CATECHOLAMINES, RENIN AND ALDOSTERONE
IN POSTURAL HYPOTENSION

By

H. Hedeland, J.-F. Dymling and B. Hökfelt

ABSTRACT

The interrelation between catecholamines, renin and aldosterone has been studied in two patients with postural hypotension. Under basal conditions both patients presented subnormal values for urinary catecholamines and plasma renin activity. Urinary aldosterone was subnormal in one of the patients and normal in the other. Attempts to increase catecholamine production using insulin induced hypoglycaemia were ineffective in both patients. Tilting was performed in one of the patients but this did not change the urinary catecholamines whereas the plasma renin levels increased in relation to the degree of tilting in a manner known to occur in healthy subjects. In both patients the infusion of noradrenaline was accompanied by an increase in plasma renin activity.

On a sodium deficient diet both patients conserved sodium at the renal level, although the response seemed delayed in one of them. During equilibration the urinary catecholamines did not increase whereas the plasma renin and urinary aldosterone values rose in both patients; again the response seemed delayed in one patient.

Potassium chloride was administered orally to one of the patients and resulted in an increased urinary output of catecholamines and aldosterone. Our results indicate that baro- and/or osmoreceptor mechanisms can stimulate the production of renin and aldosterone adequately in response to salt restriction and tilting even in the presence of severe sympathetic insufficiency.

Postural hypotension is characterized by a fall in both systolic and diastolic blood pressure on rising from a supine to an erect position. In most patients with this disorder the pulse rate is constant, but some increase may occur on rising. This syndrome was originally described by Bradbury & Eggleston (1925) and they postulated that it depends on a lack of reflex vasoconstriction.
due to damage to the autonomic nervous system. In 1953 Luft & von Euler (1953) demonstrated that this damage is associated with a subnormal production of catecholamines under basal and experimental conditions. Subnormal production of aldosterone (Hall & Hökfelt 1966; Slaton & Biglieri 1967) and decreased capacity to conserve sodium at the kidney level (Shear 1963; Hall & Hökfelt 1966) have been reported in isolated cases. The combination of subnormal production of catecholamines, aldosterone and renin has recently been demonstrated in one patient (Gordon et al. 1967). This last observation is of particular interest in view of the fact that under certain conditions an interrelation has been found between the production of catecholamines and renin on the one hand (Gordon et al. 1967; Ueda et al. 1967; Vander 1965; Vander & Luciano 1967; Brubacher & Vander 1968; Wathen et al. 1965; Bunag et al. 1966; Taquini et al. 1964) and renin-angiotensin and aldosterone on the other (Genest et al. 1960, 1961; Laragh et al. 1960).

The purpose of the present studies was to investigate the extent to which postural hypotension can be related to concomitantly occurring insufficient production of catecholamines, renin and aldosterone under various experimental conditions.

CASE REPORTS

Patient H. K. was a housewife, 56 years old when first admitted to the hospital in 1967. Two younger brothers were said to have hypotension but did not seek medical care. Family history otherwise was non-contributory. The patient had been well until 1964, when the first signs of postural hypotension appeared and thereafter steadily progressed. Prior to admission the patient had temporarily been given fluorohydrocortisone, 0.1–0.3 mg per 24 h with some beneficial effect. Ergotamine and a sympathetic imic compound (Effontil®) had been tried without noticeable effect.

On admission the patient presented with marked postural hypotension, parkinsonism, spasticity and muscular atrophies, anhidrosis, disturbed and frequent micturition and a tendency to constipation. She was clinically euthyroid and there were no signs of organic heart disease. Blood pressure in the recumbent state was 110/75 mm Hg. In the sitting position the blood pressure immediately fell to 70/40 while the pulse rate increased by 20 beats per minute and the patient fainted. The iv administration of 1 mg atropine resulted in an increase in the pulse rate of 25 beats per minute. The Valsalva manoeuvre was not followed by the typical increase in diastolic pressure and bradycardia which is seen in healthy subjects. This lack of response indicated damage to the afferent and/or the efferent nervous pathways. The cold pressor test induced no change in blood pressure, indicating damage to the efferent pathways.

Roentgenogram revealed normal heart, skull and sella turcica. Encephalography showed some central and considerable cortical atrophy, which was most pronounced in the anterior part of the cerebrum. Angiography of the vertebral and carotid arteries revealed normal vessels bilaterally. Basal laboratory data are collected in Table 1.

Patient I. N. was a woman, aged 41 years when she was first admitted in 1967.
The family history was non-contributory. She had been suffering from diarrhoea for many years, which temporarily had led to abuse of opium. She had suffered from mental depression requiring psychiatric care for several years. During the last two years prior to admission she had had dizziness and a tendency to faint in the upright posture. She had been unable to perspire for two years. Therapeutic trials using mineralocorticoids, ergotamine and/or sympathomimetic compounds had been tried without success.

