Increased excretion of kallikrein during dexamethasone administration in normal man on low and normal salt intake

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Summary

1. The effect of dexamethasone administration for 3 days on urinary kallikrein excretion was studied in 12 normal men with normal sodium intake (n=6) or low sodium intake (n=6). Urinary excretion of sodium, potassium, 17-hydroxycorticosteroids, aldosterone and water was also measured in all subjects.

2. Dexamethasone administration was associated with a significant increase in urinary kallikrein excretion (F^2,30=6.9; P<0.001) regardless of sodium intake. No significant correlation could be established between the increase in urinary kallikrein excretion and changes in urinary sodium, potassium, 17-hydroxycorticosteroids, aldosterone or water.

3. These results suggest that dexamethasone can exert a direct action on the renal kallikrein-kinin system.

Key words: dexamethasone, kallikrein, sodium.

Abbreviations: LSD, low sodium diet; NSD, normal sodium diet.

Introduction

We have previously demonstrated that the administration of dexamethasone to normal human beings can induce an acute increase in urinary kallikrein excretion [1], as it does on isolated rat kidneys perfused with a saline solution free of kallikrein or its precursors. In this preparation, the kidney releases kallikrein into the perfusate and into the urine [2].

This paper reports the influence of prolonged (3 days) dexamethasone administration on urinary kallikrein excretion in man on a normal and on a low sodium intake.

Subjects

The studies were performed on a homogeneous population of 12 healthy normotensive white male volunteers aged 18–25 years. The history, physical examination and routine laboratory tests, including complete blood cell count, blood urea nitrogen, serum sodium, potassium, chloride, bicarbonate and creatinine values, urinalysis, chest roentgenogram and ECG, were all normal.

A written informed consent was obtained from each subject according to the regulations of the Catholic University of Chile Ethics and Morals Committee.

Methods

After admission to a metabolic ward, six subjects received a diet containing 10 mmol of sodium/day (low sodium diet, LSD). Another six subjects received a diet with 140 mmol of sodium/day (normal sodium diet, NSD). Potassium intake was fixed for both groups at 60 mmol/day. Meals were given at 08.00, 12.30 and 19.00 hours. Only water was allowed between meals. During the day the subjects were seated, and watched television or read and were free to use a nearby washroom.

Twenty-four-hour sodium excretion equalled sodium intake between the second (in NSD
patients) and fourth (in LSD patients) days after admission. When sodium balance was achieved, 24-h urine samples were collected for four consecutive periods starting at 08:00 hours.

Dexamethasone (Organon-R) (0.5 mg) was given orally every 6 h to each subject from days 2 through 4, starting at 06.00 hours. Sodium and potassium concentrations were determined in urine when a daily collection was completed. A portion of the urine was frozen at -22°C for subsequent analysis of kallikrein activity, aldosterone and 17-hydroxycorticosteroids.

Urinary kallikrein activity was determined as previously described [3], by measuring on the isolated rat uterus the oxytocic effect of kinin liberated from dialysed urine incubated with human low-molecular-weight kininogen in excess for 2 min at 37°C and pH 7.4. Results were expressed in units [1 unit represents the oxytocic effect of purified standard human urinary kallikrein, capable of generating 10 ng of kinin (2 min at pH 7.4 and at 37°C) from purified human kininogen II]. This substrate was prepared by the method of Jacobsen [4]. In our laboratory the kallikrein activity measured by this method has shown to have a good correlation with that measured by radioimmunoassay [2].

Aldosterone was measured by radioimmunoassay and expressed as μg/24 h [5], and 17-hydroxycorticosteroids were measured by the method of Silber & Porter [6]. Blood pressure was measured every 8 h manually with a mercury manometer in each subject, after at least 5 min of recumbency throughout the whole observation period.

Analysis of variance was performed by using the EMDO package [7] to evaluate the following sources of variance: subjects, time (dexamethasone) and sodium condition. A P value of less than 0.05 was considered significant. A priori comparison between means was assessed by orthogonal contrast, and a posteriori comparison by Scheffe's test [8].

