP's were determined on three separate occasions in the first week after weaning. The juvenile rats were then divided randomly into two groups and bilateral adrenal demedullation of one group ($n = 7$) was performed under ether anaesthesia via flank incisions. The adrenal gland was exposed, a small incision made in the cortex and enucleation performed by gentle squeezing with forceps. A second group of animals ($n = 6$) was sham-operated at the same time. After surgery, SBP's were determined by the above method twice weekly (Tuesday and Friday at 09 h 00 min–10 h 00 min) over a period of twelve weeks.

(b) *Direct in conscious rats* In a separate series of experiments, adult rats were prepared for direct recording of blood pressure and the sampling of arterial blood whilst conscious and unrestrained. Under chloral hydrate (200 mg kg^{-1} i.p.) anaesthesia, a carotid catheter was implanted, according to the method of Popovic & Popovic (1960), and a recovery period of at least two days was allowed before the rats were used further. Then, blood pressures were recorded from conscious unrestrained animals using a Pioden UP4 pressure transducer and the heart rate was derived from the blood pressure pulse-wave using a cardiotachometer and displayed, together with the blood pressure trace, on an EMI UV oscillograph (SE 6150 Mk. II).

(c) *In pithed rats* Both series of experiments were terminated with measurements of cardiovascular reactivity in rats which had been pithed. The animals were anaesthetized with sodium pentobarbitone (60 mg kg^{-1}, i.p.) and the right carotid artery cannulated to record arterial blood pressure and heart rate. In those animals with intact adrenals, a bilateral adrenal demedullation was performed via flank incisions which were then closed. All the rats were pithed, as described by Gillespie & Muir (1967), given atropine (1 mg kg^{-1}, i.v.) and (+)-tubocurarine (2 mg kg^{-1}, i.v.) and ventilated with room air using a Harvard small animal ventilator. Ventilation parameters were adjusted to maintain blood pH, P_{O_2} and P_{CO_2} close to normal limits. The values actually recorded were: pH = 7.42 ± 0.04; P_{O_2} = 83.6 ± 6.0 mm Hg; P_{CO_2} = 28.7 ± 4.0 mm Hg, (n = 6).

Slow infusions of drugs were made via the left external jugular vein, at a rate of 5 µl min^{-1}, using an Ealing slow influsion pump, while bolus injections of drugs, in volumes of 0.1 ml flushed in with 0.2 ml of saline, were made via the right external jugular.

Assays

Blood samples (1 ml from conscious and anaesthetised rats prior to pithing) for catecholamine determination and (2 ml at the end of the experiment) for plasma corticosterone determination were obtained via the arterial catheter by free flow and collected in ice-cold centrifuge tubes. The blood cells were spun down (5500 rpm, 10 min) and the plasma taken off for assay.

Catecholamines Extraction of plasma catecholamines was carried out according to a modification of the method of Anton & Sayre (1962) and the catecholamine concentration determined using HPLC.

The adrenals of chronically demedullated and sham-operated rats were removed at the end of the experiment. The adrenal glands were homogenized in 1 ml of 0.1M perchloric acid ($HClO_4$) containing 1M $NaHSO_3$ (400 µl l^{-1}). The homogenates were centrifuged (5500 rpm, 10 min), the supernatant removed and filtered using 0.2 µm pore size filters (Millipore) to remove colloidal protein. The supernatant was then analysed for adrenal catecholamines by h.p.l.c..

Corticosterone Extractions of plasma corticosterone were made according to the method of Zenker & Bernstein (1958) and the concentrations determined by spectrofluorimetry.

Drugs

Noradrenaline hydrochloride (Sigma), phenylephrine hydrochloride (Sigma) and oxymetazoline hydrochloride (Merck, Sharp & Dohme) were made up as stock solutions containing 1 mg ml^{-1} in 0.01M HCl and diluted for injection in 0.9% w/v NaCl solution (saline) on the day of use. Adrenaline hydrogen tartrate (Sigma) was freshly dissolved in saline for each period of infusion. Doses of drugs refer to base weight.

Results are expressed as the mean ± s.e.mean where n refers to the number of observations. Differences in means were determined by Student's t test. and $P < 0.05$ was taken as significant.

