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DIURNAL VARIATIONS OF PLASMA ALDOSTERONE IN SUPINE MAN: RELATIONSHIP TO PLASMA RENIN ACTIVITY AND PLASMA CORTISOL

By
Helmut Armbruster, Wilhelm Vetter, Rainer Beckerhoff, Jürg Nussberger, Hans Vetter and Walter Siegenthaler

ABSTRACT

In order to investigate the role of renin secretion and of ACTH on the circadian rhythm of plasma aldosterone (PA), plasma renin activity (PRA), plasma cortisol (PC) and PA were determined at short-time intervals in 10 normal supine men. Six subjects were studied under a normal sodium intake and 4 under sodium restriction. In 4 subjects the secretion of ACTH was suppressed by dexamethasone. Under normal sodium intake changes in PA seemed to be more in parallel with changes in PC than by those in PRA as indicated by a higher significant correlation between PA and PC than between PA and PRA in 3 of the 4 subjects. In 1 subject no correlation was observed between PA and PC despite visual synchronism between the plasma concentrations of both hormones. Under dexamethasone medication fluctuations in PA


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were followed by those in PRA while PC was less than 2 \( \mu g/100 \) ml. In the sodium restricted state, changes in PA were closely paralleled and significantly correlated to PRA while no correlation was seen between PA and PC. Under dexamethasone medication the significant correlation between PA and PRA persisted. Our results indicate that in normal supine man the influence of ACTH and renin on PA may vary with different sodium intakes. Under normal sodium intake ACTH seems to be the dominant factor controlling PA, whereas under sodium restriction changes in PA are mediated through the renin angiotensin system. When the secretion of ACTH is suppressed by dexamethasone, renin controls PA both under normal and low sodium intake.

The simultaneous measurement of plasma aldosterone, plasma renin activity and plasma cortisol at short-time intervals has recently been applied to study the influence of the renin angiotensin system and of ACTH on the control of plasma aldosterone in normal supine man (Katz et al. 1972, 1975; Vagnucci et al. 1974; Lommer et al. 1975). The results of these reports, however, are contradictory. Since some of these studies were performed either under a normal or a low sodium diet, different sodium intake might have partly caused the controversial findings. Thus, the present study was performed both under normal and low sodium diet and in addition in some subjects while simultaneously receiving dexamethasone.

**MATERIAL AND METHODS**

Ten healthy male volunteers (20–31 year old) were studied. Five subjects received for 6 days a normal sodium diet containing 120–150 mEq. sodium/day and 4 subjects were on a low sodium diet of 10 mEq. sodium/day. Both diets contained 80 mEq. potassium/day.

In the afternoon of the 5th day the subjects were admitted to the hospital. Four hours before (18.00 or 20.00) and during the observed periods all subjects remained strictly supine except for meals which were eaten in a slightly inclined position. Nine subjects were studied over a period of 24 h (18.00–18.00) and 1 subject overnight (20.00–8.00).

To suppress endogenous ACTH-release 2 subjects with normal and 2 with low sodium intake were given 0.5 mg dexamethasone orally every 6 h the day before and during the test periods.

Blood samples (6–8 ml) were obtained at short-time intervals (30–60 min) through an intravenous catheter. Blood was drawn into vacutainers containing 1 mg/ml Na-EDTA.

Plasma aldosterone (PA) and plasma renin activity (PRA) were measured by radio-immunoassay procedures (Vetter et al. 1973; Haber et al. 1969). Plasma cortisol (PC) was determined by the protein binding method of Murphy et al. (1963) using dextrancoated charcoal to separate bound and free hormone. Sodium and potassium were
measured by atomic absorption. Serum electrolyte concentrations were determined at 2 h time intervals.

Under a daily sodium intake of 120–150 mEq our normal 8.00 supine values are: PA 20–120 pg/ml and PRA 0.3–3.0 ng/ml x 3 h. The normal range for PC is 2–25 µg/100 ml. The lower limit of detectability is: PA 8 pg/ml, PRA 0.16 ng generated angiotensin I/ml x 3 h and PC 2 µg/100 ml. A typical secretory episode in renin, aldosterone or cortisol secretion was considered to have occurred when a rise in PRA, PA or PC was seen during at least two or more successive measurements and when this increase was equal or larger than the cumulative mean so. A secretory episode had terminated when the peak concentration was followed by a decrease in PRA, PA or PC equal or larger than the cumulative mean so. Definition of secretory episodes is the same as that of Vagnucci et al. (1974).

Statistical analyses were performed by calculation of correlation coefficients between PA and PRA and PA and PC. The correlation coefficients were tested for significance by standard procedures.

In each subject urinary excretion of sodium was determined from the 5th to the 6th day. Subjects under normal sodium intake had excretion rates between 109 and 154 mEq./24 h and those under low sodium showed values between 8 and 14 mEq./24 h indicating adherence to the diets.

