Br. J. clin. Pharmac. (1979), **8**, 253–260

THE PRESSOR ACTIONS OF NORADRENALINE, ANGIOTENSIN II AND SARALASIN IN CHRONIC AUTONOMIC FAILURE TREATED WITH FLUDROCORTISONE

B. DAVIES, R. BANNISTER, P. SEVER & C. WILCOX

The Medical Unit and Department of Neurology, St Mary's Hospital Medical School, London W2

1 Treatment of postural hypotension due to chronic autonomic failure with fludrocortisone increased the pressor sensitivity to intravenous noradrenaline. Fludrocortisone increased the blood pressure in the standing but not the lying position. These effects of fludrocortisone may be the result of increased sensitivity of vascular receptors to noradrenaline.

2 The pressor action of angiotensin II, to which patients were supersensitive, may have involved the stimulation of α-adrenoceptors since it was partially antagonised by phentolamine.

3 Saralasin had a marked, paradoxical, pressor effect. This may have been mediated by vascular α-adrenoceptors because log dose-response curves of saralasin-induced increases in systolic pressure were shifted to the right in a parallel fashion after phentolamine.

4 Fludrocortisone treatment increased the pressor sensitivity to intravenous saralasin but not to angiotensin-II.

Introduction

Chronic autonomic failure may occur alone (idiopathic postural hypotension, Bradbury & Eggleston, 1925), associated with Parkinsonism (Graham & Oppenheimer, 1969) or other neurological abnormalities (multiple system atrophy or the Shy-Drager syndrome, Bannister & Oppenheimer, 1972; Shy & Drager, 1960). In all these conditions, postural hypotension may be a disabling feature. This results from degeneration of the sympathetic nervous system with impairment of vasoconstriction on standing (Bannister, Ardill & Fentem, 1967).

Fludrocortisone (9 alpha-fluoro hydrocortisone) is a mineralocorticoid used in the treatment of postural hypotension (Bannister, Ardill & Fentem, 1969). Its action may result from fluid retention with expansion of the plasma volume (Bannister *et al.*, 1969). However, in normal subjects, fludrocortisone may sensitize vascular receptors to pressor amines (Schmid, Eckstein & Abboud, 1966) to which patients with autonomic failure are usually supersensitive (Wilcox & Aminoff, 1976; Davies, Bannister & Sever, 1978; Bannister, Davies, Holly, Rosenthal & Sever, 1979). In order to obtain further information about the actions of fludrocortisone, we have studied the changes in blood pressure after intravenous noradrenaline, phentolamine, angiotensin II and saralasin (1-sarcosyl-8-alanyl angiotensin II, an angiotensin-receptor blocker; Pals, Masucci, Denning, Sipos & Fessler, 1971) before and after fludrocortisone treatment in four patients with postural hypotension caused by chronic autonomic failure.

Methods

Patients

Three male (cases 1, 2 and 4) and one female (case 3) patients, aged 56–67 years, were treated. The patients had had symptoms of postural hypotension for 2 to 9 years. In all the patients the postural hypotension was shown to be due to chronic autonomic failure. Each had other neurological signs either extrapyramidal (cases 1, 3 and 4), pyramidal (case 2), cerebellar (case 1), or evidence of bladder dysfunction (case 4). The neurological diagnosis in each case was chronic autonomic failure with multiple system atrophy of varying severity (Shy Drager syndrome). Testing of autonomic function revealed pronounced postural hypotension, loss of systolic overshoot in the Valsalva response and loss of a pressor response to stress indicating a sympathetic efferent lesion (Bannister *et al.*, 1967). All four patients were supersensitive to intravenous noradrenaline (Bannister *et al.*, 1979). All patients were admitted to hospital for the study which had their informed consent.

Throughout the study, patients ate a diet providing 90 mmol Na^+ per day. Body weight, fluid intake and

0306–5251/79/090253–08 $1.00

output, urinary urea, sodium and potassium were measured daily. Blood pressure (lying and after 5 min standing) was recorded with a sphygmomanometer daily at 06.00 and 18.00 h. Haematocrit, plasma urea, potassium and sodium and plasma proteins were measured every third day.