Results

Development of hypertension

After control SBP measurements had been taken for one week and the rats were randomly divided into two groups, no significant difference was found between the mean SBP of the animals forming the

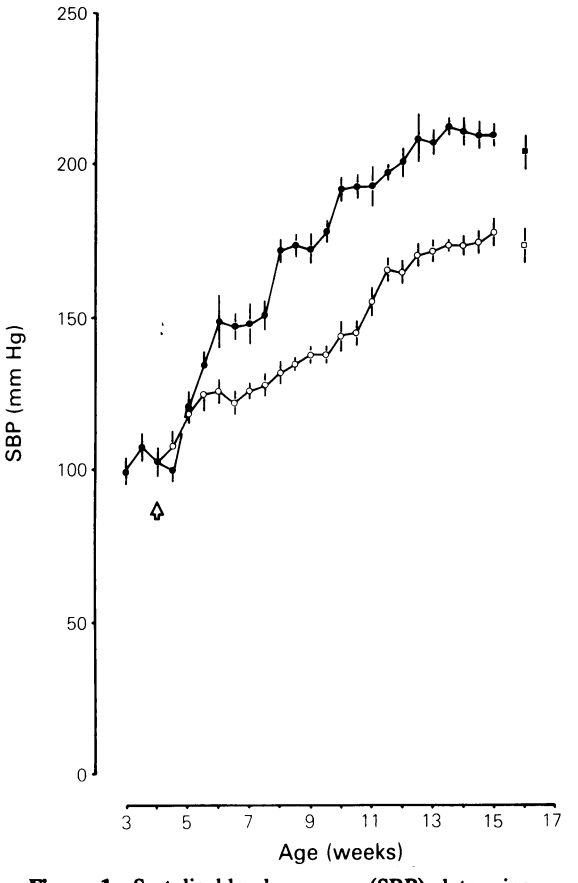

Figure 1 Systolic blood pressure (SBP) determinations, by an indirect tail-cuff method in ether anaesthetized spontaneously hypertensive (SHR) rats, in sham-operated (●) ($n=6$) and adrenal demedullated (○) ($n=7$) animals from 3 to 15 weeks of age. The arrow indicates the time of surgery and the square symbols indicate directly recorded SBP, via an indwelling carotid catheter, in the pentobarbitone anaesthetized rats, prior to pithing, at 16 weeks of age when reactivity studies were performed. Each point represents the mean with vertical lines indicating s.e. mean.

demedullated group (107.8 ± 4.8 mmHg, $n=7$) and that of the animals forming the sham-operated group (99.3 ± 5.5 mmHg, $n=6$). However, within 3 weeks of surgery, the mean SBP in the sham-operated rats was significantly higher ($P<0.01$) than that of demedullated rats and remained so for the duration of the experiment (Figure 1). The development of hypertension, in the sham-operated animals, was irregular in the first 9 weeks of recording, with rapid increases in SBP between two successive determinations followed by a plateau lasting 3–4 pressure determinations (Figure 1). As the SBP increased, to a plateau of about 210 mm Hg in sham-operated rats at 13 weeks of age, the rapid rises in SBP became smaller in magnitude. By contrast, the rise in SBP in the adrenal demedullated animals was more gradual and reached a plateau of about 170 mm Hg in animals 12 weeks old (Figure 1).

Table 1 Plasma noradrenaline (NA), adrenaline (Ad), dopamine (DA) and corticosterone levels in chronically sham-operated and adrenal demedullated spontaneously hypertensive (SHR) rats, together with adrenal gland NA and Ad contents

	Sham-operated	*Demedullated*	*%Δ*
Plasma contents			
NA ($pg\,ml^{-1}$)	288 ± 26	266 ± 27^{NS}	−7.6
Ad ($pg\,ml^{-1}$)	245 ± 33	$22 \pm 22^{*}$	−91.0
DA ($pg\,ml^{-1}$)	269 ± 67	212 ± 81^{NS}	−21.2
Corticosterone ($\mu g\,100\,ml^{-1}$)	44.9 ± 4.9	42.9 ± 1.9^{NS}	−4.5
Adrenal catecholamine content (per pair)			
NA	$7.24 \pm 0.2\,\mu g$	38.4 ± 2.8 ng*	−99.5
Ad	$24.0 \pm 1.2\,\mu g$	132.7 ± 26.8 ng*	−99.5

Values given are the mean ± s.e. mean.* $P<0.001$; NS, not significant.