On admission physical examination revealed postural hypotension but otherwise intact neurological functions. There were normal physical findings with regard to heart and lungs. Blood pressure in the recumbent state was 110/80 mm Hg, in the upright posture 60/40 with an increase in pulse rate of 16 beats per minute. Following 1 mg atropine iv the pulse rate increased by 30 beats per minute. The Val-salva manoeuvre induced neither an increase in diastolic pressure nor bradycardia. Salicylates and alcohol were administered in an attempt to induce perspiration but both were without effect and so was physical heating by the application of numerous blankets. With a cold pressor test the blood pressure remained unchanged. Roentgenograms revealed normal heart, lungs and skull. Encephalography was also normal. Basal laboratory findings from the patient's first admission are presented in Table 1. The slight to moderate increase of serum creatinine is noteworthy. Urinalysis was normal and there was no bacteriuria. The iv pyelography demonstrated normal sized kidneys with normal configuration and excretory function. The possibility of amyloidosis was considered initially, but the clinical course following completion of our studies favours the diagnosis of pyelonephritis.

LABORATORY PROCEDURES

All studies were conducted in the metabolic ward. Specified diets were prepared in the metabolic kitchen under the supervision of a dietician. The sodium deficient diet supplied less than 10 meq. of sodium/24 h.

**Catecholamines.** Urinary noradrenaline and adrenaline were determined fluorimetrically using the procedure of von Euler & Lishajko (1961). Urinary specimens were collected for periods of 2 to 24 h. The samples were acidified to pH 4.5 by the addition of glacial acetic acid.

**Renin.** Plasma renin activity was determined according to the assay described by Boucher et al. (1964) and Boucher & Genest (1966), and was expressed in terms of angiotensin formed per 100 ml plasma per 3 h of incubation.

**Aldosterone.** Aldosterone production was measured by the estimation of the 24 h urinary excretion of 3-oxo-aldosterone, using a double labelling technique (Kliman & Peterson 1960).

**Insulin test.** Crystalline insulin was administered intravenously in a dose of 0.1 IU/kg body weight. True blood glucose levels were determined at 15 min intervals using a Technicon autoanalyser.

**Tilting.** Tilting was performed using a device allowing upright posture at various angles without major activation of the patient's own muscles.

**Noradrenaline infusion.** Noradrenaline-HCl (Norexadrin®) was given in isotonic glucose containing 1–4 µg noradrenaline/ml and infused intravenously in amounts which induced and maintained a constant, significant increase of the systolic blood pressure.
Electrolytes. Sodium and potassium in the blood and urine were determined by flamephotometry.

RESULTS

Both patients presented subnormal values for urinary catecholamines and plasma renin activity under basal conditions (Table 1). In patient H. K. urinary aldosterone was also subnormal whereas patient I. N. had urinary aldosterone values within the normal range.

In both patients the administration of insulin was followed by a marked fall in blood sugar but without any increase in urinary catecholamines (Fig. 1).

Tilting could only be performed in patient I. N. Both systolic and diastolic blood pressure fell in relation to the angle of tilting and there was some increase in pulse rate (Fig. 2). There was no significant increase in catechol-

Table 1.

Relevant laboratory data on admission.