Fludrocortisone treatment and drug infusion

For the first 6 days of the study no drugs were given. On day 7 at 18.00 h, a loading dose (0.2 mg, by mouth) of fludrocortisone was given followed by 0.1 mg at 08.00 h from days 8 to 14. On day 7 before fludrocortisone therapy was begun, and again on day 14 at the same time of day as previously, the intravenous dose of, respectively, noradrenaline (noradrenaline bitartrate, Winthrop Labs.), angiotensin II (Hypertensin, Ciba-Geigy) and then saralasin (P113, Norwich-Eaton Labs) necessary to change the systolic blood pressure by 20 mmHg or more, were determined. Twenty minutes were allowed to elapse and then phentolamine (Rogitine, Ciba-Geigy, 0.1 mg kg^{-1}, total dose 5–10 mg) was given by intravenous infusion over 2 to 5 min. After a further 20, 30 and 35 min respectively, (Richards, Woodings & Prichard, 1978) the doses of noradrenaline, angiotensin II and then saralasin necessary to raise the systolic blood pressure by 20 mmHg or more, were re-determined.

The patients were recumbent during the drug infusions. The drugs were given through intravenous cannulae (Abbocath 18G, Abbot Labs.) in an antecubital vein using a constant infusion pump.

Blood pressures and pulse rates were recorded at 5 min intervals during an initial resting period of 45 minutes, and then at one minute intervals during drug infusions using a Bosomat II automatic blood pressure recorder (Bosch and Sohn, Fabrik Medizinischer Apparate D 7455, Jungingen). The instrument was calibrated at frequent intervals against a sphygmomanometer (Davies *et al.*, 1978).

Statistical analysis of data

The blood pressure values before and after fludrocortisone treatment, the changes in dose of drugs needed to produce a rise in systolic blood pressure before and after fludrocortisone, pulse rate and blood pressure changes induced by the drugs infused were all compared using paired *t*-tests. Log dose-response curves for increases in blood pressure produced by noradrenaline and saralasin were constructed using the method of least squares and tested for non-parallelism.

Results

Body weight, haematocrit and plasma proteins

There was no significant change in body weight after treatment with fludrocortisone (Table 1). Haematocrit and plasma proteins, sodium and potassium did not change significantly during the study. However, after fludrocortisone, urinary sodium excretion was decreased from 92.9 ± 35 to 56.8 ± 16 mmol/24 h ($P < 0.0025$, Table 1).

Drug infusion studies

The doses of noradrenaline, angiotensin II and saralasin necessary to change the systolic blood pressure before and after fludrocortisone treatment are shown in Table 2. After fludrocortisone treatment the dose of noradrenaline needed for a significant increase in systolic blood pressure was less than one quarter of the dose needed before fludrocortisone ($P < 0.05$). Fludrocortisone treatment did not significantly change the dose of angiotensin II required to raise the systolic pressure. Saralasin produced a paradoxical marked increase in blood pressure in all the patients. The dose necessary to cause this was

Table 1 Body weight, haematocrit, plasma proteins, sodium and potassium and urinary sodium and potassium before and after fludrocortisone

Measurement	*Before*	*After*
Body weight (kg)	78.1 ± 14.5	80.1 ± 23
Haematocrit (%)	39.5 ± 0.9	39.6 ± 1.6
Plasma proteins (g/l)	64.8 ± 2.5	65.0 ± 2.6
Plasma sodium (mmol/l)	137.0 ± 1.1	137.4 ± 1.4
potassium (mmol/l)	4.1 ± 0.3	4.0 ± 0.3
Urinary sodium (mmol/24 h)	92.9 ± 35	56.8 ± 16*
potassium (mmol/24 h)	52.4 ± 18.8	49.4 ± 16.6

Values represent the mean ± s.d. for inter-individual differences on day 7 at the end of the pre-treatment (before fludrocortisone) and treatment periods (after fludrocortisone) respectively.
*$P < 0.0025$ difference from before fludrocortisone.

Table 2 Dose of drugs to raise systolic blood pressure by 20 mmHg before and after fludrocortisone treatment

	Dose of drug		
Drug	*Before*	*After*	P
Noradrenaline (μg min^{-1})	0.65 ± 0.6	0.15 ± 0.24	<0.05
Angiotensin II (ng kg^{-1} min^{-1})	0.45 ± 0.4	0.25 ± 0.17	<0.2 >0.15
Saralasin (μg kg^{-1} min^{-1})	2.3 ± 1.99	0.79 ± 0.92	<0.05

Values represent the mean ± s.d. ($n = 4$) for inter-individual differences on day 7 at the end of the pre-treatment (before fludrocortisone) and treatment (after fludrocortisone) periods respectively.