When both groups of rats were used for reactivity studies, at 16 weeks of age, the indirectly recorded SBP's in sham-operated (210 ± 4 mmHg, $n=6$) and adrenal demedullated (178 ± 4 mmHg, $n=7$) rats were virtually identical with SBP values recorded directly, via indwelling carotid catheters, in pentobarbitone anaesthetized sham-operated (204 ± 6 mmHg, $n=6$) and adrenal demedullated (174 ± 6 mmHg, $n=7$) animals. After pithing, there was no significant difference between the mean blood pressure in the demedullated (41 ± 2 mmHg, $n=7$) and sham-operated (40 ± 2 mmHg, $n=6$) rats.

Assays of catecholamines and corticosterone

The plasma concentrations of noradrenaline and dopamine were slightly lower in the bilateral adrenal demedullated rats, but not significantly different from values in sham-operated animals, while plasma adrenaline levels were markedly reduced ($P<0.001$) in the former group (Table 1). Adrenal gland contents of noradrenaline and adrenaline were significantly reduced ($P<0.001$) in the bilateral adrenal demedullated rats when compared to intact adrenals from the sham-operated animals (by about 99.5%; see Table 1).

There was no significant difference between plasma corticosterone levels found in the adrenal de-

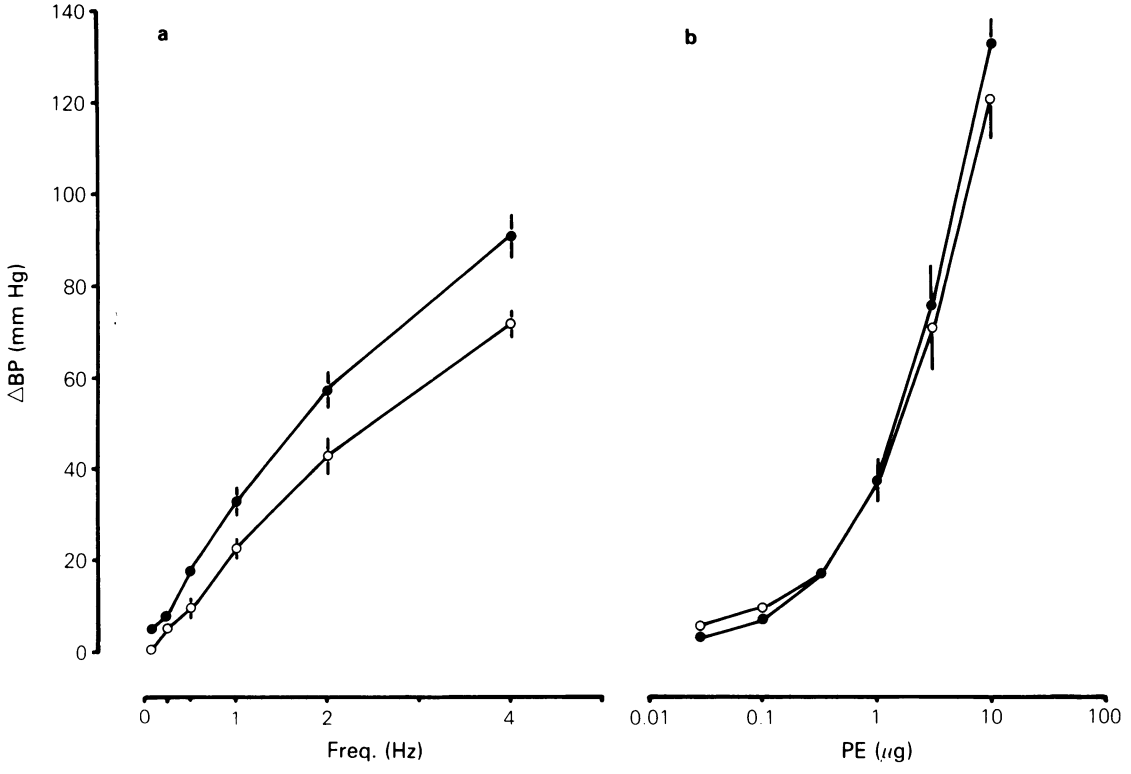

Figure 2 The increases in diastolic pressure (BP) induced by (a) electrical stimulation (Freq.) of the entire sympathetic outflow and (b) bolus injections of phenylephrine (PE) in 16 week old spontaneously hypertensive (SHR) rats which had been demedullated (○) ($n = 7$) or sham-operated (●) ($n = 6$) 12 weeks earlier. Each point represents the mean with vertical lines indicating s.e. mean.

