RELATIONSHIP BETWEEN THE ADRENERGIC NERVOUS SYSTEM AND RENIN DURING ADAPTATION TO UPRIGHT POSTURE: A POSSIBLE ROLE FOR 3,4-DIHYDROXYPHENETHYLAMINE (DOPAMINE)

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SUMMARY

1. The role of the adrenergic nervous system in the regulation of plasma renin activity was investigated in fourteen healthy volunteers. Special attention was devoted to 3,4-dihydroxyphenethylamine (dopamine) because this amine is not only a precursor of noradrenaline, but also a catecholamine with its own functions. The adrenergic nervous system was activated by a change of posture because this offers a simple and reproducible stimulus; its effects were studied during a normal diet and also after restriction of sodium.

2. With both diets, the expected increase in plasma renin activity was observed after changing from recumbency to an upright posture. This was associated with a decrease in the urinary excretion of dopamine and an increase in the urinary excretion of noradrenaline and adrenaline. In addition, a positive and significant correlation was found between the urinary excretion of dopamine and sodium.

3. Our data suggest that dopamine and noradrenaline may play a complementary role in the regulation of renin secretion, but they do not necessarily act in the same direction or through similar mechanisms. Dopamine is known to be a pharmacological natriuretic agent. It may have a similar role in the physiological regulation of urinary sodium excretion.

Key words: renin regulation, adrenergic and dopaminergic receptors, renal circulation, sodium handling, postural regulation.

The adrenergic nervous system is known to play an important role in the regulation of the renin–angiotensin system (Bunag, Page & McCubbin, 1966; Vander, 1967; Gordon, Kuchel, Liddle & Island, 1967; Kaneko, Takeda, Ikeda, Tagawa, Ishii, Takabatake & Ueda, 1970; Passo, Assaykeen, Otsuka, Wise, Goldfien & Ganong, 1971; Passo, Assaykeen, Goldfien & Ganong, 1971). This influence has been studied in different ways, but very little is known about...
the role of 3,4-dihydroxyphenethylamine (dopamine) in the regulation of renin. Dopamine is not only a precursor of noradrenaline, but is also active independently especially in the brain (Hornykiewicz, 1966), the cardiovascular system (Horwitz, Fox & Goldberg, 1962) and the kidney (Goldberg, 1970). These effects are very different from those of noradrenaline and sometimes opposite, especially in the kidney (Goldberg, 1970; Pearson & Williams, 1968). Moreover, clinical conditions with dopamine excess (neuroblastomas, for example, or high level L-dopa treatment) are not necessarily associated with hypertension (Melmon, 1968; Barbeau, 1969), and a low urinary excretion of dopamine has been reported (Serrano, Figueroa, Torres & Ramirez Del Angel, 1964; Januszewicz, Wocial & Kaliszuk, 1968) in essential hypertension. A low urinary excretion has also been reported in Parkinson's disease where blood pressure is often reduced and where plasma renin activity (PRA) is low (Barbeau, Murphy & Sourkes, 1961; Barbeau, Gillo-Joffroy, Boucher, Nowaczynski & Genest, 1969). Burn & Rand (1958) suggested a possible competitive action for dopamine and noradrenaline.

The purpose of the present study was to examine the role of different catecholamines in the regulation of plasma renin activity. Change of posture was chosen as the stimulus because it is known to induce a reproducible sympathetic discharge (Keele & Nei, 1966), with an increase in plasma renin activity (Cohen, Rovner & Conn, 1966), and urinary noradrenaline and adrenaline (Gordon et al., 1967; Sundin, 1956). It was thus of interest to investigate what happens to dopamine under the same conditions. Unfortunately we were limited by the fact that no reproducible method for measuring plasma dopamine is yet available. For this reason, we had to measure urinary dopamine, which only partially reflects changes in the circulating amine. The measurements were carried out in subjects on normal and sodium restricted diets to compare primary postural effects with those caused by sodium restriction (Vander & Luciano, 1967). The results of previous studies on catecholamines have been conflicting (Collins, Weinberger, Gonzales, Nokes & Luetscher, 1970; Kelsch, Light, Luciano & Oliver, 1971).

METHODS

Fourteen healthy Caucasian volunteers (twelve men and two women) in the age group between 21 and 54 years (mean = 25.6) were studied. All the subjects had a normal blood pressure and heart rate at rest and in the upright position.

