Is Aldosteronism Important in the Maintenance of Arterial Blood Pressure and Electrolyte Balance During Sodium Depletion?

THOMAS E. LOHMEIER, PH.D., PHILIP R. KASTNER, PH.D., MANIS J. SMITH, JR., PH.D., AND ARTHUR C. GUYTON, M.D.

SUMMARY To evaluate quantitatively the importance of aldosteronism in the maintenance of sodium balance and arterial blood pressure during sodium depletion, dogs were subjected to 2 weeks of dietary sodium restriction first while intact and, subsequently, after adrenalectomy, while continuously infused with basal ("sodium-replete") amounts of aldosterone and cortisol. Mean arterial pressure (MAP) was recorded continuously. During the control period (sodium intake = 50 mEq/day), the values for all measured variables in the adrenalectomized dogs were similar to those observed when the dogs were intact. When the dogs were intact and sodium intake was severely restricted, sodium balance was achieved with a 10- and 14-fold increase in plasma renin activity (PRA) and plasma aldosterone concentration, respectively; MAP did not change. During sodium restriction in the adrenalectomized state, plasma aldosterone concentration was unchanged; this was associated with relatively small disturbances in sodium and water balance but more prominent perturbations in potassium balance. Establishment of sodium balance in the adrenalectomized dogs was associated with a 50% greater increase in PRA than in the intact state and a small fall in MAP (only 8 mm Hg). Changes in renal function were similar in both groups of dogs during sodium depletion — GFR was unchanged and effective renal plasma flow (ERPF) fell 7%-9%. The data from the 2-week period of sodium restriction indicate that the maintenance of sodium balance and arterial pressure during sodium depletion is not critically dependent upon enhanced aldosterone secretion. (Hypertension 2: 497-505, 1980)

KEY WORDS  • aldosterone  • plasma renin activity  • angiotensin II  • arterial pressure  • sodium depletion  • sodium balance  • potassium balance  • renal function

ALDOSTERONE is the major sodium-retaining hormone secreted by the adrenal cortex. Although it has been known for years that adrenal insufficiency results in renal sodium wastage and that injections of extracts of the adrenal gland prevent such sodium loss, the quantitative importance of aldosterone in helping to maintain arterial pressure during sodium restriction has yet to be determined. That aldosterone secretion is inversely related to sodium intake further points to an important role of this potent mineralocorticoid in the regulation of sodium balance. However, patients with adrenal insufficiency on a fixed dosage of both mineralocorticoids and cortisone maintain sodium balance despite an inability to regulate secretion of these hormones. Further, during variations in sodium intake, renin secretion and aldosterone secretion parallel one another, and recent studies from our laboratory indicate that angiotensin II, independent of its actions on aldosterone secretion, has pronounced direct effects on renal sodium excretion and arterial pressure. These effects appear to be even more important than the indirect effects mediated via aldosterone secretion. It is conceivable, therefore, that the major role of the renin-angiotensin-aldosterone system in the control of arterial pressure resides in the ability of Aldosterone secretion to regulate renal sodium excretion directly.

The purpose of this study was to evaluate quantitatively the importance of aldosteronism in the maintenance of sodium balance and arterial blood pressure during sodium depletion. Mean arterial pressure (MAP) was recorded continuously during 2 weeks of sodium depletion in intact dogs and, subsequently, in the same dogs after adrenalectomy when...
the plasma aldosterone concentration was maintained at sodium replete levels by continuous infusion of exogenous aldosterone. Also, the changes in plasma aldosterone concentration, plasma renin activity (PRA), electrolyte balance, and renal function were studied.

Methods

Materials

Five male dogs weighing 23.3 ± 1.2 (SE) kg were used in this study. Chronic indwelling catheters made of Tygon tubing (Norton) were placed in the femoral artery and vein. The tip of the femoral artery catheter was advanced into the aorta distal to the bifurcation of the renal arteries, and the end of the femoral vein catheter was positioned in the vena cava. A Silastic elbow prevented kinking of the catheters in the femoral area. The catheters were tunneled subcutaneously and exteriorized in the posterior thoracic region. Two weeks after surgery the dogs were placed in metabolic pens and fitted with an aluminum and canvas backpack housing a Statham arterial blood pressure transducer (model P23 ID) at heart level. The electrical connections to the transducer and an intravenous infusion line were brought to the top of the cage through a flexible tube attached to the top of the backpack. Continuous intravenous infusions were made through the femoral vein catheter by means of a Sage tubing pump (model 375A), and MAP was recorded continuously, 24 hours per day, from the femoral artery catheter on a Grass polygraph (model 7D).

The dogs were studied first while intact according to the experimental protocol described below; subsequently, they were bilaterally adrenalectomized in two stages as previously described and then, while infused with maintenance levels of cortisol and aldosterone (see below), subjected to the same protocol.

