Effect of Plasma Sodium on Aldosterone Secretion During Angiotensin II Stimulation in Normal Humans

David C. Merrill, Thomas J. Ebert, Meredith M. Skelton, and Allen W. Cowley Jr.

Studies were carried out in normal male subjects (n=6, age 20–35 years) to determine the interaction of angiotensin II and plasma sodium on aldosterone secretion. These relations were quantified by elevation of plasma sodium with an infusion of 5% sodium chloride (4 ml/kg/30 min i.v.) with measurements of plasma aldosterone, atrial natriuretic factor (ANF), and arginine vasopressin (AVP) over 3 hours. Two hours before sodium chloride infusion, an intravenous infusion of angiotensin II was begun at 0.5 or 5.0 ng/kg/min and continued throughout the study. Plasma potassium was maintained constant by the addition of potassium to the infusate. NaCl/KCl infusion raised plasma sodium 4 meq/l with no decreases of plasma potassium. Plasma aldosterone averaged 7±1.8 ng/dl before NaCl infusion in subjects infused with 0.5 ng angiotensin II and was not significantly reduced with sodium chloride infusion. Angiotensin II infused at 5 ng/kg/min resulted in average plasma aldosterone levels of 31±3.6 ng/dl, which sodium chloride infusion decreased to 16.6±1.7 ng/dl (p<0.05) in 60 minutes. Plasma aldosterone remained depressed for the remaining period of study. Plasma ANF increased from 40 to 60 pg/ml with sodium chloride infusion. We conclude that small physiological elevations of plasma sodium concentrations can signal substantial decreases of plasma aldosterone in normal human subjects in situations where plasma angiotensin II is moderately elevated. The precise mechanisms of these responses remain to be determined.

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It is a common belief that aldosterone secretion in humans is controlled mainly through the renin-angiotensin system.1 In a variety of clinical situations, however, a dissociation between plasma renin activity (PRA) and plasma aldosterone has been demonstrated. Situations in which there does not appear to be a tight correlation between PRA and plasma aldosterone include acclimatization to hypoxia,2 normal human pregnancy,3 and acute renal failure.4 We have also documented a dissociation of PRA from plasma aldosterone in normal conscious dogs.5 In that study, we observed that in the sodium-deprived conscious dog (elevated angiotensin II state), H2O deprivation resulted in a significant reduction in plasma aldosterone. This decrease in aldosterone could not be accounted for by changes in plasma potassium or angiotensin II, but it was associated with an elevation of plasma sodium concentration.

Changes in plasma sodium concentration are not normally thought to be potent controllers of aldosterone secretion in either humans or experimental animals.6 However, considerable data is accumulating to suggest that various controllers may interact to regulate aldosterone secretion. In addition, there is evidence that the adrenal gland may become more sensitive to various stimuli in the sodium-deplete state. It has consistently been shown that the aldosterone response to a given level of angiotensin II increases with sodium restriction.7 In addition, it has recently been reported that elevations of angiotensin II8 or dietary sodium restriction9 may enhance the action of potassium on aldosterone secretion. Furthermore, pharmacological blockade of angiotensin II by captopril has been shown to severely blunt the aldosterone response to changes in plasma potassium.10

The interaction of plasma sodium concentration and various other controllers has not as yet been systematically studied in humans. There is evidence from animal experimentation, however, suggesting that the adrenal gland may be more sensitive to
changes in plasma sodium concentration in high angiotensin II states. Blair-West et al. observed in sheep that elevations of plasma sodium from 8 to 13 meq/l could acutely decrease the excess aldosterone secretion observed after angiotensin II administration. Schneider et al. have reported that small (4–7 meq/l) elevations in sodium concentration markedly reduced aldosterone excretion in angiotensin II-stimulated isolated adrenal gland. Finally, we have observed in conscious dogs an increased aldosterone response to changes in plasma sodium with elevated background levels of angiotensin II.