Fig. 1.
Short-time fluctuations in plasma aldosterone (A), renin activity (PRA) and plasma cortisol (C) in 4 supine male subjects examined under a daily sodium intake of 120–150 mEq. Three subjects (W. G., K. B. and F. B.) were observed over a period of 24 h and 1 subject (B. M.) overnight.
RESULTS

Studies under normal sodium intake

1. Unaffected ACTH secretion. – In all 4 subjects renin, aldosterone and cortisol secretion followed a typical circadian (or night-day) rhythm with

Table 1.

Correlation analysis between the plasma concentrations of cortisol and aldosterone, and of renin activity (PRA) and aldosterone. Subjects 1–6 were studied under normal sodium intake, subjects 8–11 were examined under sodium restriction. n. s. = not significant.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Cortisol:aldosterone</th>
<th>PR:aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. F. B.</td>
<td>n = 34 r = 0.693 P &lt; 0.001</td>
<td>n. s.</td>
</tr>
<tr>
<td>2. W. G.</td>
<td>n = 37 r = 0.455 P &lt; 0.01</td>
<td>n = 37 r = 0.406 P &lt; 0.05</td>
</tr>
<tr>
<td>3. B. M.</td>
<td>n = 13 r = 0.874 P &lt; 0.001</td>
<td>n = 13 r = 0.609 P &lt; 0.05</td>
</tr>
<tr>
<td>4. K. B.</td>
<td>n. s.</td>
<td>n. s.</td>
</tr>
<tr>
<td>5. A. H.*</td>
<td>–</td>
<td>n = 35 r = 0.431 P &lt; 0.01</td>
</tr>
<tr>
<td>6. R. K.*</td>
<td>–</td>
<td>n = 35 r = 0.690 P &lt; 0.001</td>
</tr>
<tr>
<td>7. W. V.</td>
<td>n. s.</td>
<td>n = 43 r = 0.507 P &lt; 0.001</td>
</tr>
<tr>
<td>8. F. N.</td>
<td>n. s.</td>
<td>n = 35 r = 0.714 P &lt; 0.001</td>
</tr>
<tr>
<td>9. H. V.*</td>
<td>–</td>
<td>n = 27 r = 0.737 P &lt; 0.001</td>
</tr>
<tr>
<td>10. H. A.*</td>
<td>–</td>
<td>n = 42 r = 0.691 P &lt; 0.001</td>
</tr>
</tbody>
</table>

* Subjects studied under dexamethasone administration.
Fig. 2.
Circadian rhythm of plasma aldosterone (A) and renin activity (PRA) of 2 supine male subjects (A.H. and R.K.) obtained under a daily sodium intake of 120–150 mEq. and suppression of ACTH secretion by dexamethasone.

relatively low PRA, PA and PC values in the evening and early night and higher values after midnight and in the early morning (Fig. 1). Each subject showed typical secretory episodes as demonstrated by the occurrence of characteristic fluctuations in PRA, PA and PC. Beside these typical secretory episodes, however, sudden increases and decreases in PRA, PA or PC during two successive points were at times observed except in subject B.M. These rapid fluctuations in hormone concentrations were especially seen in subject K.B.

Visual analysis of the 24 h (12 h) curves of PRA, PA and PC seemed to indicate that changes in PA and PC were more parallel than those in PA and PRA (Fig. 1). Correlation analysis in subjects W.G. and B.M. showed a higher significance between PA and PC than between PA and PRA (Table 1). In subject F.B. a significant correlation was observed between PA and PC while no correlation was obtained between PA and PRA. In subject K.B. no significant correlation was seen between PA and PC despite apparent synchronism of the plasma concentrations of both hormones.

Serum sodium and serum potassium showed only minor fluctuations throughout the test periods without any correlation to the observed changes in PRA or PA. Serum sodium values ranged between 138 and 142 mEq./l and serum potassium levels were between 3.8 and 4.2 mEq./l.

2. Dexamethasone medication. – Two subjects were examined under normal sodium intake and suppression of ACTH secretion by dexamethasone (Fig. 2). In these subjects PC was constantly below 2 μg/100 ml. Both subjects showed a circadian rhythm of PA and PRA similar to that found under unaffected
ACTH secretion. In both subjects nearly all secretory episodes in aldosterone secretion coincided with those in renin secretion as demonstrated by parallel fluctuations in the plasma concentrations of PA and PRA. Only in subject R.K. a secretory episode in aldosterone secretion was observed at noon while PRA declined. In both subjects significant correlations were found between PA and PRA (Table 1).

Serum sodium and serum potassium showed only minor fluctuations. These changes in serum electrolytes were not related to fluctuations in PA or PRA.

**Studies under sodium restriction**

1. **Unaffected ACTH secretion.** – Two subjects (W. V. and F. N.) were examined under sodium restriction and unaffected ACTH secretion (Fig. 3). Under these conditions the circadian rhythm of PA and PRA was set at a 3 to 5 fold higher level than under a daily sodium intake of 120–150 mEq. while the PC values were not different from those observed under normal sodium intake.