Table 2 Mean blood pressure (MBP), heart rate (HR) and plasma adrenaline and noradrenaline levels in conscious, pithed intact and pithed acutely demedullated SHR rats during the slow infusion of adrenaline

	Conscious	*Pithed intact*	*Pithed demedullated* *Rate of adrenaline infusion* (ng per animal min^{-1})			
			0	5	50	500
MBP (mm Hg)	155±6	41±2	36±2	31±1	49±4	63±6**
HR (bm^{-1})	337±9	283±11	300±11	285±11	368±16**	435±9***
Plasma adrenaline ($ng\,ml^{-1}$)	0.57±0.03	0.08±0.02	0***	0.38±0.04**	6.36±1.34***	18.28±1.80***
Plasma noradrenaline ($ng\,ml^{-1}$)	0.34±0.06	0.13±0.02	0.09±0.03	NR	NR	NR

*$P < 0.05$; **$P < 0.001$; ***$P < 0.001$ indicate significant differences between values in pithed demedullated rats compared to pithed intact animals. Values given are the mean ± s.e. mean. $n = 6$ in all cases, except for conscious rats where $n = 14$. NR, not recorded.

medullated rats and the sham-operated animals (Table 1).

Studies in pithed rats

(a) *Chronically demedullated rats* In animals demedullated 12 weeks earlier, bolus injections of phenylephrine (0.03–10 μg, i.v.) produced dose-dependent increases in diastolic blood pressure (DBP) of similar magnitude to those recorded in sham-operated rats (Figure 2).

Electrical stimulation of the entire sympathetic outflow (0.125–4 Hz; 30V; 1 ms; 15 s) caused frequency-dependent increases in DBP in both the sham-operated and adrenal demedullated rats (Figure 2). These increases in DBP were significantly lower ($P < 0.05$) at all frequencies of stimulation in the demedullated rats when compared to responses in sham-operated animals.

(b) *Acutely demedullated rats*

Effects of bilateral adrenal demedullation and adrenaline infusion on basal parameters The mean blood pressures in conscious unrestrained and in pithed SHR rats and also in pithed rats after acute adrenal demedullation are shown in Table 2. Pithing the pentobarbitone anaesthetized animals reduced the plasma adrenaline levels by 86% when compared to the levels in conscious rats, while plasma adrenaline in pithed adrenal demedullated rats was undetectable. Plasma noradrenaline levels were reduced by 60% in pithed rats, and by 72% in pithed adrenal demedullated rats, when compared to conscious animals. The slow i.v. infusion of adrenaline in adrenal demedullated rats raised the plasma adrenaline levels above those found in pithed intact animals in all cases (Table 2). However, only the highest rate of adrenaline infusion raised the resting blood pressure significantly above ($P < 0.01$) that found in pithed intact animals (Table 2).

Pressor responses to electrical stimulation of the sympathetic outflow Electrical stimulation of the entire sympathetic outflow (0.125–4 Hz; 30 V; 1 ms; 15 s) caused frequency-dependent increases in DBP (Figure 3), with the increase in DBP at 4 Hz being 83 ± 5 mmHg ($n = 15$). Acute bilateral adrenal demedullation significantly reduced ($P < 0.001$) the pressor responses at all frequencies of stimulation; the increase in DBP at 4 Hz being reduced to 41 ± 6 mmHg ($n = 7$). The subsequent slow infusion of adrenaline (5–500 ng per animal min^{-1}, i.v. in a volume of 5 μl min^{-1}) produced a dose-dependent restoration of the stimulation-induced pressor responses (Figure 3). This restoration of stimulation-induced responses was not maintained upon cessation of adrenaline infusion.