The present study was designed to systematically examine the interaction of angiotensin II and plasma sodium on aldosterone secretion in normal human subjects. These relations were quantified by selectively altering plasma sodium in the presence of differing steady-state levels of angiotensin II. Since plasma potassium normally decreases with administration of excess sodium, sufficient potassium was administered to maintain plasma potassium at a constant level.

Subjects and Methods

Description of Subjects

A total of six normal, healthy male volunteers, aged 20–35 years were studied. Each subject underwent a complete history and physical examination before experimentation. In addition, routine urinalysis and blood chemistry were performed. Any evidence of cardiovascular, endocrine, gastrointestinal, neurologic, or renal disease was considered grounds for exclusion from the protocol. The protocol was approved by the Institutional Human Research Review Committee. Subjects gave informed consent after explanation of the nature and consequences of the study.

Experimental Protocol

To assess sodium and potassium intake during the period just before the study, the subjects were instructed to perform a complete 24-hour urine collection on the day before each scheduled experimental period. On the night before the study, the subjects were instructed to fast after midnight (excluding H2O).

On the morning of experimentation (approximately 7:00 AM), the subjects reported to the Cardiovascular Research Center (CRC) and were placed supine in bed. At that time, two separate venous cannulae (18 and 16 g) were placed in peripheral veins with the aid of 1% lidocaine local anesthetic. One catheter was used for venous blood sampling, and the other catheter was used for intravenous infusions. Approximately 20 minutes after insertion of the catheters, control venous blood samples were obtained. An intravenous infusion of angiotensin II (Hypertensin, Ciba Pharmaceutical Co., Summit, New Jersey) in lactated Ringer’s solution was subsequently initiated at a rate of 0.6 ml/kg/hr with a motor-driven roller infusion pump (Travenol, Morton Grove, Illinois). The infusate was prepared such that a dose of either 0.5 or 5.0 ng/kg/min was delivered. This infusion of angiotensin II was continued for the duration of the study (5 hours). After 2 hours of angiotensin II infusion, a hypertonic saline (5%) infusion was initiated. A total of 4.0 ml/kg of this solution was administered over 30 minutes and terminated. To maintain plasma potassium constant, a total of 20 meq KC1 was added to each 500 ml 5% NaCl solution and 4 meq/l was added to the angiotensin infusate, thus delivering a total of 0.17 meq/kg KC1 to the subject during the protocol. Venous blood samples for analysis of electrolyte and hormones were obtained before and at 20, 120, 150, 180, 240, and 300 minutes after initiation of the angiotensin II infusion. A total of 20 ml blood was obtained at each sampling interval (140 ml total).

Seven to 10 days after the initial experiment, the subjects again reported to the CRC, and the protocol was repeated with a different dose of angiotensin II. The order in which the various doses were administered was completely random. Venous blood samples were analyzed for plasma aldosterone, vasopressin, atrial natriuretic factor (ANF), sodium, and potassium. Blood pressure was measured at 10-minute intervals throughout the study by a sphygmomanometer. Data for control and infusion periods were taken as the mean of four to six measurements. Body weight was measured before and at the end of each study in the CRC.

Chemical and Radioimmunoassay Analysis

Plasma and urine sodium and potassium concentrations were determined using ion specific electrodes (NOVA Biomedical, Boston, Massachusetts).

Plasma vasopressin concentration was determined with antisera and radioimmunoassay procedures developed in this laboratory and described in detail previously. Plasma aldosterone was extracted with dichloromethane and radioimmunoassayed using a highly specific antisera and [125I] aldosterone provided by Diagnostics Biochem, Canada, Inc. (London, Ontario, Canada). Plasma ANF was determined by radioimmunoassay (Peninsula Labs., Inc., Belmont, California) after extraction on C18 columns (Sep-pak, Waters, Boston, Massachusetts) using methods previously reported.

Statistical Analysis

All values in these studies are expressed as mean±SEM. A two-way analysis of variance for repeated measures was followed by a Duncan’s test for significance for within-group comparisons. Changes were considered statistically significant if p<0.05.