<table>
<thead>
<tr>
<th></th>
<th>Patient H. K.</th>
<th>Patient I. N.</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, g/100 ml</td>
<td>11.9</td>
<td>11.2</td>
<td>11.6–14.9</td>
</tr>
<tr>
<td>Sodium, meq./l</td>
<td>143</td>
<td>138</td>
<td>138–148</td>
</tr>
<tr>
<td>Potassium, meq./l</td>
<td>4.1</td>
<td>6.3</td>
<td>3.6–4.7</td>
</tr>
<tr>
<td>Stand. bicarb., meq./l</td>
<td>24</td>
<td>22</td>
<td>19–26</td>
</tr>
<tr>
<td>Urea, mg/100 ml</td>
<td>39</td>
<td>54–58</td>
<td>10–44</td>
</tr>
<tr>
<td>Creatinine, mg/100 ml</td>
<td>1.1</td>
<td>1.4–2.2</td>
<td>0.4–1.1</td>
</tr>
<tr>
<td>Fasting blood sugar, mg/100 ml</td>
<td>86</td>
<td>89</td>
<td>50–100</td>
</tr>
<tr>
<td>Iv glucose tol. test</td>
<td>normal</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Wassermann reaction</td>
<td>negative</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>Vitamin B:12, pg/ml</td>
<td>365</td>
<td>350</td>
<td>150–900</td>
</tr>
<tr>
<td>Folic acid, ng/ml</td>
<td>7.4</td>
<td>4.1</td>
<td>3.1–15</td>
</tr>
<tr>
<td>PBI, μg/100 ml</td>
<td>7.5</td>
<td>7.9</td>
<td>4–8</td>
</tr>
<tr>
<td>Cortisol, μg/100 ml</td>
<td>20</td>
<td>22</td>
<td>6–25</td>
</tr>
<tr>
<td>Cortisol, diurnal variat.</td>
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<td>present</td>
<td></td>
</tr>
<tr>
<td>Renin, ng/100 ml/3 h</td>
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<td>70–160</td>
<td>100–450</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>negative</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>negative</td>
<td>negative</td>
<td></td>
</tr>
<tr>
<td>Bacteriuria</td>
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<td>negative</td>
<td></td>
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<tr>
<td>Catecholamines,μg/24 h</td>
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<td>1.7–9.6</td>
<td>20–70</td>
</tr>
<tr>
<td>17-KS, mg/24 h</td>
<td>2.3–4.2</td>
<td>4.5–8.4</td>
<td>3–10</td>
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<tr>
<td>17-OHCS, mg/24 h</td>
<td>5.8–11.7</td>
<td>8.0–9.8</td>
<td>5–15</td>
</tr>
<tr>
<td>Aldosterone, μg/24 h</td>
<td>0.3–3.0</td>
<td>4.9–10.5</td>
<td>3–14</td>
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</table>
The effect of insulin induced hypoglycaemia on catecholamine excretion in two patients with postural hypotension.

The effect of tilting to 40 degrees and 70 degrees respectively on blood pressure, pulse-rate, catecholamine excretion and plasma renin activity in patient I. N.
amine excretion which is in contrast to the finding in healthy subjects (Sundin 1958). Plasma renin activity increased in a normal manner in direct relation to the degree of tilting (Gordon et al. 1967).

Plasma renin activity increased in both patients during the iv infusion of noradrenaline (Fig. 3). In patient H.K. the plasma renin value immediately before the infusion of noradrenaline was somewhat above the basal level. This might have been due to the potassium chloride, which had been administered during the period immediately before the noradrenaline infusion experiment (vide infra).

Sodium conservation at the kidney level was adequate in both patients (Figs. 4 and 5). Patient I.N. probably required a little more time to achieve sodium conservation as compared to the rather rapid response seen in healthy subjects. Salt restriction was followed by an increase in plasma renin activity and urinary aldosterone in both patients but again the response in patient I.N. seemed somewhat delayed. There was no increase in urinary catecholamines. The relatively high value for urinary catecholamines seen in patient I.N. at the beginning of the sodium restriction period, could be due to the preceding infusion of noradrenaline.

Potassium chloride given orally induced an increase in the urinary catecholamines and the aldosterone and plasma renin activity exceeded the basal level

![Fig. 3.](image)

The effect of noradrenaline infusion on blood pressure and plasma renin activity in two patients with postural hypotension.
The effect of sodium restriction on urinary sodium, catecholamines and aldosterone, plasma renin activity and blood pressure in patient I. N.

(Fig. 6). The administered potassium chloride caused no change in the serum potassium concentration.

With the exception of the noradrenaline infusion, treatment of various kinds as reported above did not influence the blood pressure in the recumbent state and the postural reaction remained unaltered.

DISCUSSION

The diagnosis of postural hypotension seems to be well established in the two patients described. They both demonstrated the typical fall in blood pressure in response to upright posture and their production of catecholamines was far below the normal under basal and experimental conditions and compatible with marked insufficiency of the sympathetic nervous system. The moderate increase in the pulse rate seen under certain conditions does not invalidate the diagnosis (Hickler et al. 1960).

Damage to the autonomic nervous system resulting in postural hypotension can occur as a secondary phenomenon in several diseases (Wagner 1959) or the
The effect of sodium restriction on urinary sodium, catecholamines and aldosterone, plasma renin activity and blood pressure in patient H. K.

Aetiology may be unknown, so called idiopathic postural hypotension. It has been claimed that at least some patients labelled as idiopathic postural hypotension actually suffer from a primary, progressive, degenerative disorder involving mainly the autonomic and motor function, which may occur in families (Shy & Drager 1960; Lewis 1964; Schwarz 1967). In our patient H. K. cerebral atrophy was found and this could represent a primary disease resulting in postural hypotension. On the other hand, the cerebral atrophy could have been caused by multiple episodes of severe fall in blood pressure over a rather long period of time. In recent years amyloidosis has been discussed as a possible cause of postural hypotension (Wagner 1959; Munsat & Poussaint 1962). This possibility was considered in patient I. N. in view of diarrhoea of several years duration and evidence of renal insufficiency. Unfortunately the patient refused any kind of biopsy and accordingly the diagnosis of amyloidosis could neither be verified nor excluded. There was no evidence of diabetes, syphilis or B12-avitaminosis in either of our patients nor was there any history of physical trauma.