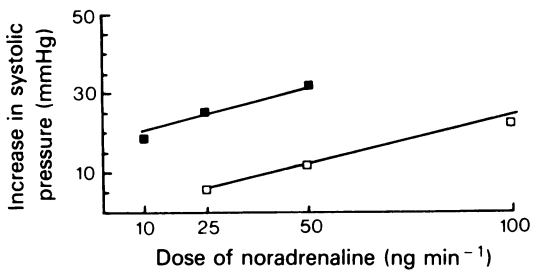

Figure 1 Parallel shift to the left of the log dose-response curve for noradrenaline (in case 4) after treatment with fludrocortisone.
□ before, ■ after fludrocortisone.

decreased by a factor of 3 ($P < 0.05$) after fludrocortisone treatment.

Log dose-response curves for the change in systolic pressure caused by noradrenaline infusion in one patient (case 4) before and after treatment for 7 days with fludrocortisone are shown in Figure 1. The effect of fludrocortisone was to produce a parallel shift to the left of the dose-response curve. Similar results were obtained after plotting the diastolic pressure. The results were similar for all the patients.

Effect of phentolamine on pressor responses

A total dose of 10 mg phentolamine caused an initial increase in heart rate and when followed immediately by tilt to 60° (Figure 2) produced a greater fall in blood pressure than that resulting from tilt alone. After 20 min were allowed to elapse and tilt was repeated, the fall in blood pressure was again greater than before phentolamine. Similar results were obtained in all four patients.

The changes in systolic blood pressure caused by noradrenaline and saralasin before and after phentolamine are shown for one patient (case 4) in Figure 3;

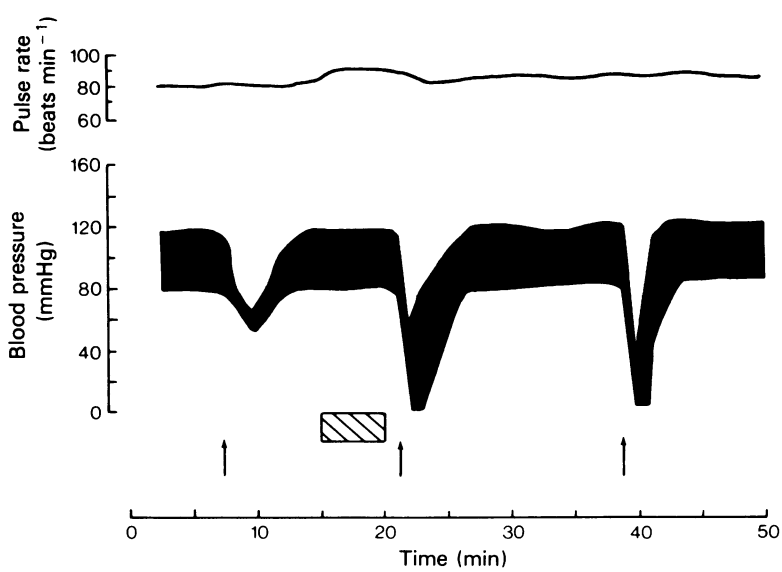

Figure 2 Effect of phentolamine infusion and tilt in case (4). Arrow represents 45° tilt for 2 min. Cross-hatched box (▨) represents duration of phentolamine infusion (2 mg min^{-1}).

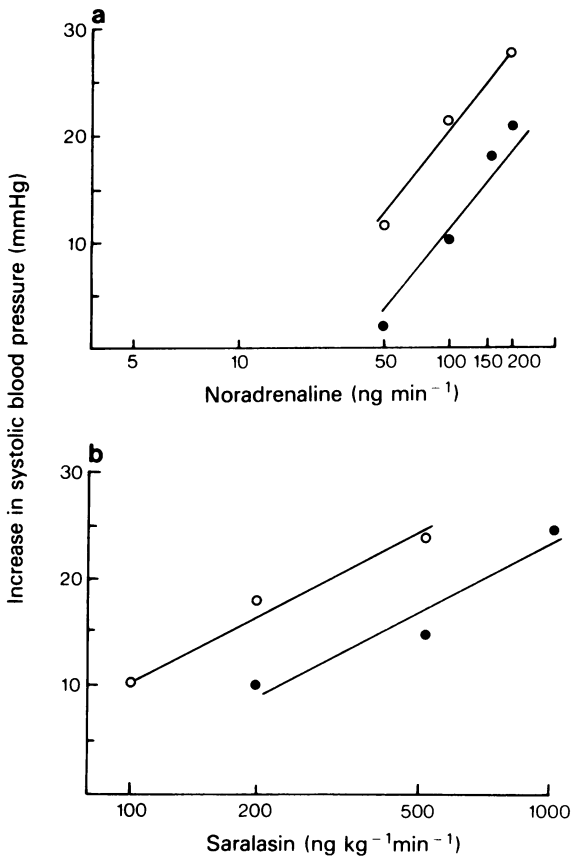

Figure 3 Effect of phentolamine on log dose-response curves for (a) noradrenaline and (b) saralasin (in case 4). ○ before, ● 20 min after phentolamine.