Results

As shown in Fig. 1, there was no difference between kallikrein excretion on the normal salt diet and on the low salt diet during the control period (NSD = 182 ± 68 units/24 h; LSD = 194 ± 49 units/24 h; P > 0.05). Dexamethasone produced a significant rise in kallikrein excretion in both groups (Table 1) (F3,30 = 6.9; P < 0.001). There was no significant difference in the response to dexamethasone between the groups when the overall effect of dexamethasone was analysed for each group. The mean urinary kallikrein excretion during the control day in LSD and NSD groups (188 ± 40 units/24 h) was less than the mean of urinary kallikrein excretion under the effect of

**FIG. 1.** Effect of 3 days of dexamethasone administration on urinary kallikrein excretion in normal subjects on 140 mmol sodium/day intake (n = 6) or on 10 mmol of sodium/day intake (n = 6). Statistical significance was determined by ANOVA for subjects, time (dexamethasone) and sodium intake as described in the Results section.
Dexamethasone and urinary kallikrein

TABLE 1. Effect of dexamethasone on urinary excretion of kallikrein, sodium, potassium, 17-hydroxycorticosteroids, aldosterone and water in normal men on a normal sodium diet (n = 6) or a low salt diet (n = 6)

Results are means ± SEM. Sodium intake: A, 140 mmol/24 h; B, 10 mmol/24 h. 17-OHCS, 17-Hydroxycorticosteroids.

<table>
<thead>
<tr>
<th>Days...</th>
<th>Control</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Kallikrein (units/24 h)</td>
<td>182 ± 68</td>
<td>1194 ± 322</td>
</tr>
<tr>
<td>(mmol/24 h)</td>
<td>194 ± 49</td>
<td>520 ± 121</td>
</tr>
<tr>
<td>Sodium (mg/24 h)</td>
<td>136 ± 7</td>
<td>138 ± 14</td>
</tr>
<tr>
<td>Potassium (mmol/24 h)</td>
<td>12 ± 1</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>17-OHCS (mg/24 h)</td>
<td>42 ± 5</td>
<td>71 ± 5</td>
</tr>
<tr>
<td>(ml/24 h)</td>
<td>61 ± 2</td>
<td>72 ± 4</td>
</tr>
<tr>
<td>Aldosterone (mg/24 h)</td>
<td>4.4 ± 1.1</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>(mg/24 h)</td>
<td>5.5 ± 0.4</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>Water</td>
<td>1143 ± 126</td>
<td>2017 ± 116</td>
</tr>
<tr>
<td>(ml/24 h)</td>
<td>1564 ± 351</td>
<td>2055 ± 608</td>
</tr>
</tbody>
</table>

Blood pressure did not change in any of the subjects throughout the experiment.

Discussion

Urinary kalligrein excretion on the control day (day 1), when sodium balance was achieved, was not significantly different between the groups (Table 1). This occurred in spite of substantial differences (P < 0.002) in aldosterone excretion determined by the sodium intake conditions. This finding is in accordance with our own previous observations [1], and with the results reported in dogs by Mills & Newport [9], but it impugns the report of a direct relationship between aldosterone and urinary kallikrein excretion [10].

In our experiment low sodium balance was achieved by dietary manipulation alone. This can be different from experiments in which diuretics are used to induce sodium depletion [10]. Frusemide itself vigorously increases the release of kallikrein in the isolated rat kidney [2].

Although sodium state appears to be related to the magnitude of the urinary kallikrein excretion in response to dexamethasone, as shown in Fig. 1, differences between the groups are not statistically significant (P > 0.05).

On days 2, 3 and 4 urinary kallikrein excretion presented a similar profile in the groups. It is characterized by a brisk increment on the first day on dexamethasone and a later progressive decrement (Fig. 1), regardless of sodium intake (P < 0.01). The consistent response of urinary kallikrein excretion to dexamethasone suggests that
this synthetic steroid can exert a direct action upon the renal kallikrein-kinin system. In this respect, our group has demonstrated that dexamethasone can acutely induce a considerable increase in urinary kallikrein excretion by isolated rat kidney perfused with a kallikrein-free saline solution; the kidney releases kallikrein into the perfusate and into the urine [2]. In addition, binding of dexamethasone to renal tubular receptors has been reported [11, 12].

The transient character of this response to dexamethasone, already discussed, could imply a renal escape mechanism involving the renal cells that produce kallikrein.

Since our study was performed in normal subjects we cannot completely rule out that a physiological compensatory mechanism could have operated, counterbalancing the initial dexamethasone-induced kallikrein increase.

In summary, our results show a remarkable stimulatory effect of dexamethasone upon the renal kallikrein-kinin system, which appears to be independent of aldosterone. It represents another example of the close but still obscure relationship between adrenal and steroidal activity and the renal kallikrein-kinin system.

Acknowledgments

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References