During the entire experiment, the dogs were given free access to water and maintained on a fixed daily diet of two 15.5 oz cans of H/D prescription diet (Riviana Foods, Inc.); two cans of H/D provide < 5 mEq sodium and 45-50 mEq potassium. Daily infusions of 310 ml of 0.9% saline plus 5% dextrose were given (48 mEq sodium/day) except during sodium depletion when only 310 ml of 5% dextrose were administered. Daily hormonal supplements of aldosterone (d-aldosterone, Ciba) and hydrocortisone (Cortisol, Upjohn) were added to the infusate to maintain the dogs following adrenalectomy.

Body temperature was measured daily, and ampicillin (Principen, E. R. Squibb and Sons) and a trimethoprim-sulfamethoxazole combination (Bactrim, Roche Laboratories) were given prophylactically. To promote accurate measurements of 24-hour urinary sodium and potassium excretion rates, the bladder was catheterized daily using aseptic techniques. The bladder was washed with a nitrofurazone solution (Vet Products Co.) to prevent bacterial infection.

Experimental Protocol

While intact and also while maintained in the adrenalectomized state, the dogs were subjected to 2 weeks of sodium depletion after a 10-14 day control period (sodium intake = 50 mEq/day). Following the sodium depletion period, sodium intake was restored to control level during a 7-14 day recovery period. Adrenalectomized dogs were infused with 18-25 µg aldosterone and 0.9-1.2 mg cortisol/day. In each dog the plasma concentrations of aldosterone and cortisol achieved during the infusion were determined along with the plasma levels of these steroids for the previous intact control period. For each dog, the infusion rates of these steroids were adjusted until the plasma steroid levels were comparable to those measured for the intact control period. Once comparable hormonal levels were achieved, the 10-14 day control period was begun. Subsequently, the infusion rate of aldosterone and cortisol was maintained during the two week period of sodium depletion and during the recovery period. Throughout the study, 5-15 ml blood samples were taken periodically for measurement of PRA, plasma aldosterone and cortisol concentrations, plasma sodium and potassium concentrations, hematocrit, and plasma protein concentration. Additionally, GFR and effective renal plasma flow (ERPF) were determined in duplicate during the control period, on days 13 and 14 of sodium depletion, and on the last 2 days of the recovery period. All blood samples were taken at 8-9 a.m., 18-20 hours after feeding. Renal function was determined between 9 a.m. and 12 noon. At noon, 24-hour urine collections were made just after bladder catheterization and just prior to feeding. Heart rate, body weight, and daily water consumption were also monitored.

Analytical Methods

The PRA was measured by a radioimmunoassay procedure for angiotensin I (Al) (New England Nuclear, Angiotensin I [125I] RIA Kit) and is expressed as nanograms of Al generated per milliliter of plasma per hour incubation (ng AI/ml per hour). Plasma aldosterone concentration (Diagnostic Products Corporation, [125I] Aldosterone RIA Kit) and plasma cortisol concentration (New England Nuclear, Cortisol [125I] RIA Kit) were also measured by radioimmunoassays. The standard curves for cortisol and aldosterone were adapted down to 1 µg/dl and 1.25 ng/dl, respectively. Glomerular filtration rate and effective renal plasma flow were calculated from the clearances of [125I] iodochlorhydroxyquin (Hippuran, Mallinckrodt Nuclear), respectively, by methods previously described in detail. The volume of distribution of [125I] iodochlorhydroxyquin (used as an index of changes in extracellular fluid volume) was measured using the technique of Sapirstein et al. Plasma and urine concentrations of sodium and potassium were determined by flame photometry (Instrumentation Laboratory, IL 343) and plasma protein concentration by refractometry (American Optical).
The MAP was recorded continuously on the Grass recorder and simultaneously on a PDP 11/70 Digital Corporation Computer using an analog to digital converter. The analog signal from the Grass recorder was sampled every 60 seconds, and the digitized information was used by the computer to calculate hourly values for MAP based on 60 sample points/hour. Daily values presented for MAP were calculated from the 960 data points generated during the 16-hour period extending from 4 p.m.-8 a.m.

All values presented are means ± se. Student's t test for paired observations was used to determine statistical significance. Statistical significance was considered to be \( p < 0.05 \).

Results

It is evident from table 1 that the control values for all measured variables were similar in the intact and adrenalectomized state.