the changes in diastolic pressure were similar. For both noradrenaline and saralasin given 20 min and 35 min respectively, after phentolamine, the effect of the phentolamine was to shift the log dose response curve to the right in a parallel manner; however, the slopes of the curves obtained with noradrenaline and saralasin differ from each other. The results were similar in the other three patients.

The pressor response to angiotensin infusion is shown (for case 4) in Figure 4. At an infusion rate of 0.5 ng kg^{-1} min^{-1}, a rise of about 20 mmHg systolic and 15 mmHg diastolic was produced. When infusion of angiotensin was repeated about 10 min after a total dose of 10 mg phentolamine, the increase in systolic and diastolic pressures were about 10 and 5 mmHg respectively. Similar results were obtained in the other patients.

Changes in pulse rate in response to drug infusions are shown in Table 3. The basal heart rate before fludrocortisone was not significantly different from the rate after fludrocortisone treatment ($P < 0.4 > 0.35$). Before and after fludrocortisone treatment, infusion of noradrenaline, angiotensin II and saralasin produced significant increases in pulse rate in all the patients. Fludrocortisone treatment did not significantly affect the degree of the increase in pulse rate obtained with any drug.

Blood pressure changes after fludrocortisone treatment

The average mean blood pressures recorded at 06.00 and 18.00 h for the 7 days before and after fludrocortisone treatment are shown in Figure 5. At all times the pressures with the patients lying were higher than pressures after standing, ($P < 0.001$). There was no significant difference between the lying pressures before or during fludrocortisone treatment. However, during fludrocortisone treatment the pressures with the patients standing at both 06.00 and 18.00 h were significantly higher (60 ± 19 and 69 ± 29, respectively, $P < 0.05$) than before the treatment period (54 ± 16 and 57 ± 16, respectively).

Discussion

Fludrocortisone did not appear to cause fluid retention in our patients since body weights,

Table 3 Changes in pulse rate caused by drug infusions before and after fludrocortisone.

	Before			*After*		
Drug	*Basal rate*	*After infusion*	P*	*Basal rate*	*After infusion*	P*
Noradrenaline	71 ± 7	76 ± 5	<0.005	72 ± 7	81 ± 8	<0.0005
Angiotensin II	71 ± 7	76 ± 7	<0.005	72 ± 7	82 ± 10	<0.0005
Saralasin	71 ± 7	84 ± 8	<0.0005	72 ± 7	78 ± 6	<0.0005

The s.d. represents the inter-individual differences. For doses of drugs see table 2.
Values are means ± s.d. for pulse rate immediately before and at the end of drug infusions.
*P comparing rate after infusion with basal rate.

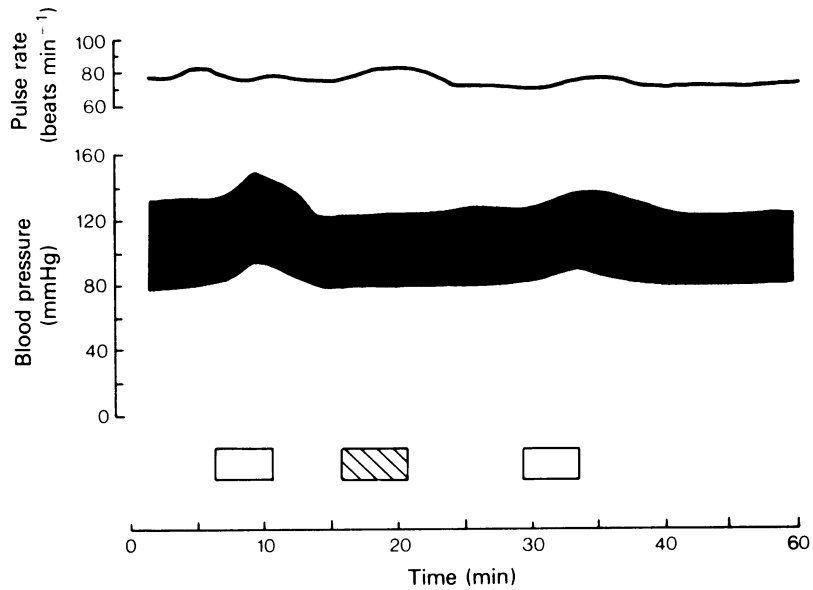

Figure 4 Effect of phentolamine on the pressor response to intravenous angiotensin II in case 4. Open block (□) represents duration of angiotensin II infusion (0.5 ng kg^{-1} min^{-1}) and cross-hatched block (▨) represents duration of phentolamine infusion (2 mg min^{-1}).