For 3 days before the experiment, the subjects were kept on a diet calculated to contain 135 mEq of sodium and 90 mEq of potassium per day. To eliminate variations caused by postural stimulation, the subjects were maintained in a recumbent position the night before the days of the experiment. Throughout the experiment blood pressure and heart rate were measured at the same time, first in the supine and then in the upright position three times a day and expressed as a daily mean. Specially trained nurses measured the blood pressure by ordinary mercury manometer in subjects first when they were recumbent and then when they had been upright for 2 min; the first sound was used to record systolic pressure and the point of abrupt diminution for diastolic pressure. Body weight was recorded each morning.

The effect of posture was studied on two consecutive experimental days (fourth and fifth day of the diet) in the following way:

At 08.30 hours on the first day the subjects emptied their bladders after being confined to bed from the previous evening. A 4 h urinary collection was then started in the recumbent position for the subsequent determination of catecholamines, creatinine, sodium and potassium. At
12.30 hours a blood sample was drawn for the determination of plasma renin activity (PRA). These will be considered as baseline tests.

On the second morning the subjects remained recumbent until they had emptied their bladders at 08.30 hours. They were then kept either standing or sitting but never recumbent until 12.30 hours and urine was collected for a 4 h period. At 12.30 hours a blood sample was drawn for determination of PRA.

All subjects subsequently continued on a low sodium diet containing 10 mEq of sodium and 90 mEq of potassium daily. The process of sodium depletion was accelerated by the administration of hydrochlorothiazide and spironolactone (Aldactazide, 25 mg) four times during the first 36 h of low sodium diet. In addition, nine of the fourteen subjects received frusemide (40 mg intravenously) on the first morning of the low sodium diet (sixth day of protocol). The degree of sodium depletion was judged by weight loss (mean = 3.3 kg) and by the level of urinary sodium excretion (mean = 2–3 mEq/l) after 3 days.

On the third day of low sodium diet the baseline tests were performed as previously described and the following day the same tests were done under orthostatic stimulation.

Plasma renin activity was assayed by the method of Boucher, Veyrat, de Champlain & Genest (1964). Urinary dopamine, noradrenaline and adrenaline were determined by the method of Sourkes & Murphy (1961). Urinary sodium and potassium were measured by Technicon AutoAnalyzer (method SMA 12/60) and creatinine by the method of Cooper & Biggs (1961).

Statistical analysis
We used two-by-two factorial design with repeated measures on each of n = 14 subjects (k = index for each subject, i.e., k1 . . . k14) taken as their own controls. Factor A, posture, was studied at p = 2 postural positions; i1 = 4 h of supine position (08.30–12.30 hours), and i2 = 4 h of upright posture (08.30–12.30 hours). Factor B, sodium intake, was studied at q = 2 levels of sodium intake: j1 = fourth day of normal sodium intake, and j2 = third day of low sodium intake. Three-dimensional variance analysis was carried out according to the plan shown in Table 1 (Winer, 1962). The significance (F) for main effects, was calculated by dividing
the mean square for posture and for salt intake by that of error. The 95% confidence limits shown in Figures were computed by multiplying $t_{0.95}^{D.F.}$ (the critical $t$ at 0.95 for D.F., where D.F. = degrees of freedom) by $\sqrt{M.S. \_error/n}$ (M.S. = mean square; $n$ = number of subjects).

No control was exerted over the effect of time; this systematic bias may have influenced some of our results since the duration of sodium restriction is known to affect such measurements as urinary sodium excretion and PRA.

RESULTS

On both diets the change from the recumbent to the upright position induced a statistically significant increase in heart rate and diastolic pressure with a decrease in systolic pressure.

| Table 2. Effects of upright posture on cardio-renal functions in healthy subjects |
|---------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Sodium intake                   | Normal                        | Low                          |
|                                 | Recumbent                      | Upright                      | Recumbent                      | Upright                      |
|                                 | Heart rate (beats/min)         | 68.6+P<0.01→81.2             | 73.4+P<0.01→91.7              | 3.27                         |
|                                 | Systolic pressure (mmHg)       | 113.1+P<0.01→109.9           | 110.4+P<0.01→104              | 2.62                         |
|                                 | Diastolic pressure (mmHg)      | 65.1+P<0.01→72.2             | 66.8+P<0.01→71.6              | 1.97                         |
|                                 | Urinary volume (ml/min)        | 3.71+P<0.01→1.49             | 2.81+P<0.01→0.98              | 0.66                         |
|                                 | Urinary creatinine (mg kg⁻¹ 4 h⁻¹) | 4.521+P<0.05→3.695          | 4.469+P<0.05→3.655            | 0.627                        |
|                                 | Urinary sodium (mEq/4 h)       | 42.7+P<0.01→9.68             | 2.33+P<0.01→0.53              | 3.47                         |
|                                 | Urinary potassium (mEq/4 h)    | 29.8+P<0.01→15.1             | 13.3+P<0.01→7.54              | 7.53                         |
|                                 | Urinary Na/K ratio             | 2.27+P<0.01→0.86             | 0.21+P<0.01→0.08              | 0.31                         |