The damage to the autonomic nervous system seemed rather pronounced in both patients. As a result, catecholamine production was subnormal at rest.
The effect of treatment with potassium chloride on blood pressure, urinary catecholamines, aldosterone excretion and plasma renin activity in patient H. K.

and did not increase in response to tilting. The failure of insulin induced hypoglycaemia to bring about an increase in adrenaline production indicated that the nervous lesion(s) functionally also included the adrenal medulla bilaterally.

The importance of the sympathetic nervous system for sodium homeostasis is not clear. In previous studies several patients with idiopathic postural hypotension were found to be incapable of conserving sodium adequately (Shear 1963; Hall & Hökfelt 1966; Gordon et al. 1967). In the present studies both patients were able to conserve sodium at the kidney level although the response was delayed in one of them. The finding that sodium restriction was not followed by any change in the catecholamine production in our patients is noteworthy. Gordon et al. (1967) found that sodium restriction in normal subjects induced a rather marked increase in catecholamine production but this finding was not verified in studies performed by Greene et al. (1968). Faecal losses of sodium were not determined in our patients and this is relevant in this connection as Gill & Bartter (1966) reported that sympathetic blockade with guanethidine was followed by an increased sodium excretion in the stools.

Our investigations do not support the hypothesis put forward by Gordon et al. (1967) namely that increased production of catecholamines is a necessary prerequisite for adequate stimulation of renin formation and aldosterone
secretion in the upright posture and following salt restriction. The possibility of isolated, intact sympathetic innervation of the kidney(s) can, however, not be excluded (vide infra). Our studies confirm that infused catecholamines can induce elevation of the plasma renin activity (Gordon et al. 1967).

The reason for studying the effect of the administration of potassium chloride was an earlier observation (Hökfelt, unpublished) that such treatment in one patient with postural hypotension was followed by an increase in blood pressure and tachycardia. Although no such circulatory effects were seen in the present patient, the findings of an increase in the urinary catecholamines and aldosterone are of interest. One possible explanation for the increase in catecholamines could be that potassium exerted an effect similar to acetylcholine in stimulating the sympathetic neurons and/or the adrenal medulla. This effect of potassium has been ascribed to membrane depolarization (Douglas 1966). The liberation of the catecholamines could then have induced an increased formation of renin, leading to a stimulation of aldosterone production. With regard to aldosterone a direct, stimulating effect of potassium on the adrenal cortex leading to the production and/or liberation of aldosterone should be considered (Liddle et al. 1955; Laragh & Stoerck 1955).

The mechanism leading to an increase in plasma renin activity following tilting in patient I. N. is not clear. It seems possible that decreased renoperfusion, perhaps in connection with changes in sodium reabsorption could be of importance in view of the findings of Cohen et al. (1967) that the upright posture is connected with a reduction in renal perfusion. It seems likely that the marked reduction in diuresis, which occurred in connection with tilting of our patient I. N., was a result of a lowered renal blood flow. The increase in plasma renin activity accompanying sodium restriction in both our patients could probably be explained on the basis of reduced blood volume leading to a decreased renal blood flow.

The fact that sodium restriction in our studies was followed by increased levels of plasma renin, increased production of aldosterone and sodium conservation but without a concomitant rise in catecholamine production, is in agreement with results obtained in animal experiments. Thus, it has been reported that renal denervation and/or the administration of ganglionic blocking agents and α- and β-blocking compounds do not prevent the increase in plasma renin activity following sodium restriction (Vander & Luciano 1967; Brubacher & Vander 1968). These animal experiments give some evidence that sympathetic activity can play a role in initiating an acute increase in renin release. Further support for the view that renal sympathetic innervation is not a prerequisite for increased renin release following sodium restriction has also been found in patients with transplanted kidneys (Greene et al. 1968). In these patients the renin response to salt restriction was temporarily delayed but otherwise adequate. The possibility that circulating catecholamines could be of
importance must be considered. The above mentioned animal experiments in which plasma renin activity increased following sodium restriction in spite of blockade of \( \alpha \)- and \( \beta \)-receptors, are evidence against such a possibility.

Our investigations show that adequate renin production can occur in the upright posture and following sodium restriction without a concomitant increase in catecholamine production. Thus, the present studies indirectly support the view, that baro- and/or osmoreceptors play an essential role in regulating renin production and aldosterone secretion in connection with upright posture as well as restriction of sodium intake. Our studies also show that renal sodium conservation can occur even in the presence of pronounced sympathetic insufficiency.

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