haematocrits and plasma proteins did not change significantly after treatment with this drug. However, fludrocortisone did have some mineralocorticoid effect since it decreased significantly urinary sodium excretion. There was no change in plasma sodium after fludrocortisone although an increase has been recorded (Schmid *et al.*, 1966) in normal subjects given 0.2 mg daily.

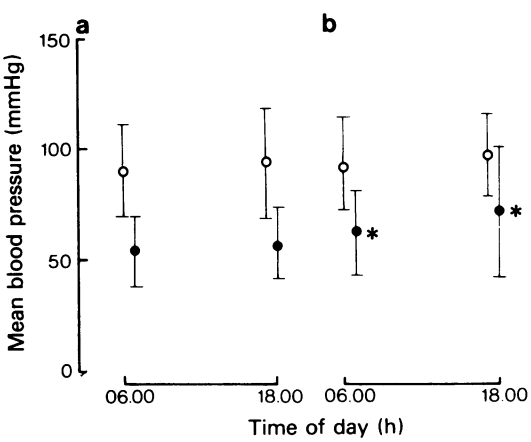

Figure 5 Average mean blood pressures with patients lying (○) or standing (●) before and after fludrocortisone treatment. Values are means ± s.d. *BP higher after fludrocortisone, ($P < 0.05$). Values represent the mean ± s.d. for inter-individual differences in the average mean blood pressure for the 7 day pre-treatment period (a, before fludrocortisone) and the 7 day treatment period (b, after fludrocortisone), respectively.

Treatment with fludrocortisone markedly increased the sensitivity of our patients to intravenous noradrenaline as shown by the smaller dose of noradrenaline needed to produce a significant rise in blood pressure (20 mmHg) and by the displacement to the left of the log dose-response curve for noradrenaline after fludrocortisone treatment. This increased response to noradrenaline occurred against a background of supersensitivity, since all these patients had increased sensitivity to intravenous noradrenaline without fludrocortisone, and for each patient, the degree of supersensitivity to noradrenaline before fludrocortisone treatment was identical to that observed during a previous study (Bannister *et al.*, 1979). Therefore, although no formal control for the fludrocortisone administration was made, it is likely that the change in sensitivity to noradrenaline was due to the fludrocortisone.

The mechanism of this change is obscure. It has been suggested that fludrocortisone may reduce distensibility of the resistance vessels by increasing the water content of vessel walls (Tobian & Redleaf, 1958). However, simple oedema of vessel walls which would be a non-specific change cannot explain why there was increased sensitivity to noradrenaline but not to angiotensin II. It is likely that some change occurs in sympathetic receptors in chronic autonomic failure because of the denervation supersensitivity

(Trendelenburg, 1972; Bannister *et al.*, 1979), and this may be either an increase in the number of receptors or a change in their structure.

Increases in intracellular sodium and decreases in intracellular potassium have been shown to occur with the use of mineralocorticoids (Green, Reynolds & Girerd, 1955; Tobias & Binion, 1954; Bohr, Brodie & Chen, 1958). It has also been suggested that changes in transcellular gradients of sodium and potassium increase the responsiveness of smooth muscle to contractile stimuli (Bohr *et al.*, 1958). Thus fludrocortisone by changing sodium and potassium shifts across the vascular cell membranes may have altered the properties of the surface adrenergic receptors.

Another factor thought to be of importance in supersensitivity after sympathetic nerve degeneration is a lack of neuronal reuptake of catecholamines (Trendelenberg, 1972). For example, it has been shown in the rat mesenteric vasculature *in vivo*, that uptake by adrenergic nerve terminals (uptake 1) affects the sensitivity of arterial vessels to topically applied noradrenaline (Marshall, 1977).