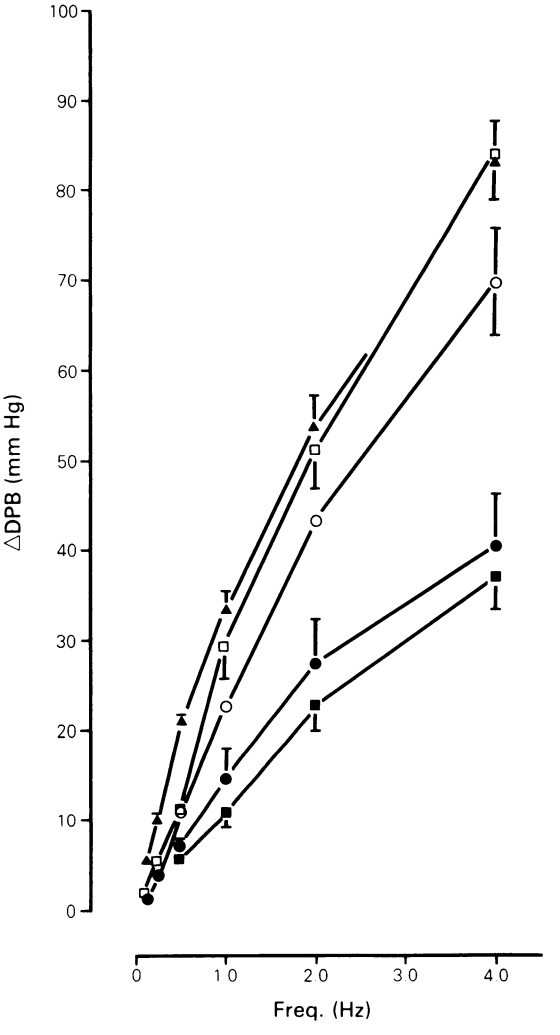

Figure 3 The effects of acute bilateral adrenal demedullation and the subsequent slow infusion of adrenaline on the increase in diastolic blood pressure (ΔDBP) in response to electrical stimulation of the entire sympathetic outflow in pithed spontaneously hypertensive (SHR) rats. Intact (▲), ($n = 5$); demedullated (●), ($n = 7$); demedullated and treated with adrenaline (5 ng per animal min^{-1}) (■), ($n = 9$); demedullated and treated with adrenaline (50 ng per animal min^{-1}) (○), ($n = 6$); demedullated and treated with adrenaline (500 ng per animal min^{-1}) (□), ($n = 6$). Each point represents the mean with vertical lines indicating s.e. mean.

Pressor responses to noradrenaline, phenylephrine and oxymetazoline Bolus injections of noradrenaline or phenylephrine (0.03–10 μg, i.v.) or oxymetazoline (0.03–1 μg, i.v.) produced dose-dependent increases in DBP (Figure 4). Acute bilateral adrenal demedul-