Results

Table 1 summarizes the changes in all variables before and during the angiotensin II infusion before the NaCl/KCl infusion. The values obtained at 120
TABLE 1. Changes in Hemodynamics, Plasma Hormones, and Plasma Electrolytes Before and 60 and 120 Minutes After an Infusion of Angiotensin II

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>60 minutes</th>
<th>120 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
<td>5.0</td>
<td>0.5</td>
</tr>
<tr>
<td>MAP</td>
<td>88±1</td>
<td>97±2*</td>
<td>100±5*</td>
</tr>
<tr>
<td>HR</td>
<td>57±2</td>
<td>57±3</td>
<td>53±0.7</td>
</tr>
<tr>
<td>PALDO</td>
<td>7±1.8</td>
<td>8.1±1.5</td>
<td>33.7±7.1*</td>
</tr>
<tr>
<td>PANF</td>
<td>39±4</td>
<td>39±4</td>
<td>42±2</td>
</tr>
<tr>
<td>PAVP</td>
<td>3.9±0.9</td>
<td>4.5±1</td>
<td>3.9±0.2</td>
</tr>
<tr>
<td>PNa</td>
<td>142.7±0.5</td>
<td>143.5±0.4</td>
<td>142.2±0.2</td>
</tr>
<tr>
<td>PK</td>
<td>3.99±0.05</td>
<td>4.16±0.09</td>
<td>4.48±0.13</td>
</tr>
</tbody>
</table>

Values given are mean±SEM. Ang II, angiotensin II; MAP, mean arterial pressure; HR, heart rate; PALDO, plasma aldosterone; PANF, plasma atrial natriuretic factor; PAVP, plasma arginine vasopressin; PNa, plasma sodium; PK, plasma potassium.

*Indicate differences from baseline (p<0.05).

minutes of angiotensin II infusion served as the control values in the figures described below.

Figure 1 summarizes the changes in hormonal levels in response to NaCl/KCl infusion after 120 minutes of angiotensin II infusion at 0.5 and 5.0 ng/kg/min. Plasma aldosterone had increased from a (preangiotensin II) control level of 7.8±1 ng/dl to a steady-state level of 30.7±4 ng/dl with 120 minutes of angiotensin II infusion at 5.0 ng/kg/min. On infusion of NaCl/KCl, a significant fall in plasma aldosterone was observed and was maintained throughout the experiment. This decrease in plasma aldosterone was associated with a small but significant increase of plasma ANF (from 41±4 to 63±6 pg/ml). At the lower dose of angiotensin II (0.5 ng/kg/min), plasma aldosterone remained unchanged, and plasma ANF increased slightly but significantly 120 minutes after NaCl/KCl infusion. Similar elevations in plasma vasopressin were observed in both groups.

Figure 2 summarizes the changes in plasma sodium and plasma potassium after initiation of the NaCl/KCl infusion at the steady-state control levels after 2 hours of angiotensin II infusion. Plasma sodium was increased similarly at both doses of angiotensin II with the peak increase of +4 meq/l 30 minutes after initiation of the NaCl/KCl infusion. Plasma potassium increased to a small extent transiently in both groups with significance observed only at the 60-minute mark after saline infusion in the low dose angiotensin II group.

Figure 3 summarizes the hemodynamic changes after initiation of the NaCl/KCl load at the two steady-state levels of angiotensin II. Mean arterial pressure (MAP) increased from 88 to 95 mm Hg with 0.5 ng/kg/min angiotensin II (Table 1) and was elevated 5 mm Hg further by the end of the 30-minute infusion of NaCl/KCl. With the higher dose of angiotensin II, MAP increased from 91 to 102 mm Hg (Table 1) followed by a similar increase of 5 mm Hg with infusion of NaCl/KCl. No change in heart rate was observed in response to angiotensin II at either dose but a transient significant increase of 7–10 beats/min was observed in both groups after NaCl/KCl infusion.