In autonomic failure, degeneration of sympathetic nerve endings may result in reduced ability to clear catecholamines from the receptors. However, although uptake 1 is thought to be of significance in the removal of catecholamines from blood (Iversen, 1967; Whitby, Axelrod & Weil-Malherbe, 1961), it is known that the smooth muscle of blood vessels near to the lumen is only sparsely innervated with sympathetic nerves (De La Lande & Waterson, 1967; De La Lande, Hill, Yellett & McNeill, 1970). Therefore, uptake of catecholamines into this smooth muscle (uptake 2, Gillespie, 1973) may be of greater importance in the inactivation of circulating catecholamines, especially after degeneration of sympathetic nerve endings. Hydrocortisone potentiates the action of noradrenaline on aortic strips (Kalsner, 1969) and corticosterone and deoxycorticosterone inhibit uptake of noradrenaline by uptake 2 (Salt & Iversen, 1972). Fludrocortisone, which is a 9 α-fluoro derivative of hydrocortisone, may have increased the sensitivity of our patients to noradrenaline by decreasing its rate of clearance by inhibition of uptake 2. This point is being further investigated.

Fludrocortisone did not change significantly the blood pressures with the patients lying. However, during fludrocortisone treatment, the pressures with the patients standing were significantly higher. This may have been the result of an increase in sympathetic tone in response to a postural stimulus.

The α-adrenoceptor blocking agent, phentolamine, when given to our patients, produced an immediate rise in heart rate and when the patients were tilted produced a greater fall in blood pressure than with tilt alone. These initial effects were probably due to a non-specific vasodilating action which has been described in normal subjects, (Taylor, Sutherland, Mackenzie, Staunton & Donald, 1965). However, when 20 min were allowed to elapse, tilt again produced a fall in blood pressure which was greater than before phentolamine was given. This may be explained in terms of the α-adrenoceptor blockade which lasts longer than the vasodilating effects which disappear 20 min after infusion of the drug (Richards *et al.*, 1978). The resulting blockade of the effects of stimulation of remaining sympathetic pathways by tilt produced a greater fall in blood pressure than when patients were tilted before a dose of phentolamine. Stimulation of vascular adrenoceptors did not appear to be important in the maintenance of supine blood pressure because this was unaffected by infusion of phentolamine.

Saralasin (1-sarcosyl 8-alanyl angiotensin II) the angiotensin receptor blocker, (Pals *et al.*, 1971) produced a marked, paradoxical rise in blood pressure in all the patients and this rise in blood pressure was accompanied by a significant increase in pulse rate. Phentolamine, when infused about 20 min before noradrenaline or 35 min before saralasin, produced a parallel shift to the right in the log dose response curves for noradrenaline and saralasin. The slopes of the noradrenaline and saralasin dose response curves were, however, different.

In patients with essential hypertension, saralasin can increase blood pressure. A rise in plasma noradrenaline (McGrath, Ledingham & Benedict, 1977, Davies, unpublished observations) has been shown to accompany this pressor response which may be blocked by intravenous phentolamine (Davies, unpublished observations). Furthermore, the l-sarcosyl and 8-alanyl derivatives of angiotensin II have been shown, like the parent compound, to be potent stimulators of adrenal medullary catecholamine release (Peach & Ober, 1974). In our study, the pressor sensitivity to saralasin as well as to noradrenaline was increased by fludrocortisone therapy. These observations suggest that the pressor action of saralasin in autonomic failure is mediated by adrenoceptors. However, our patients, when compared with normal subjects (Streeton, Anderson, Freiberg & Dalakos, 1975) were supersensitive to angiotensin II and previous studies have explained pressor responses to saralasin in terms of partial agonism of saralasin at vascular angiotensin II receptors (Hollenberg, Williams, Burger, Ishikawa & Adams, 1976). Therefore, some of the pressor response with saralasin could have been due to stimulation of angiotensin II receptors. The concepts of partial agonism and stimulation of α-adrenoceptors are not mutually exclusive, for angiotensin II may increase release of noradrenaline by sympathetic nervous stimulation, may act on presynaptic α-adrenoceptors (Starke & Endo, 1976) and may interact with the autonomic nervous system

in other ways (Peach, 1977; Severs & Daniel-Severs, 1977; Regoli, Park & Rioux, 1974).