(Table 2). In the recumbent position restriction of sodium induced a statistically significant increase in heart rate and a decrease in systolic pressure.

In the upright posture the well-known antidiuretic, antinatriuretic and antikaliuretic effects were observed (Table 2). The statistically significant decrease of urinary excretion of creatinine in the upright position suggested a decrease in glomerular filtration rate, however, the restricted sodium diet itself did not induce variations in urinary creatinine excretion. On both sodium diets there was a statistically significant decrease in the urinary sodium/potassium ratio in the upright position, suggesting preferential reabsorption of sodium over potassium.

This group of fourteen subjects can be considered homogeneous for the five variables measured in this experiment since there was no statistically significant variation between subjects.
A statistically significant increase in PRA (Table 3) was observed on changing to the upright position at both levels of sodium intake and there was an increase in the recumbent position as a result of changing from a normal to a restricted sodium diet.

The results for urinary catecholamines are shown in μg/4 h ('total excretion') and in μg/g of creatinine to correct for possible variations in filtration rates among subjects. We did not observe any difference between the normal and restricted sodium diet in the recumbent position.

The main finding (Table 3 and Fig. 1) is that at both levels of sodium intake, dopamine excretion decreased after changing to the upright position while noradrenaline and adrenaline excretion increased; the increase only achieved statistical significance, however, when expressed as μg/g of creatinine. Since some of the actions of dopamine and noradrenaline are opposed, it would be justified to use their ratio as a measure of the final biological effect on some target organs. We observed a statistically significant decrease of the dopamine/noradrenaline ratio in the upright posture; in the recumbent position there was no difference in this ratio between subjects on normal and low sodium diets.

In analysing for variations between subjects, we observed a statistically significant (P<0.01) variation of response of urinary dopamine and noradrenaline to upright posture. This inhomogeneous pattern was not observed with the dopamine/noradrenaline ratio. Similarly, there was no significant variation between subjects in the response of urinary adrenaline to

<table>
<thead>
<tr>
<th>Sodium intake</th>
<th>Normal</th>
<th>Low</th>
<th>Confidence limits at 95%</th>
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<tr>
<td></td>
<td>Recumbent</td>
<td>Upright</td>
<td>Recumbent</td>
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<tr>
<td>Plasma renin activity (ng h⁻¹ ml⁻¹)</td>
<td>0.292⁻⁻P&lt;0.05→1.013</td>
<td>2.993⁻⁻P&lt;0.05→5.166</td>
<td>1.09</td>
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<tr>
<td>Urinary dopamine (μg/4 h)</td>
<td>98⁻⁻P&lt;0.01→76.2</td>
<td>91⁻⁻P&lt;0.01→59</td>
<td>15.9</td>
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<tr>
<td>Urinary noradrenaline (μg/4 h)</td>
<td>9.38⁻⁻N.S.→13.5</td>
<td>11.2⁻⁻N.S.→16.5</td>
<td>5.06</td>
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<tr>
<td>Urinary adrenaline (μg/4 h)</td>
<td>2.17⁻⁻N.S.→3.98</td>
<td>2.14⁻⁻N.S.→2.41</td>
<td>1.27</td>
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<tr>
<td>Urinary dopamine (μg/g of creatinine)</td>
<td>322⁻⁻P&lt;0.05→258</td>
<td>303⁻⁻P&lt;0.05→246</td>
<td>48.9</td>
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<td>Urinary noradrenaline (μg/g of creatinine)</td>
<td>38.4⁻⁻P&lt;0.05→60.7</td>
<td>34.9⁻⁻P&lt;0.05→49.7</td>
<td>15.2</td>
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<tr>
<td>Urinary adrenaline (μg/g of creatinine)</td>
<td>6.8⁻⁻P&lt;0.05→13.7</td>
<td>6.95⁻⁻P&lt;0.05→9.7</td>
<td>3.87</td>
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<tr>
<td>Urinary dopamine/noradrenaline ratio</td>
<td>12.8⁻⁻P&lt;0.05→6.5</td>
<td>11.8⁻⁻P&lt;0.05→4.9</td>
<td>3.55</td>
</tr>
</tbody>
</table>