The control levels of plasma aldosterone obtained after 120 minutes of angiotensin II infusion were compared with the values observed 3 hours after

FIGURE 1. Graph summarizing changes in plasma aldosterone (PALDO), plasma atrial natriuretic factor (PANP), and plasma arginine vasopressin (PAVP) after 120 minutes of angiotensin II infusion (CON) in response to a 30-minute infusion of NaCl/KCl (shaded area). Dashed lines indicate the group infused at 5.0 ng/kg/min angiotensin II; solid lines indicate the group infused at 0.5 ng/kg/min. * Indicate significant differences from group control (p<0.05). Values given are mean±SEM.
Figure 2. Graphs summarizing the changes in plasma sodium (PNa) and plasma potassium (PK) after 120 minutes of angiotensin II infusion (CON) in response to a 30-minute infusion of NaCl/KCl (shaded area). Dashed lines indicate the group infused at 5.0 ng/kg/min angiotensin II; solid lines indicate the group infused at 0.5 ng/kg/min. * Indicate significant differences from group control (p<0.05). Values given are mean±SEM.

Figure 3. Graphs summarizing the changes in mean arterial pressure (MAP) and heart rate (HR) after 120 minutes of angiotensin II infusion (CON) in response to a 30-minute infusion of NaCl/KCl (shaded area). Dashed lines indicate the group infused at 5.0 ng/kg/min angiotensin II; solid lines indicate the group infused at 0.5 ng/kg/min. * Indicate significant differences from group control (p<0.05). Values given are mean±SEM.

Figure 4. Graph summarizing changes in plasma aldosterone (PALDO) after a step increase in plasma sodium (PNA) at the two doses of angiotensin II. Dashed lines indicate the group infused at 0.5 ng/kg/min angiotensin II and the solid line indicates the group infused at 5.0 ng/kg/min angiotensin II. Values given are mean±SEM.

decreased plasma aldosterone from 30.0±4.9 to 18.2±2.4 ng/dl (p<0.05). At the lower dose of angiotensin II (0.5 ng/kg/min), similar elevations of plasma sodium had little influence on plasma aldosterone concentrations.

Discussion

Plasma sodium concentration has primarily been thought of as a weak modulator of plasma aldosterone. Davis et al. demonstrated in nephrectomized, hypophysectomized dogs that rather large changes in plasma sodium were required to influence aldosterone secretion. In fact, they observed that the smallest decrease in plasma sodium that produced a definite elevation in aldosterone secretion was 14 meq/l.

Despite these reports, there is some evidence that sodium may be an important controller of aldosterone in certain situations. Blair-West et al. observed in sheep that elevations of plasma sodium from 8 to 13 meq/l could acutely decrease the excess aldosterone secretion observed after angiotensin II infusion. Recently, Schneider et al. have demonstrated in the angiotensin II-stimulated, isolated, perfused canine adrenal gland that small changes in sodium concentration (5-10 meq/l) resulted in significant changes in aldosterone secretion. In a recent study, we demonstrated a significant interaction between angiotensin II and plasma sodium in the control of aldosterone secretion in conscious dogs. Using the same protocol as employed in the present studies, we observed a convincing interaction of plasma sodium and angiotensin II on aldosterone secretion. This response appeared to be biphasic, whereas in the presence of physiological elevations of angiotensin II (5.0 ng/kg/min), plasma aldosterone was decreased nearly 55% from the stimulated control levels as plasma sodium was increased. With a supraphysiological
dose of angiotensin II (20.0 ng/kg/min), the influence of increased plasma sodium was diminished as seen by only a 25% decrease of plasma aldosterone. Plasma sodium was increased an average of 7 meq/l, somewhat greater than increases obtained in the present study.

For the present studies, only physiological doses of angiotensin II were studied, which resulted in enhanced adrenal sensitivity to increased plasma sodium at the higher dose of 5.0 ng/kg/min. With increases in plasma sodium of only 3.5–4.0 meq/l, plasma aldosterone was observed to decrease 39% (from 30.0±4.9 to 18.2±2.4 ng/dl). At the low level of angiotensin II, which resulted in little elevation of plasma aldosterone, plasma sodium appeared to have only minimal effects on plasma aldosterone. Saruta et al. have observed in isolated bovine adrenocortical slices that a decrease in sodium concentration stimulates the conversion of corticosterone to aldosterone, but has no effect on the early site of regulation (cholesterol to pregnenolone). Angiotensin II, on the other hand, has been shown to stimulate both early and late steps of steroid biosynthesis in rat and dog adrenal cells.