Previous studies have shown an increased pressor response to angiotensin II in autonomic failure (Scroop & Whelan, 1968; Bannister *et al.*, 1969), and this was confirmed in the present study. It has been shown that after denervation, blood vessels are sensitive to small doses of angiotensin II (Page, McCubbin, Schwarz & Bumpus, 1957). Some of this supersensitivity may involve changes in angiotensin vascular receptors since the pressor sensitivity to angiotensin, unlike that to noradrenaline and saralasin, was not affected by fludrocortisone treatment. However, phentolamine did partially block the blood pressure rise in response to angiotensin II (Figure 4) indicating that part of the pressor response was due to α-adrenoceptor stimulation.

The pulse rates of all the patients were significantly increased by noradrenaline, saralasin and angiotensin II. This abnormal response probably resulted from a combination of denervation supersensitivity of sympathetic cardiac receptors and a defect of baroreceptor reflexes (Davies *et al.*, 1978; Bannister *et al.*, 1979).

In conclusion, we have shown that the beneficial effects of fludrocortisone in chronic autonomic failure could be the result of increased sensitivity of vascular receptors to noradrenaline. The increase in sensitivity to angiotensin II in autonomic failure may involve, in addition to changes in angiotensin receptor sensitivity, interactions with sympathetic nerves and adrenal medullary catecholamine release. The pressor response to saralasin is probably mediated by stimulation of vascular alpha-adrenoceptors.

I.B.D. is a CIBA Research Fellow.
Saralasin was a gift from Norwich-Eaton Laboratories.

References

BANNISTER, R., ARDILL, L. & FENTEM, P. (1967). Defective control of blood vessels in idiopathic postural hypotension. *Brain*, **90**, 725–746.

BANNISTER, R., ARDILL, L. & FENTEM, P. (1969). An assessment of various methods of treatment of idiopathic orthostatic hypotension. *Q. J. Med.*, **38**, 377–395.

BANNISTER, R., DAVIES, B., HOLLY, E., ROSENTHAL, T. & SEVER, P. (1979). Defective cardiovascular reflexes and supersensitivity to sympathomimetic drugs in autonomic failure. *Brain*, **102**, 163–176.

BANNISTER, R. & OPPENHEIMER, D.R. (1972). Degenerative diseases of the nervous system associated with autonomic failure. *Brain*, **95**, 457–474.

BANNISTER, R., SEVER, P. & GROSS, M. (1977). Cardiovascular reflexes and biochemical responses in progressive autonomic failure. *Brain*, **100**, 327–344.

BOHR, D.F., BRODIE, D.C. & CHEN, D.H. (1958). Effects of electrolytes on arterial muscle contraction. *Circulation*, **17**, 746–749.

BRADBURY, S. & EGGLESTON, C. (1925). Postural hypotension: an autopsy upon a case. *Am. Heart J.*, **1**, 73–86.

DAVIES, B., BANNISTER, R. & SEVER, P. (1978). Pressor amines and monoamine oxidase inhibitors for treatment of postural hypotension in autonomic failure. *Lancet*, **i**, 172–175.

DE LA LANDE, I.S., HILL, B.D., JELLET, L.B. & MCNEILL, J.M. (1970). The role of monoamine oxidase in the response of the isolated artery of the rabbit ear to tyramine. *Br. J. Pharmac.*, **40**, 249–256.

DE LA LANDE, I.S. & WATERSON, J.G. (1967). Site of action of cocaine on the perfused artery. *Nature*, **214**, 313–314.

GILLESPIE, J.S. (1973). Uptake of noradrenaline by smooth muscle. *Br. med. Bull.*, **29**, 136–141.

GRAHAM, J.G. & OPPENHEIMER, D.R. (1969). Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy. *J. Neurol Neurosurg. Psychiat.*, **32**, 28–34.

GREEN, D.M., REYNOLDS, T.B. & GIRERD, R.J. (1955). Mechanisms of desoxycorterone action, *X*: effects on tissue sodium concentration. *Am. J. Physiol.*, **181**, 105–113.

HOLLENBERG, N.K., WILLIAMS, G.H., BURGER, B., ISHIKAWA, I. & ADAMS, D.F. (1976). blockade and stimulation of renal, adrenal and vascular angiotensin II receptors with 1-sarcosyl-8-alanyl angiotensin II in normal man. *J. clin. Invest.*, **57**, 39–46.

IVERSEN, L.L. (1967). In *The uptake and storage of noradrenaline in sympathetic nerves*, pp. 135–139. London: Cambridge University Press.

KALSNER, S. (1969). Steroid potentiation of responses to sympathomimetic amines in aortic strips. *Br. J. Pharmac.*, **36**, 582–593.

