Time Course of Enhanced Adrenal Responsiveness to Angiotensin on a Low Salt Diet

Suzanne Rogacz, Gordon H. Williams, and Norman K. Hollenberg

To assess the rate of activation of the renin-angiotensin-aldosterone axis and enhancement of adrenal responsiveness to angiotensin II (Ang II) with restriction of sodium intake, 16 healthy male subjects were placed initially on a 200 meq daily sodium intake; adrenal responsiveness to Ang II was assessed, and then daily sodium intake was reduced abruptly to 10 meq. Adrenal responses to Ang II were assessed again during the non–steady state interval 24 and 48 hours later, and after balance was achieved in 5–7 days. Renin-angiotensin system activation was evident within 24 hours after sodium intake was restricted. The increase in basal plasma aldosterone concentration and enhancement of the adrenal response to Ang II, on the other hand, tended to lag. Within 24 hours of restricting sodium intake, despite a significant increase in both plasma renin activity (1.0±0.2 vs. 2.4±0.7 ng/ml/hr, p<0.01) and Ang II concentration (22.0±1.9 vs. 29.5±1.3 pg/ml, p<0.05), there was no increase in basal plasma aldosterone concentration (10.4±1.3 vs. 11.7±1.2 ng/dl). At 48 hours, despite little further change in plasma renin activity or plasma Ang II concentration, there was a sharp increase in basal plasma aldosterone concentration (22.5±3.6 ng/dl, p<0.01). The adrenal response to Ang II was increased significantly at 24 hours, evident at only a 10 ng/kg/min dose, but showed progressive further enhancement with time. Early enhancement was not related to shifts in potassium balance as none occurred, but later progressive enhancement could reflect in part negative potassium balance, as a small but consistent element of negative balance occurred. These observations add further support to the concept that some unidentified factor other than plasma Ang II concentration or potassium balance, but related to sodium balance, modifies the adrenal response to Ang II. Available evidence suggests that enhancement reflects events at the terminal step of aldosterone biosynthesis. (Hypertension 1990;15:376–380)

Shifts in sodium intake are accompanied by reciprocal shifts in vascular and adrenal responsiveness to angiotensin II (Ang II) in normal humans1,2 and in animals.3,4 On a high sodium intake, the adrenal response is suppressed, whereas the vascular response is enhanced. Conversely, on a low sodium intake the adrenal response is enhanced and vascular responses blunted. There is substantially greater unanimity on the responsible mechanism for shifts in vascular smooth muscle responsiveness than for adrenal responsiveness. In the case of vascular smooth muscle, all of the available evidence from the more direct studies possible in animals,3,5–7 and less direct studies in humans,8–10 suggest a mechanism involving the number or availability of angiotensin receptors. For the adrenal, some studies have supported a receptor mechanism,3,7 and others have not.4 In the normal human, converting enzyme inhibition modified vascular responsiveness to Ang II8–10 but not that of the adrenal responsiveness.8–11 This observation suggests a different responsible mechanism in vascular smooth muscle than in the adrenal in humans.

All of the reported studies on adrenal responsiveness have been performed under steady-state conditions of sodium balance. In the present study, we assessed the adrenal response to Ang II during the first several days of a shift from a high to a low sodium intake. If factors in the transduction process are responsible for the
enhanced adrenal response to Ang II with reduced sodium intake, it would be anticipated that time would be required to increase adrenal sensitivity to Ang II, as suggested by studies in animals. The present study demonstrates that is indeed the case.

Methods

Subjects and Protocol

Sixteen normal male subjects ranging in age from 19 to 44 years and in weight from 68 to 90 kg were admitted to the Clinical Research Center of the Brigham and Women’s Hospital. During their entire stay, subjects were maintained on isocaloric-constant diets containing 100 meq potassium. The subjects were first brought into balance on a 200 meq sodium intake, and their adrenal responsiveness was assessed. Sodium intake was decreased abruptly to 10 meq daily; adrenal responsiveness was assessed again, either at 24 or 48 hours after the dietary shift, and repeated when 10 meq sodium balance was attained in 5–7 days.

Daily 24-hour urine collections were made for measurement of volume, sodium, potassium, and creatinine content. Because of known fecal losses of potassium, potassium excretion on the day before the shift from a high sodium to a low sodium intake was used for calculation of net cumulative potassium balance (Table 3).

