COMPARISON OF THE RENIN RESPONSE TO DOPAMINE AND NORADRENALINE IN NORMAL SUBJECTS AND PATIENTS WITH AUTONOMIC INSUFFICIENCY

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(Received 26 November 1973)

SUMMARY

1. The effect on plasma renin activity (PRA) of dopamine and noradrenaline infusions was studied in three patients with Shy–Drager syndrome, three patients with Parkinson’s disease and normal autonomic reflexes, and three healthy volunteers. The patients with the Shy–Drager syndrome had functional evidence of a peripheral lesion of the sympathetic nervous system and subnormal PRA on a controlled sodium intake.

2. In all subjects catecholamines were infused step-wise for 4 min until a 30% rise in systolic blood pressure occurred.

3. In each subject, PRA fell after noradrenaline but rose after dopamine. The mean fractional increase in PRA after dopamine was no less in the Shy–Drager patients than in the control groups.

4. The results suggest, first, that stimulation of dopamine receptors can release renin, and secondly, that inadequate renin stores cannot explain the low PRA found in our patients with autonomic failure.

Key words: dopamine, noradrenaline, renin, Parkinson’s disease, Shy–Drager syndrome, autonomic insufficiency.

Activation of the sympathetic nervous system is a dominant feature of the physiological response to orthostasis. It is now clear that the increase of plasma renin activity (PRA) in response to orthostasis can be greatly reduced by β-adrenergic blockade (Tobert, Slater, Fogelman, Lightman, Kurtz & Payne, 1973). Barbeau (1970) has suggested that the stimulus to renin secretion involves an increase of the ratio noradrenaline/dopamine in the kidney. This report tests this hypothesis by a comparison of the renin response to noradrenaline and dopamine in normal people.

Autonomic insufficiency, when due to a peripheral lesion of the sympathetic nervous system, Correspondence: Dr C. S. Wilcox, Department of Pharmacology, Middlesex Hospital Medical School, London W1N 8AA.

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often attenuates the renin response to orthostasis (Love, Brown, Chinn, Johnson, Lever, Park & Robertson, 1971; R. C. Turner & J. D. H. Slater, unpublished work). This report also tests the concept that this attenuated response is caused by a reduction of the stimulus to renin release (Gordon, Kuchel, Liddle & Island, 1967), rather than by a reduction of the stores of renin (Taquini, Blaquier & Taquini, 1964; Tobian, Braden & Maney, 1965; Ueda, Tagawa, Ishii & Kaneko, 1967). Evidence of renin depletion was sought in patients with sympathetic denervation (Shy–Drager syndrome; Shy & Drager, 1960) by infusion of noradrenaline and dopamine. Since catecholamines can stimulate renin release directly from the kidney (Michelakis, Caudle & Liddle, 1969), any deficiency in renin stores should be apparent as a reduction of renin response to catecholamine infusions.

**PATIENTS AND METHODS**

The experimental group comprised three patients with sympathetic denervation and Parkinsonism (Shy–Drager syndrome); the contrast group comprised three patients with normal autonomic reflexes and Parkinsonism (Parkinson's disease), and three healthy volunteers. The two groups of patients were well matched for age, recumbent blood pressure and neurological disability (Table 1). Cardiovascular reflex responses were normal in the three patients with Parkinson's disease but were grossly attenuated in the three with the Shy–Drager syndrome. The latter patients had postural hypotension and an abnormal response to the Valsalva

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<th>Table 1. Details of subjects studied</th>
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<td>For explanation, see text. +, Present; −, absent; blank, not tested. Neurological signs present in patients with Shy–Drager syndrome, shown under 'Other motor systems', were: pyramidal (three patients); cerebellar (one patient); lower motor neurone (three patients). b.p., Blood pressure.</td>
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<td>Hyperpnoea with i.v. lobeline (3 mg)</td>
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<td>Spreading pilo-erection and sweating with intradermal acetylcholine</td>
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<td>PRA after 7 days on a daily sodium intake of 189 mmol (ng h⁻¹ ml⁻¹)</td>
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manoeuvre. Their respiratory response to intravenous lobeline was normal, indicating that afferent chemoreceptor fibres were intact. The failure of intradermal acetylcholine to induce a spreading piloerection and sweating response around the site of injection indicated a functional lesion of the postganglionic sympathetic nervous system (Bárány & Cooper, 1956). Details of the methods employed in testing the autonomic nervous system, and the interpretation of the results obtained, have been previously published (Aminoff & Wilcox, 1971).