MARSHALL, J.M. (1977). the effect of uptake by adrenergic nerve terminals on the sensitivity of arterial vessels to topically applied noradrenaline. *Br. J. Pharmac.*, **61**, 429–432.

MCGRATH, B.P., LEDINGHAM, J.G.G., BENEDICT, C.R. (1977). Plasma catecholamines and the pressor response to sar-1-Ala-8-Angiotensin II in man. *Clin. Sci. mol. Med.*, **53**, 341–348.

PAGE, I.H., MCCUBBIN, J.W., SCHWARZ, H. & BUMPUS, F.M. (1957). Pharmacological aspects of synthetic angiotonin. *Circulation Res.*, **5**, 552–555.

PALS, D.T., MASUCCI, F.D., DENNING, G.S., SIPOS, F. & FESSLER, D.C. (1971). Role of the pressor action of angiotensin II in experimental hypertension. *Circulation Res.*, **29**, 673–681.

PEACH, M.J. (1977). Renin-angiotensin system: bio-

chemistry and mechanisms of action. *Physiol. Rev.*, **57**, 313–370.

PEACH, M.J. & OBER, M. (1974). Inhibition of angiotensin-induced adrenal catecholamine release by 8-substituted analogues of angiotensin II. *J. Pharmac. exp. Ther.*, **190**, 49–58.

REGOLI, D., PARK, W.K. & RIOUX, F. (1974). Pharmacology of angiotensin. *Pharmac. Rev.*, **26**, 69–123.

RICHARDS, D.A., WOODINGS, E.P. & PRICHARD, E.N.C. (1978). Circulatory and α-adrenoceptor blocking effects of phentolamine. *Br. J. clin. Pharmac.*, **5**, 507–513.

SALT, P.J. & IVERSEN, L.L. (1972). Inhibition of the extraneuronal uptake of catecholamines in the isolated rat heart by cholesterol. *Nature, New. Biol.*, **238**, 91–92.

SCHMID, P.G., ECKSTEIN, J.W. & ABBOUD, F.M. (1966). Effect of 9-α-f'uorohydrocortisone on forearm vascular responses to norepinephrine. *Circulation*, **34**, 620–626.

SCROOP, G.C. & WHELAN, R.F. (1968). The effects of alpha-adrenergic receptor blockade and sympathetic denervation on the pressor action of angiotensin in man. *Aust. J. exp. Biol. med. Sci.*, **46**, 563–572.

SEVERS, W.B. & DANIEL-SEVERS, A.E. (1973). Effects of angiotensin on the central nervous system. *Pharmac. Rev.*, **25**, 415–449.

STARKE, K. & ENDO, T. (1976). Presynaptic α-adrenoceptors. *Gen. Pharmac.*, **7**, 307–312.

SHY, G.M. & DRAGER, G.A. (1960). A neurological syndrome associated with orthostatic hypotension. *Archs. Neurol. Chicago*, **2**, 511–527.

STREETEN, D.H.B., ANDERSON, G.H., FREIBERG, J.M. & DALAKOS, T.G. (1975). Use of angiotensin II antagonist (saralasin) in the recognition of angiotensinogenic hypertension. *New Engl. J. Med.*, **292**, 657–662.

TAYLOR, S.H., SUTHERLAND, G.R., MACKENZIE, G.R., STAUNTON, H.S. & DONALD, K.W. (1965). The circulatory effects of intravenous phentolamine in man. *Circulation*, **31**, 741–754.

TOBIAN, L. & BINION, J. (1954). Artery wall electrolytes in renal and D C A hypertension. *J. clin. Invest.*, **33**, 1407–1414.

TOBIAN, L. & REDLEAF, P.D. (1958). Ionic composition of the aorta in renal and adrenal hypertension. *Am. J. Physiol.*, **192**, 325–330.

TRENDELENBURG, U. (1972). Factors influencing the concentration of catecholamines at the receptors. In *Catecholamines*, Handb. exp. Pharmac. Vol. 33, ed. Blaschko, H. & Muscholl, E. pp. 726–761. Berlin and Heidelberg: Springer-Verlag.

WILCOX, C.S. & AMINOFF, M.J. (1976). Blood pressure responses to noradrenaline and dopamine infusions in Parkinson's disease and the Shy-Drager syndrome. *Br. J. clin. Pharmac.*, **3**, 207–214.

WHITBY, L.G., AXELROD, J. & WEIL-MALHERBE, H. (1961). The fate of H^3-norepinephrine in animals. *J. Pharmac. exp. Ther.*, **132**, 193–201.

(Received October 30, 1978)