The mechanism of the interaction of sodium and angiotensin II in the present studies is unclear. It is possible that stimulation of the adrenal glomerulosa in other ways, such as excess potassium or adrenocorticotropic hormone, could result in enhanced responses to elevations of plasma sodium. It is also unclear whether the effects of hypertonic saline infusion were due to increases in the sodium ion per se or, possibly, were secondary to the increase in osmolality. Blair-West et al. using an autotransplanted adrenal gland preparation, concluded that increases in sodium concentration rather than osmolality inhibit aldosterone secretion. Schneider et al., however, concluded that osmolality, not sodium, was the important parameter in the isolated canine adrenal gland. A similar inhibition of angiotensin II-stimulated aldosterone secretion was observed with NaCl, sucrose, mannitol, or glucose. Furthermore, hyperosmolality initiated by urea had no effect on aldosterone secretion, thus suggesting that intracellular volume or composition was the important parameter. Similar results in humans have been reported, where hyperglycemia or increases in osmolality have been shown to suppress plasma aldosterone.

Other factors must also be considered that could have influenced aldosterone secretion in the present study. The hypernatremia induced in the present study undoubtedly resulted in some degree of plasma volume expansion, which probably accounted for the elevation of ANF. ANF has been shown in humans to suppress aldosterone production independent of changes in PRA or electrolytes. ANF has also been shown to inhibit the hypersecretion of aldosterone in response to angiotensin II infusion and sodium depletion in humans. Recently, Richards et al. have reported that ANF could suppress the renin-angiotensin-aldoosterone system even with infused amounts that induced perturbations in immunoassayable plasma ANF within the physiological range. It remains to be determined whether these levels of ANF can suppress aldosterone in the absence of decreases of PRA.

Finally, it has been observed that in sodium-depleted humans, dopamine inhibits the aldosterone response to angiotensin II, suggesting that the fluid and electrolyte status may modify adrenal secretion via specific dopamine receptors, which have been demonstrated in rat and bovine adrenal zona glomerulosa cells.

Although much remains uncertain as to the mechanism and modulators of this response, an interaction between angiotensin II and sodium clearly may have important clinical implications. Dissociations between the renin-angiotensin and aldosterone systems have been described in a variety of clinical situations. We have recently reported that, in the sodium-deprived, conscious dog (elevated angiotensin II state), water deprivation results in a significant reduction in plasma aldosterone. This decrease in aldosterone could not be attributed to changes in plasma potassium or angiotensin II, but was associated with a rise in plasma sodium. Similar results have been observed in a child with hydration secondary to diabetes insipidus and adiposia. A new clinical entity, hyperreninemic hypoadosteronism, has recently been described in the critically ill. In this situation, low aldosterone levels persist despite markedly elevated PRA. Those patients with low plasma aldosterone levels were observed to have significantly higher serum sodium values than control subjects. Interestingly, previous studies have indicated that, in high angiotensin II states, the aldosterone secretory response to a variety of stimuli appears to be hypersensitive.

In summary, the present studies demonstrate that physiological elevations of plasma sodium can signal substantial decreases of plasma aldosterone levels in normal human subjects when circulating levels of angiotensin II are moderately elevated. Possible mechanisms of this interaction are discussed, but are speculative at present. Elevations of plasma ANF may be in part responsible for the suppression of aldosterone with hypernatremia. The implications of this rather potent interaction are significant when considering the factors that control aldosterone secretion in situations of sodium and water restriction. In addition, this interaction may be of importance in a variety of normal and pathological situations in which the renin activity is altered with varying states of fluid and electrolyte balance.

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