Some weeks before the study began, PRA was measured in all patients, after they had taken a controlled high sodium diet (calculated to contain 189 mmol of sodium and 70 mmol of potassium daily) for 1 week. Measurements were made after patients had been recumbent for 12 h and standing for 4 h. In the three patients with Parkinson's disease the results were normal, but in the Shy–Drager patients they were subnormal (Table 1). The normal range of PRA (expressed as angiotensin generated in the assay system) for subjects of similar age, taking the same sodium and potassium intake and also receiving anticholinergic drugs, is 1.0–2.6 ng h⁻¹ ml⁻¹ (recumbent) and 2.4–4.5 ng h⁻¹ ml⁻¹ (standing) \((n = 5, \text{unpublished observations})\).

All subjects (including the healthy volunteers) were taking benzhexol, 2 mg, thrice daily for at least 2 days before the study, but none was receiving L-dopa.

Informed consent was obtained from all participants. The catecholamine infusions were undertaken with approval of the Clinical Investigations Panel of the Middlesex Hospital.

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**Fig. 1.** Response of a typical healthy subject (weight 64 kg) to noradrenaline (solid columns) and dopamine (hatched columns) infusions. The plasma renin activity (PRA), heart rate, blood pressure (b.p.) and rates of catecholamine infusions are plotted against the time after starting the experiment. At time 0 the insertion of the intravenous cannula was completed.
Subjects were recumbent throughout the study and for 90 min preceding it. After a light breakfast at 08.00 hours an intravenous cannula was inserted into an arm vein; 200–400 ml of 0.28 mol/l (5 g/100 ml) dextrose was infused during the course of the study to maintain the patency of the cannula. After an interval of 90 min either noradrenaline or dopamine was infused by constant infusion pump for 4 min. Heart rate and blood pressure, measured with a sphygmomanometer, were recorded during each infusion. Values reported here relate to readings taken just before and during the last minute of the infusions. After a 4 min rest, the infusion was recommenced but the catecholamine concentration was increased until a 30% rise in systolic blood pressure was achieved. After 90 min the procedure was repeated with the other catecholamine. The order in which patients received each catecholamine was randomized.

The noradrenaline infusion was started at 0.5 µg min⁻¹ and increased as shown in Fig. 1. The dopamine infusion was started at 200 µg min⁻¹ and increased in increments of 200 µg min⁻¹.

Blood samples were taken before the beginning of the infusion and 3 min after that rate of infusion which gave the specified pressor response. Additional samples were taken 30 and 60 min after the pressor response to ensure that PRA had returned to pre-infusion levels. The plasma was separated immediately and deep-frozen. The PRA of each sample was subsequently determined in quadruplicate from the rate of formation of angiotensin I, during a 3 h incubation at 37°C measured by the labelled antibody method of Kurtz (1971).

The drugs dopamine hydrochloride and noradrenaline acid tartrate were freshly made up in sodium chloride (154 mmol/l) on the day of the study.

Wilcoxon's Rank test (Armitage, 1971) was used to assess the significance of the changes in PRA observed after the catecholamine infusions. Because of the small number of patients, between-group statistical analysis is not appropriate.

**RESULTS**

The design of the experiment and the response of a healthy control subject is illustrated in Fig. 1. Fig. 2 shows the grouped data for all subjects. All patients with the Shy-Drager syndrome had a pre-infusion level of PRA less than 3 ng h⁻¹ ml⁻¹, and five of the six others had values above this.