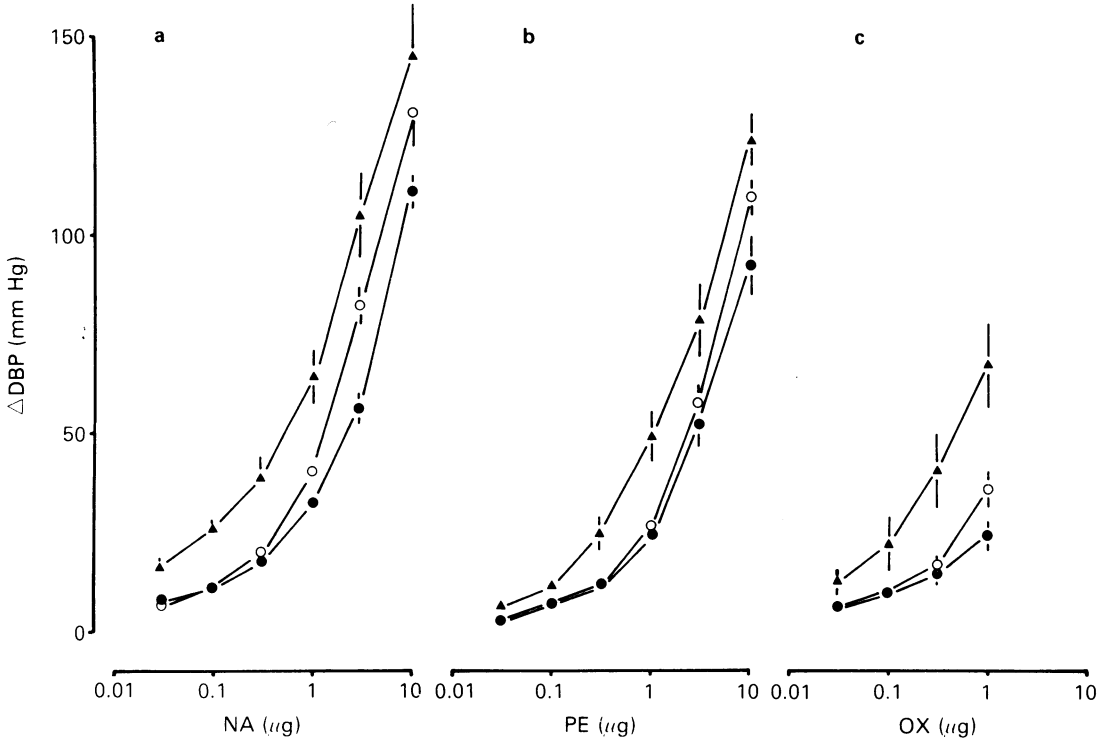

Figure 4 The effects of acute bilateral adrenal demedullation and the subsequent slow infusion of adrenaline on the increase in diastolic blood pressure (ΔDBP) in response to bolus injections of: (a) noradrenaline; (b) phenylephrine and (c) oxymetazoline in pithed (SHR) rats. Intact (▲); demedullated (●); demedullated and treated with adrenaline (500 ng per animal min^{-1}) (○). Each point represents the mean of 6 observations with vertical lines indicating s.e. mean.

Table 3 The effects of acute bilateral adrenal demedullation and the subsequent infusion of adrenaline (500 ng per animal min^{-1}, i.v.) on the pressor response induced by α-adrenoceptor agonists

	Increases in DBP				
	Intact	*Demedullated*		*Demedullated + adrenaline*	
	(mmHg)	(mmHg)	(%Δ)	(mmHg)	(%Δ)
Stim. Freq (Hz)					
0.6	22.5	10.0	−56	15.5	−31
2.95	67.5	33.5	−50	76.0	−1
Noradrenaline (μg)					
0.07	22.5	10.0	−56	10.5	−53
1.10	67.5	34.0	−50	48	−29
Phenylephrine (μg)					
0.28	22.5	11.0	−51	10	−56
2.10	67.5	45.0	−33	47	−30
Oxymetazoline (μg)					
0.1	22.5	9.5	−58	9.5	−58
1.0	67.5	24.5	−64	36.0	−47

The doses of α-adrenoceptor give increases in diastolic blood pressure (DBP), in intact pithed rats, which are 25% and 75% of the maximal increases in DBP induced by electrical stimulation of the entire sympathetic outflow. Percentage changes in responses (%Δ) compare the pressor effects in demedullated rats and those on adrenaline infusion against responses in pithed intact animals.

lation caused a marked reduction in the pressor responses to all three agonists and the subsequent slow i.v. infusion of adrenaline was unable to effect a full restoration of the agonist-induced increases in DBP, even at the highest adrenaline-infusion rate used (Figure 4).

Comparison of the effects of adrenaline infusion on vasoconstrictor responses The maximal increase in DBP (90 mmHg), to stimulation of the entire sympathetic outflow in intact animals, was obtained at a frequency of stimulation of 6 Hz. In order to test whether adrenaline infusion restored pressor responses to sympathetic stimulation, in demedullated rats, purely by affecting vascular smooth muscle tone in these animals; the effects of adrenaline infusion on the frequencies of stimulation and doses of α-adrenoceptor agonists which produced comparable increases in DBP (25% and 75% of the stimulation induced maximum in intact rats) were compared.

The frequencies of stimulation and doses of α-adrenoceptor agonists which induced increases in DBP of 22.5 mmHg (25%) and 67.5 mmHg (75%) in intact pithed rats are shown in Table 3. Bilateral adrenal demedullation decreased the induced increases in DBP by approximately 50% (Table 3). The subsequent infusion of adrenaline (500 ng per animal min^{-1},i.v.) effected a marked restoration of pressor responses to stimulation while leaving the α-adrenoceptor agonist-induced pressor responses substantially unaltered (Table 3).

Discussion

An increased sympathetic neuronal activity has been demonstrated in young SHR rats (Grobecker, Roizen, Weise, Saavedra & Kopin, 1975) and would appear to be an essential factor in the development of genetic hypertension since neonatal sympathectomy with 6-OHDA prevents the development of a raised blood pressure in these animals (Provoost & De Jong, 1978). Adrenaline might play a significant role in the increased sympathetic neuronal activity, leading to the development of genetic hypertension, since it has been shown to facilitate sympathetic neurotransmitter release (Stjarne & Brundin, 1975) and Majewski *et al.* (1981) have shown that normotensive rats, implanted with a slow-release depot preparation of adrenaline, develop a raised blood pressure. Hence, adrenaline depletion might be expected to attenuate the development of a raised blood pressure in young SHR rats and reduce blood pressure in adult rats.