In analysing for variations between subjects, we observed a statistically significant (P<0.01) variation of response of urinary dopamine and noradrenaline to upright posture. This inhomogeneous pattern was not observed with the dopamine/noradrenaline ratio. Similarly, there was no significant variation between subjects in the response of urinary adrenaline to
FIG. 1. Orthostatic response of plasma renin activity, urinary dopamine and noradrenalin in fourteen healthy subjects. After the change to an upright posture, there is an increase of PRA, with associated opposing variations in the urinary excretion of catecholamines: dopamine decreases, whereas noradrenalin increases. Values are the mean ± 95% confidence limits.

FIG. 2. Urinary dopamine and sodium relationship in healthy subjects on normal sodium intake (135 mEq of Na, 90 mEq of K). With a normal sodium diet, regardless of position, a natriuretic role for dopamine is suggested by the observed positive and significant correlation between urinary concentration of dopamine and sodium.
postural stimulation; adrenaline seemed to change with a more uniform direction and amplitude than dopamine or noradrenaline.

With a normal sodium diet, we observed (Fig. 2) a positive and significant correlation between urinary dopamine and urinary sodium in the supine as well as in the upright posture. No correlation was observed between noradrenaline and sodium excretion.

**DISCUSSION**

As expected, we observed a statistically significant decrease in systolic pressure associated with an increase in diastolic pressure and heart rate when the subjects assumed an upright posture both on normal and low sodium diets. A low sodium diet by itself was associated with a slight but statistically significant increase of heart rate and a decrease of systolic pressure in the recumbent position with no change in diastolic pressure. This conclusion, however, needs to be qualified in two respects: first, there was a statistically significant variation between subjects, suggesting an inhomogeneous response to upright posture (Schneider & Truesdell, 1922) and secondly, the variations in systolic and diastolic pressure induced by upright posture were less than 10%, which is probably too small a change to be of clinical significance in individual patients.

The well-known antidiuretic, antinatriuretic and antikaliuretic effects induced by the upright posture were also observed in our experiments. This could be partly explained by a decrease in glomerular filtration rate (GFR) as reflected by the decrease in urinary creatinine. A more specific increase in sodium reabsorption is suggested by the decrease in the urinary sodium/potassium ratio; this pattern of sodium retention could partly be due to an activation of the renin–angiotensin–aldosterone system, but could also be due to factors other than changes of GFR or aldosterone secretion (de Wardener, Mills, Clapham & Hayter, 1961; Barger, 1966; Earley, Martino & Friedler, 1966). The increase in PRA observed after both the change to the upright posture and sodium restriction in our experiments has been reported by numerous investigators.

In the upright posture, we observed a decrease in dopamine excretion and an increase of noradrenaline and adrenaline excretion. Such divergent changes of these catecholamines may be of biological significance in the light of the known differences in their action. Noradrenaline can induce a decrease in renal plasma flow (RPF), GFR, and sodium excretion (Pearson & Williams, 1968) associated with a decrease in heart rate and no change in cardiac output (Innes & Nickerson, 1970). Dopamine, however, induces an increase in RPF, GFR, and sodium excretion (Goldberg, 1970) associated with no change in heart rate and an increase in cardiac output (Horwitz et al., 1962). Taking into consideration those opposite biological actions of dopamine and noradrenaline, we used their ratio as a measure of final biological activity upon the kidney. After the change to the upright posture, a significant decrease of this ratio was observed.

The clinical, physiological and experimental observations reported above also suggest a possible complementary action of dopamine and noradrenaline upon plasma renin activity. There are three possible mechanisms of action of dopamine on renin secretion, by analogy with the three postulated actions of noradrenaline.

involved in the control of renin secretion. Dopamine possesses some alpha-adrenergic action, but little or no beta-adrenergic activity (Goldberg, 1970). In the kidney its action could be mediated either through specific dopaminergic receptors (Goldberg, 1970) with a different effect from those of noradrenaline, or by competing with noradrenaline on the receptors of the renin-producing cells. In both cases dopamine could induce a competitive inhibition of the noradrenaline effect (Burn & Rand, 1958). Such an effect would mean a direct action of both catecholamines on the juxtaglomerular cells.