Angiotensin II Infusion

Each infusion of Ang II amide (Hypertensin, CIBA-GEIGY Corp., Summit, New Jersey) was begun between 8:30 and 9:00 AM with an electronic infusion pump (Harvard Apparatus Co., Millis, Massachusetts) at doses of 3 and 10 ng/kg/min for 45 minutes at each dose. All subjects remained supine. Blood samples were obtained for measurement of potassium, sodium, aldosterone, cortisol, and Ang II concentration at the start of the infusion and at the completion of each dose of Ang II.

Laboratory Procedures

Blood samples were collected on ice, immediately cold centrifuged, and the plasma separated and frozen until the time of assay. Sodium and potassium were measured by means of an ion-selective electrode system (Nova I, Nova Biomed, Waltham, Massachusetts). Serum creatinine was measured by an autoanalyzer technique (Beckman Creatinine Analyzer II, Beckman Instrs., Inc., Fullerton, California). Ang II, plasma renin activity, aldosterone, and cortisol were analyzed by radioimmunoassay. Group means are presented with the standard error of the mean as the index of dispersion. Statistical probability was assessed with linear regression and analysis of variance. The null hypothesis was rejected when \( p \) achieved a level of 0.05 or less. The protocol was approved by the Committee for the Protection of Human Subjects from research risks at the Brigham and Women’s Hospital and written consent was obtained from each subject.

Results

During the first 24 hours of restricted sodium intake, sodium excretion fell from 217±11 to 105±7 meq/24 hr, so that during that day excretion exceeded intake by 95 meq (Table 1). The 95 meq negative sodium balance was associated with a sharp increase in plasma renin activity (1.0±0.2 to 2.4±0.7 ng/ml/hr, \( p<0.01 \)) and plasma Ang II concentration (22.0±1.9 to 29.5±1.3 pg/ml, \( p<0.01 \)). Basal plasma aldosterone concentration, however, did not increase (10.4±1.3 to 11.7±1.2 ng/dl). During the next 24 hours, sodium excretion fell to 59±7 meq/24 hours, exceeding intake by 49 meq. During that interval, neither plasma renin activity (2.4±0.7 ng/ml/hr) nor plasma Ang II concentration (30.8±2.5 pg/ml) increased further, but plasma aldosterone concentration rose sharply (22.5±3.6 ng/dl, \( p<0.01 \)). When low salt balance had been achieved in 5–7 days,
TABLE 2. Aldosterone Response to Intravenous Angiotensin II

<table>
<thead>
<tr>
<th>Diet</th>
<th>Angiotensin II dose (ng/kg/min)</th>
<th>0</th>
<th>3</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>High salt</td>
<td>10.4±1.3</td>
<td>20.3±2.3</td>
<td>27.2±2.9</td>
<td></td>
</tr>
<tr>
<td>Low salt: 24 hours</td>
<td>11.7±1.2</td>
<td>27.1±4.1</td>
<td>41.6±3.9</td>
<td></td>
</tr>
<tr>
<td>Low salt: 48 hours</td>
<td>22.5±3.6</td>
<td>37.4±6.6</td>
<td>46.3±7.6</td>
<td></td>
</tr>
<tr>
<td>Low salt: 120–168 hours</td>
<td>35.7±5.5</td>
<td>55.8±6.1</td>
<td>72.8±7.1</td>
<td></td>
</tr>
</tbody>
</table>

Values are plasma aldosterone concentration (ng/dl)±SEM. p<0.05; p<0.01 significantly different from high salt diet.

plasma renin activity, plasma Ang II concentration, and plasma aldosterone all showed a further rise (Table 1).

Ang II infusion brought out the anticipated difference in response between the subjects when in balance on a high salt intake and on a low salt intake (Table 2). Plasma aldosterone rose from 10.4±1.3 to 27.2±2.9 ng/dl with a 10 ng/kg/min Ang II infusion on a high sodium intake and from 35.7±5.5 to 72.8±7.1 ng/dl at that angiotensin dose on a low salt intake. The 3 ng/kg/min Ang II dose induced an intermediate response. Although basal plasma aldosterone had not increased 24 hours after instituting a restricted sodium intake, the Ang II infusion brought out evidence of sensitization. Not only was the increment in plasma aldosterone concentration larger at the high salt balance studied were found (Figure 1). Regression analysis revealed a significant difference in both the intercept (15.8±2.4 vs. 41.3±7.0, p<0.01) and in the slope (0.067±0.026 vs. 0.41±0.14, p<0.01) and aldosterone concentration (16.7±3.46) did not differ from that on a high salt diet, but the slope had increased significantly (0.11±0.020, p<0.025) (Figure 2). At the lower end of the plasma Ang II concentration range (below 75 pg/ml) the values were randomly distributed around the regression line for high salt balance. Above that plasma Ang II concentration, 14 of 15 points were above the line (p<0.01). At 48 hours, intermediate values were found.