**Response to dopamine**

PRA rose in all subjects after dopamine was infused \( (P<0.01, n = 9) \). The mean increase was 82% in the Shy-Drager patients, 28% in those with Parkinson's disease and 53% in the healthy subjects. There was therefore no suggestion of diminished response in patients with sympathetic denervation. In comparison with pre-infusion levels, the mean PRA for all subjects remained elevated 30 min after the infusion had ceased (+25%) but by 60 min had declined to pre-infusion levels (−2%). During the pressor response, the heart rate increased in all subjects (range +13 to +29 beats min⁻¹); it was similar in the three groups. However, there were considerable differences between them in their pressor sensitivity to dopamine (Fig. 2). Thus the mean rate of dopamine infusion necessary to produce the pressor response in the healthy subjects was 9.5 µg min⁻¹ kg⁻¹; the patients with the Shy-Drager syndrome were supersensitive (requiring only a mean of 5 µg min⁻¹ kg⁻¹) and those with Parkinson's disease were subsensitive (requiring a mean of 23 µg min⁻¹ kg⁻¹).
Plasma renin and catecholamines

Response to noradrenaline

In contrast, PRA fell in all subjects after noradrenaline was infused ($P<0.01$, $n=9$). In comparison with pre-infusion levels, the mean PRA remained depressed 30 min after the infusion had ceased ($-15\%$) but by 60 min it had returned to pre-infusion levels ($+5\%$). During the pressor response the heart rate decreased in the healthy subjects and patients with Parkinson's disease ($-5$ to $-18$ beats min$^{-1}$), but it increased in the Shy–Drager patients.
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(range +9 to +16 beats min$^{-1}$). Again, there were differences between the groups in their pressor sensitivity to noradrenaline (Fig. 2). The mean rate of noradrenaline infusion necessary to produce the pressor response in the healthy subjects was 230 ng min$^{-1}$ kg$^{-1}$. The patients with the Shy–Drager syndrome were considerably supersensitive (requiring a mean of only 40 ng min$^{-1}$ kg$^{-1}$), and those with Parkinson's disease were rather less supersensitive (requiring a mean of 80 ng min$^{-1}$ kg$^{-1}$).

No symptoms were produced by the drugs except in one healthy subject who became aware of tachycardia during dopamine infusion.

DISCUSSION

There were considerable differences in pressor sensitivity to the infused catecholamines in the groups of subjects studied. Supersensitivity to noradrenaline and dopamine in the Shy–Drager patients can be ascribed to denervation since they had evidence of a functional lesion of postganglionic sympathetic neurones. In addition, their failure to develop a reflex bradycardia during noradrenaline infusion must contribute to their enhanced sensitivity to this catecholamine. However, there was no evidence of defective function of peripheral sympathetic pathways amongst the patients with Parkinson's disease. Moreover, they had a normal reflex bradycardia during the pressor response with noradrenaline. The cause for their supersensitive pressor response to noradrenaline is uncertain and is being investigated further. Their subsensitivity to dopamine may be a consequence of the greatly increased rate of dopamine metabolism reported in this disease (Barbeau & Trombitas, 1967).

A comparison of the renin response to dopamine and noradrenaline is of particular interest because, although both catecholamines are vasopressor, they have largely contrary actions on the renal vasculature. Thus dopamine is a renal vasodilator (McDonald, Goldberg, McNay & Tuttle, 1964) whereas noradrenaline is a renal vasoconstrictor (Gambos, Hulet, Bopp, Goldberg, Baldwin & Chasis, 1962). The rise in PRA that followed dopamine infusions was probably due to an increased rate of renin release, since systemic renin levels have been found to reflect renin release during catecholamine infusions (Watthen, Kinsbury, Stouder, Schneider & Rostorfer, 1965).