In our experiments, bilateral adrenal demedullation of 4 week old SHR rats significantly attenuated, but did not prevent, the development of a raised blood pressure. This is unlikely to be due to adrenal cortical damage, caused during demedullation, since plasma corticosterone concentrations were similar in both demedullated and sham-operated animals. However, since demedullation reduced adrenal noradrenaline and adrenaline contents by 99.5%, leading to a 91% reduction in plasma adrenaline concentration, the attenuated development of hypertension in adrenal demedullated SHR rats may be explained in terms of (1) a reduced vasoconstrictor effect due to depletion of plasma catecholamines of adrenal origin, (2) a reduced adrenaline-mediated facilitation of sympathetic neurotransmitter release, or (3) a combination of these two phenomena.

Nevertheless, while bilateral adrenal demedullation depleted plasma adrenaline concentrations, the noradrenaline concentrations were not significantly reduced, as might be expected if a facilitatory stimulus were being removed, a result which tends to suggest that normal circulating plasma levels of adrenaline do not facilitate sympathetic neurotransmitter release. It is, of course, possible that the re-uptake of neuronally released transmitter, in the whole animal, is sufficient to prevent plasma noradrenaline concentrations from rising, even though adrenaline-induced facilitation may be taking place, so that no change in plasma noradrenaline levels is observed in the absence of adrenaline-induced facilitation of transmitter release.

Nolla-Panades & Smirk (1964) demonstrated that bilateral adrenalectomy had no effect on the blood pressure difference between adult normotensive and SHR rats. This is at variance with our findings that bilateral adrenal demedullation of juvenile SHR rats attenuates the development of hypertension and may be explained by the previous authors' use of adult animals, with an established hypertension, in which secondary vascular changes (hypertrophy of blood vessel walls, narrowing of the lumen, etc.) will maintain a raised blood pressure. In addition, the adrenalectomised animals had to be maintained by substituting saline for drinking water, while adrenal demedullated rats require no such post-operative intervention.

Although chronic bilateral adrenal demedullation attenuated the development of a raised blood pressure, in SHR rats, it did not affect vascular smooth muscle reactivity since the pressor responses to bolus injections of phenylephrine were remarkably similar in demedullated and sham-operated animals. However, acute adrenal demedullation reduced the pressor responses to noradrenaline, phenylephrine and oxymetazoline, which suggests that adrenal demedullation might produce a short-lasting reduction in vascular reactivity.

Drew & Leach (1970) showed a similar reduction in vascular reactivity of adrenalectomised rats, which

could be restored by cortisone administration but not by adrenaline infusion. However, in our experiments, pretreating the rats with corticosterone, a naturally occurring steroid in rat plasma (Bernstein, 1950), did not prevent the reduction in responses to pressor stimuli induced by acute adrenal demedullation (Borkowski & Quinn, unpublished observations). This would indicate that the reduced responsiveness to pressor stimuli, observed in adrenal demedullated rats, is not explicable in terms of the effects of alterations in plasma steroid levels brought about by possible damage to the adrenal cortex or its blood supply caused during adrenal demedullation. Indeed, the almost identical plasma corticosterone levels measured in chronically demedullated and sham-operated rats suggests that the adrenal cortex remains both intact and functional.

However, the pressor responses to electrical stimulation of the entire sympathetic outflow were significantly lower, at all frequencies of stimulation, in both chronically and acutely demedullated rats. The subsequent infusion of adrenaline, in acutely demedullated animals, was able to restore pressor responsiveness to sympathetic stimulation in a dose-dependent manner. Although the highest rate of adrenaline infusion significantly raised the resting blood pressure, the restoration in responsiveness to electrical stimulation of the entire sympathetic outflow was not accompanied by an equivalent restoration of responsiveness to bolus injections of α-adrenoceptor agonists. This result indicates that the reduction in pressor response to sympathetic stimulation, induced by adrenal demedullation, and its subsequent restoration by the infusion of adrenaline cannot be explained solely in terms of a generalized change in vascular smooth muscle reactivity and probably involves adrenaline-induced facilitation of sympathetic transmitter release.

At the highest rate of adrenaline infusion, which completely restored pressor responses to sympathetic stimulation, the plasma adrenaline levels recorded were well above those measured in conscious, unrestrained rats. However, it is not yet known what amounts of adrenaline are released into the circulation when the sympathetic outflow is electrically stimulated in intact pithed rats. The observed levels of plasma adrenaline during adrenaline infusions compare very favourably with the concentrations of adrenaline, recorded by Dahlof (1981), required to facilitate the electrically induced release of [^{3}H]-noradrenaline in the rat portal vein preparation. Dahlof (1981) showed a 35% increase in [^{3}H]-noradrenaline overflow in the presence of 0.5 μM adrenaline, while we obtained a 100% increase in stimulation-induced pressor activity with a plasma adrenaline concentration of approximately 0.1 μM.