(2) After the sympathetic discharge induced by the upright posture, a decrease (Werko, Bucht & Josephson, 1949) and a redistribution (Hollenberg, Epstein, Basch, Merrill & Hickler, 1969) of renal blood flow (RBF) has been observed. Noradrenaline seems to play a major role because the same intra-renal redistribution of RBF has been observed after experimental nerve stimulation and intra-renal infusion of noradrenaline (Aukland, 1968) and it is possible that the action of noradrenaline is secondary to its vasoconstrictor effects (see Vander, 1967). Barnardo, Summerskill, Strong & Baldus (1970) have shown a decrease of PRA after dopamine infusion in cirrhotic patients with a low RPF. The response is not present in normal subjects (Atuk, Ayers & Westfall, 1968). Thus in conditions with a low RPF, dopamine seems to have an inhibiting effect on PRA release. Such an action of dopamine could be mediated by renal blood flow dependent changes of pressure at the juxtaglomerular cells.

(3) Finally, with a normal sodium diet the positive and significant correlation between urinary sodium and dopamine concentrations and the decrease of both dopamine and sodium excretion after the change to the upright posture suggest a very close relationship between these two variables. A pharmacological natriuretic effect of dopamine was suggested by Goldberg, McDonald & Zimmerman (1963), independent of the effects of dopamine on GFR (Lindheimer, Lalone & Levinsky, 1967; Burns & McGiff, 1967; Davis, Walter & Murdaugh, 1968). Our findings may indicate that dopamine plays a role in the physiological regulation of sodium excretion and could have an indirect and inhibiting effect on PRA regulation through changes in the sodium load at the level of the macula densa.

Thus, the upright posture causes haemodynamic changes and these lead to a sympathetic discharge serving to offset the circulatory effects of being upright. Because there is need for a rapid adjustment, the first response to the sympathetic discharge is vascular. Soon afterwards, however, an increase in plasma renin activity is noted and this activates the more slowly working renin–angiotensin–aldosterone sodium-retention mechanism. We now demonstrate that the adoption of the upright posture is usually accompanied by the well-known increase of PRA and urinary noradrenaline excretion on the one hand, and a decrease in the urinary dopamine excretion and in the dopamine/noradrenaline ratio on the other. The most likely explanation is that dopamine competes with noradrenaline either at receptor sites, or through haemodynamic or tubular actions which influence renin release. How the nervous system controls the relative proportions of dopamine and noradrenaline released from the same or different terminals upon the renin-releasing trigger, and to what an extent the activity of the dopamine to noradrenaline converting enzyme (dopamine β-hydroxylase) plays a role remains to be elucidated.

Some results showing a low level of dopamine β-hydroxylase activity in familial dysautonomia (Weinshilboum & Axelrod, 1971) with consequent dopamine excess, noradrenaline deficiency and postural hypotension may offer an extreme example of changes resulting from alterations in the activity of this enzyme.
Catecholamines and renin regulation in man

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RÉSUMÉ

Chez quatorze sujets volontaires en bonne santé, nous avons étudié le rôle du système nerveux adrénergique dans la régulation de la renine; un intérêt plus particulier fut apporté à la dopamine, parce que cette amine n’est pas seulement un précurseur de la noradrenaline mais aussi une catécholamine avec des propriétés qui lui sont propres. Comme moyen de notre étude nous avons choisi la stimulation par l’orthostatisme parce qu’elle induit une décharge sympathique simple et reproductible; les effets de cette stimulation furent étudiés, les sujets recevant une diète normale puis pauvre en sodium. Dans les deux conditions diététiques, nous avons observé sous l’effet de l’orthostatisme, d’une part une augmentation de l’activité de la renine plasmatique et d’autre part une diminution de l’excrétion urinaire de la dopamine associée à une augmentation de celle de la noradrenaline et de l’adrenaline. De plus, il existe une corrélation directe et significative entre les excrétions urinaires respectives de la dopamine et du sodium. Nos résultats suggèrent l’hypothèse d’une activité antagoniste de la dopamine et de la noradrenaline dans la régulation de la renine. D’autre part la dopamine déjà connue pour son effet natriuretique à doses pharmacologiques, pourrait avoir un rôle dans la régulation physiologique de l’excrétion urinaire du sodium.

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