In our subjects, PRA decreased after the infusion of noradrenaline. Noradrenaline has a stimulant action on renin release in animals only if its pressor effect on the kidney is prevented (Vander, 1967; Bunag, Page & McCubbin, 1966). This could explain the inconsistent response of PRA to pressor quantities of noradrenaline in man (De Champlain, Genest, Veyrat & Boucher, 1966). Thus a 1 : 10 mixture of adrenaline and noradrenaline produced a considerable rise in one patient with autonomic failure who was kept standing to counteract any pressor response (Gordon et al., 1967). Therefore, in our study, it is likely that any stimulant action of noradrenaline upon PRA was overcome by the inhibiting influence of the rise in blood pressure.

Renal function was not studied in the present work, but McDonald et al. (1964) have shown that similar dopamine infusion in man increases renal blood flow, glomerular filtration rate and sodium excretion. Recently, Hollenberg, Adams, Mendell, Abrams & Merrill (1973) have confirmed that intravenous infusion of dopamine in man increases renal blood flow. Both these renal responses and the rise in blood pressure are normally associated with an inhibition of systemic renin release (Vander, 1967). We therefore attribute the rise in PRA with dopamine to a direct stimulant action upon the renin-releasing mechanism. Moreover, the rise in PRA
cannot be a reflex induced by alteration of plasma volume (Vander & Luciano, 1967) since it occurred in patients with absent cardiovascular reflexes. We observed a consistent increase in PRA with dopamine yet a consistent decrease with equipressor doses of noradrenaline. This suggests that it is not the activation of an α-receptor but the activation of the kidney’s specific dopamine receptor (Yeh, McNay & Goldberg, 1969) that leads to renin release. This would be consistent with the functional resemblance of the dopamine receptor to a renal β-adrenergic receptor (McNay, McDonald & Goldberg, 1965); renal β-adrenergic receptor stimulation increases renin release (Otsuka, Assaykeen, Goldfien & Ganong, 1970) and inhibition reduces renin release (Tobert et al., 1973).

In contrast to our observations, Barnardo, Summerskill, Strong & Baldus (1970) found that dopamine infusions depressed PRA. However, their results cannot be compared with ours since they studied patients with cirrhosis of the liver whose pre-infusion levels of PRA were greatly elevated. Moreover their subjects received only a low dose of dopamine and experimental results in the dog suggest that dopamine stimulates renin release only at high dosage (Otsuka et al., 1970).

Barbeau (1970) has postulated that an increase in the dopamine/noradrenaline ratio at the kidney inhibits renin release. Accordingly, an infusion of dopamine, by increasing this ratio, might be expected to decrease PRA. However, our results show that PRA increases after dopamine infusion and they therefore provide no evidence that dopamine depresses renin release.

We found that dopamine produced a normal increase in PRA in patients with autonomic failure and a lesion of the peripheral sympathetic nervous system. This shows that their low resting levels of PRA and subnormal responses to standing are not due to depletion of renin stores. This accords with previous reports of considerable increases in plasma renin during prolonged catecholamine infusions in patients with orthostatic hypotension (Gordon et al., 1967; Hedeland, Dymling & Hökfelt, 1969).

Our results in the Shy–Drager patients are not inconsistent with the data derived from studies in animals. Such studies have shown that the renin content of a denervated kidney is reduced only if the other kidney is left in situ (Ueda et al., 1967). This is not applicable to our patients, who are presumed to have functional denervation of both kidneys. Thus the present results suggest that chronic denervation of both kidneys may not reduce their stores of renin.

ACKNOWLEDGMENTS

We are grateful to Dr Michael Kremer for allowing us to study patients under his care, to Dr F. S. Nashat for his helpful advice, to Mrs Nadia Payne for performing the plasma renin estimations, and to Mr G. Bryan, hospital pharmacist, for preparing the catecholamines. We are also indebted to the Clinical Research Committee of the Middlesex Hospital for facilities in the Institute of Clinical Research, and to the Medical Research Council for a grant to J.D.H.S.

REFERENCES