Changes in potassium balance during the first 48 hours were modest and tended to be slightly positive (Table 3). Thereafter, net potassium balance became progressively more negative (Table 3). Although the changes were small, potassium excretion increased in 15 of the 16 subjects during the third to the seventh day after institution of a restricted sodium intake.

Discussion

In the first 24 hours after a shift to a very low sodium intake, with a reduction in total body sodium of over 100 meq, there was a sharp increase in plasma renin activity and plasma Ang II concentration but no increase in plasma aldosterone concentration.

FIGURE 1. Scatterplot showing relation of plasma aldosterone to plasma angiotensin II (AII) concentration at steady state on a very low (10 meq) and high (200 meq) NaCl intake. The two regression relations differ in both slope and intercept.

FIGURE 2. Scatterplot showing relation between plasma angiotensin II (AII) aldosterone concentration 24 hours after initiating a restricted NaCl intake. Regression relations defined in Figure 1 are shown as well. At 24 hours, slope is increased significantly in comparison with a high salt diet (p<0.025), but intercept was unchanged.

TABLE 3. Sodium Potassium Excretion and Balance

<table>
<thead>
<tr>
<th>Day</th>
<th>Excretion (meq/24 hr)*</th>
<th>Cumulative excretion (meq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>0</td>
<td>217±11</td>
<td>83±5</td>
</tr>
<tr>
<td>1</td>
<td>105±7</td>
<td>74±5</td>
</tr>
<tr>
<td>2</td>
<td>59±7</td>
<td>85±4</td>
</tr>
<tr>
<td>3</td>
<td>30±3</td>
<td>91±3</td>
</tr>
<tr>
<td>4</td>
<td>18±2</td>
<td>90±3</td>
</tr>
<tr>
<td>5</td>
<td>12±1</td>
<td>92±4</td>
</tr>
<tr>
<td>6</td>
<td>10±1</td>
<td>94±4</td>
</tr>
<tr>
<td>7</td>
<td>13±4</td>
<td>93±7</td>
</tr>
</tbody>
</table>

*Values are mean±SEM.
Ang II infusion at that time, however, brought out a subtle but clear enhancement of the adrenal response to Ang II that was evident in an increase in the values of plasma aldosterone concentration with increasing doses of administered Ang II (Table 2) and in an increase in the slope relating plasma Ang II to plasma aldosterone concentration at that time (Figure 2). With a continued but more limited reduction in total body sodium over several days, basal plasma aldosterone concentration rose, and there was a further increase in the slope relating plasma Ang II and plasma aldosterone concentration. The shift in the slope relating angiotensin and aldosterone concentration at extremes of sodium intake confirms earlier reports and provides the most compelling evidence favoring sensitization of the adrenal response as the analysis was performed over a wide and overlapping range of plasma Ang II concentration. This is important as analyses of the Ang II dose–adrenal response relation potentially could have been altered by the rise in basal plasma aldosterone concentration with time.

The factors responsible for increasing adrenal sensitivity remain obscure, reflecting the complexity of the regulatory processes involved in aldosterone biosynthesis. All factors that acutely modify aldosterone secretion increase the rate of conversion of cholesterol to pregnenolone (early pathway) and may also modify the late pathway (the conversion of corticosterone to aldosterone). In both human and rat tissue, sodium restriction does not modify early pathway activity but does substantially increase the rate of activity of the late pathway. Thus, this change alone could account for the enhanced adrenal response to Ang II with sodium restriction. Whether the adrenal Ang II receptor also participates in this change in sensitivity remains uncertain. In the rat, the number of binding sites for Ang II increases with sodium restriction, but plasma aldosterone concentration rises more gradually over a 48-hour period. Subsequent in vitro studies confirm the delay in sensitization and are compatible with a gradual, progressive enhancement of adrenal biosynthetic capacity for aldosterone.

Whatever the responsible mechanism for the shift in adrenal sensitivity, the results of this study indicate that there is a lag in the increased sensitivity of the adrenal responsiveness to Ang II with restriction of sodium intake, as opposed to the rapid adaptation of the renin-angiotensin system to the state of sodium balance, consistent with a crucial role for biosynthetic elements in the late pathway of aldosterone synthesis.

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References


Key Words: adrenal glands, angiotensin II, sodium, aldosterone, potassium
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