It is concluded that the adrenaline-induced restoration of responsiveness to stimulation of the entire sympathetic outflow in pithed adrenal demedullated rats involves, at least in part, a facilitation of sympathetic neurotransmitter release and that such a facilitatory effect plays a significant, but not crucial, role in the development of genetic hypertension. Whether the adrenaline-induced facilitation, of pressor responses to sympathetic nerve stimulation in our pithed rats, is mediated via pre-junctional β_2-adrenoceptors, as is the facilitation of [^{3}H]-noradrenaline release in human omental arteries (Stjarne & Brundin, 1975; 1976), remains to be seen.

P.Q. is an SERC-CASE student in conjunction with Imperial Chemical Industries plc. We wish to thank ICI and Merck, Sharp & Dohme for the generous gifts of drugs; Mr S. Ashmore for the corticosterone determinations and Mrs J.A. Lewis for the prompt and accurate typing of this manuscript.

References

ANTON, A.H. & SAYRE, D.F. (1962). A study of the factors affecting the aluminium oxide trihydroxyindole procedure for the analysis of catecholamines. *J. Pharmac. exp. Ther.*, **138**, 360–375.

BERNSTEIN, D.E. (1950). Autotransplantation of adrenal gland in spleen and mesentery of rats. *Proc. Soc. exp. Biol. Med.*, **73**, 175.

DAHLOF, C. (1981). Studies on β-adrenoceptor mediated facilitation of sympathetic transmission. *Acta physiol. scand.*, Suppl. 500.

DREW, G.M. & LEACH, G.D.H. (1970). The effect of acute adrenalectomy on the blood pressure responses to noradrenaline and to preganglionic nerve stimulation. *J. Pharm. Pharmac.*, **22**, 811–817.

GILLESPIE, J.S. & MUIR, T.C. (1967). A method of stimulating the complete sympathetic outflow from the spinal cord to blood vessels in the pithed rat. *Br. J. Pharmac. Chemother.*, **30**, 78–87.

GROBECKER, H., ROIZEN, M.F., WEISE, V., SAAVEDRA, J.M. & KOPIN, I.J. (1975). Sympathoadrenal medullary activity in young, spontaneously hypertensive rats. Nature, **258**, 267.

KUBO, T., ESUMI, K. & ENNYU, K. (1977). Effects of chronic treatment with propranolol on blood pressure and cardiovascular reactivity in spontaneously hypertensive rats. *Arch. Int. Pharmacodyn.*, **227**, 30–40.

MAJEWSKI, H., TUNG, L.H. & RAND, M.J.(1981). Adrenaline induced hypertension in rats. *J. cardiovasc. Pharmac.*, **3**, 179–185.

NOLLA-PANADES, J. & SMIRK, F.H. (1964). Effect of bilateral adrenalectomy on the blood pressure of rats with spontaneous inherited hypertension. *Austral. Ann. Med.*, **13**, 320–321.

OKAMOTO, K. & AOKI, K. (1963). Development of a strain of spontaneously hypertensive rats. *Jap. Circ. J.*, **27**, 283–293.

POPOVIC, V. & POPOVIC, C (1960). Permanent cannulation of aorta and vena cava in rats and ground squirrels. *J. appl. Physiol.*, **15**, 727–728.

PROVOOST, A.P. & DE JONG, W. (1978). Differential development of renal, DOCA-salt and spontaneous hypertension in the rat after neonatal sympathectomy. *Clin. exp. Hypertens.*, **1**, 178–189.

STJARNE, L. & BRUNDIN, J. (1975). Dual adrenoceptor-mediated control of noradrenaline secretion from human vasoconstrictor nerves: Facilitation by β-receptors and inhibition by α-receptors. *Acta physiol. scand.*, **94**, 139–141.

STJARNE, L. & BRUNDIN, J. (1976). β_2-adrenoceptors facilitat ng noradrenaline secretion from human vasoconstrictor nerves. *Acta physiol. scand.*, **97**, 88–93.

ZENKER, N. & BERNSTEIN, D.E. (1958). The estimation of small amounts of corticosterone in rat plasma. *J. biol. Chem.*, **231**, 695–701.

(*Received March 10, 1983.*
Revised June 17, 1983.)