![Fig. 3.](image)

Circadian rhythm of plasma aldosterone (A), renin activity (PRA) and plasma cortisol (C) of 4 supine male subjects obtained under a daily sodium intake of 10 mEq. Two subjects were examined under unaffected ACTH secretion (W. V. and F. N.) and 2 (H. V. and H. A.) under dexamethasone medication.
intake. Under sodium restriction secretory episodes in aldosterone and renin secretion were much greater. Visual analysis of the 24 h curves of PA, PRA and PC seemed to indicate that in the sodium restricted state a higher synchronism existed between fluctuations in PA and PRA than between PA and PC (Fig. 3). This assumption was supported by the finding of significant correlation coefficients between PA and PRA while in both subjects no correlation was found between PA and PC (Table 1).

Only minor fluctuations were observed in serum sodium and serum potassium.

2. Dexamethasone medication. – Two subjects (H.V. and H.A.) were examined under sodium restriction and dexamethasone medication (Fig. 3). Under these conditions 24 h curves of PA and PRA were similar to those observed under unaffected ACTH secretion (see subjects W.V. and F.N., Fig. 3) while in both subjects PC was constantly below 2 µg/100 ml. Under suppressed ACTH secretion nearly parallel fluctuations in PA and PRA were observed as demonstrated by a highly significant correlation between PA and PRA (Table 1). Both serum sodium and serum potassium showed only minor variations.

**DISCUSSION**

At present only few studies have applied simultaneous determinations of plasma renin activity, plasma cortisol and plasma aldosterone at short-time intervals to examine the influence of both the renin angiotensin system and ACTH on the control of plasma aldosterone in normal supine man (Katz et al. 1972, 1975; Vagnucci et al. 1974; Lommer et al. 1975). The results of some of these studies, however, are contradictory. While in subjects tested under normal sodium intake Katz et al. (1972, 1975) observed significant correlations between plasma aldosterone and plasma cortisol Lommer et al. (1975) in their brief report, were unable to correlate changes in the plasma concentrations of both hormones but described parallel fluctuations between plasma aldosterone and plasma renin activity.

Our results show that under normal sodium intake and unaffected ACTH secretion plasma aldosterone values in 3 of 4 subjects tested were higher correlated to the plasma cortisol levels than to fluctuations in plasma renin activity. These results confirm the observation of Katz et al. (1972) that under normal sodium intake (and unaffected ACTH release) ACTH may be more dominant in controlling plasma aldosterone than renal renin secretion. One subject (subject K.B., Fig. 1) showed no significant correlation between aldosterone and cortisol despite an apparent synchronism between the plasma concentrations of both hormones. This probably demonstrates the difficulty of
studying factors influencing the secretion of different hormones by means of correlation analysis. In such a case a significant correlation may perhaps be obtained by using much more sophisticated statistical methods (Vagnucci et al. 1974).

Under dexamethasone medication plasma cortisol values were constantly below 2 \( \mu \)g/100 ml. Thus, total suppression of endogenous ACTH secretion can be assumed. Under normal sodium intake and dexamethasone medication significant correlations were observed between aldosterone and renin activity indicating that in case of suppressed ACTH secretion, fluctuations in plasma aldosterone were mediated through the renin angiotensin system. These findings are in contrast to the observations of Katz et al. (1975) who under similar conditions observed no correlation between renin activity and plasma aldosterone.

Under sodium restriction the 24 h curves of plasma aldosterone were set at a markedly higher level than under normal sodium intake. The simultaneous rise in renin activity indicates that the increase in aldosterone was caused by an increase in renin secretion. In both subjects tested under sodium restriction and unaffected ACTH secretion highly significant correlations were observed between plasma aldosterone and renin activity while no correlation was found between aldosterone and cortisol. Hence, it can be assumed that in the sodium restricted state renal renin secretion is the prime determinant of changes in plasma aldosterone while ACTH seemed to have no effect. Similar results were reported by Vagnucci et al. (1974). Under dexamethasone medication the highly significant correlation between aldosterone and renin activity persisted.

In this study only few changes in plasma aldosterone were observed which could not be related to simultaneous changes in renin activity or plasma cortisol. Thus, our results do not support the existence of an as yet unidentified factor influencing plasma aldosterone in normal supine man although such a factor seems to be involved in the control of plasma aldosterone both in anephric experimental animals and in anephric patients (McCaa et al. 1974; Vetter et al. 1975).

There are two factors which might have influenced adrenal aldosterone release independent of changes in renin or ACTH secretion: potassium and sodium (Blair-West et al. 1963; Dluhy et al. 1972). In this study only minimal fluctuations in serum potassium and serum sodium were observed. These changes could not be related to the observed fluctuations in plasma aldosterone. Thus, it seems unlikely that changes in plasma aldosterone were mediated through alterations in serum electrolytes.
REFERENCES


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