Mean Arterial Pressure and Heart Rate

The MAP was virtually unchanged in all intact dogs during the 2 weeks of sodium depletion (fig. 1). In the adrenalectomized dogs (fig. 2) infused with basal levels of aldosterone and cortisol, MAP fell in all animals, but after 2 weeks of sodium depletion MAP was reduced only an average of 8 ± 3 mm Hg (\( p < 0.05 \)). The fall in MAP ranged from 2 to 12 mm Hg. Also, in all animals, MAP reached its nadir during the first 10 days of sodium depletion and actually increased slightly in all dogs during the last few days of the low sodium regimen.

In both groups of dogs, heart rate was unchanged during the entire experimental period.

Plasma Aldosterone Concentration, Plasma Cortisol Concentration, and PRA

After 2 weeks of sodium depletion, plasma aldosterone concentration was elevated to nearly 14 times that of control in the dogs when their adrenal glands were intact versus 1.6 times when the dogs were adrenalectomized and infused with a constant, basal amount of aldosterone (figs. 1-3). The increase in aldosterone concentration in the adrenalectomized dogs was not statistically significant. Thus, after 2 weeks of sodium depletion, the increase in plasma aldosterone concentration in the intact dogs was 8.6 times that observed in the adrenalectomized state.

Throughout the entire experiment, plasma cortisol concentration was unchanged in both groups of dogs (figs. 1 and 2).

On the other hand, during sodium depletion, PRA increased more in the adrenalectomized than in the intact dogs (figs. 1-3). When the adrenals were present, PRA increased to 6.0 ± 2.0 ng Al/ml/hr or to ap-
MEAN ARTERIAL PRESSURE (mmHg)

URINARY SODIUM EXCRETION (mEq/day)

PLASMA ALDO. CONC. (ng/dl)

PLASMA CORTISOL CONC. (μg/dl)

PLASMA RENIN ACTIVITY (ngAI/ml/hr)

FIGURE 2. Changes in mean arterial pressure, urinary sodium excretion, plasma aldosterone concentration, plasma cortisol concentration, and plasma renin activity during two weeks of sodium restriction in adrenalectomized dogs (n = 5) continuously infused with maintenance ("sodium-replete") amounts of aldosterone and cortisol. * = p < 0.05 compared to control.

proximately 10 times control; when the adrenals were absent, PRA increased to 9.0 ± 1.5 ng AI/ml/hr. Thus, after 2 weeks of sodium depletion, PRA was only 1.5 times as great in the adrenalectomized dogs that were unable to secrete aldosterone during sodium depletion as in the intact dogs, where plasma aldosterone concentration increased to approximately 14 times control.

Sodium Balance, Sodium-Iothalamate Space, Body Weight, Water Consumption, and Potassium Balance

During the entire first week of sodium depletion, the intact dogs excreted 48 ± 8 and the adrenalectomized dogs 55 ± 5 mEq sodium (figs. 1 and 2); the difference between these means was not statistically significant. Throughout the final week of sodium depletion, urinary sodium excretion averaged less than 3 mEq/day in both groups of animals.

Coinciding with the loss of sodium was a fall in sodium-iothalamate space after 2 weeks of sodium depletion to 96% ± 2% and 95% ± 2% of control in the intact and adrenalectomized dogs, respectively (fig. 4); again, the difference between the means was not statistically significant. In both groups of animals, mean values for body weight were unchanged after 2 weeks of sodium depletion.

In both intact and adrenalectomized animals, more sodium was retained during the 7-day recovery period than was lost during the 2 weeks of sodium depletion and, consequently, both sodium-iothalamate space and body weight increased to above control values (fig. 4). Following sodium depletion and before normal daily sodium balance was achieved during the recovery period, sodium intake exceeded sodium excretion by approximately 110 and 230 mEq in the intact and adrenalectomized dogs respectively. Apparently, by Day 7 of the recovery period, net retention of sodium in the intact dogs was rather small and, consequently, the increases in body weight and sodium-iothalamate space was not statistically significant. In the adrenalectomized dogs, on the other hand, the recovery values for body weight (to 105% ± 2% of control) and sodium-iothalamate space (to 109% ± 2% of control) were significantly elevated (p < 0.05). Presumably, overcompensation to the sodium and water deficit occurred during the recovery period, particularly in the adrenalectomized dogs. However, in three adrenalectomized dogs in which the recovery period was extended to two weeks, this overcompensatory response proved to be only transient. In all three dogs, values for body weight and sodium-iothalamate space returned to control by the end of the second recovery week.
Water consumption averaged 80 ± 37 ml/day while the dogs were intact, and was virtually unchanged when the animals were studied in the adrenalectomized state. In neither the intact nor the adrenalectomized animals did water consumption change during sodium depletion or during the subsequent recovery period.

There were no significant changes in urinary potassium excretion with one exception: in both intact and adrenalectomized dogs, a kaliuresis was observed during the recovery period. In the intact dogs urinary potassium excretion exceeded intake by an average of 2 to 5 mEq/day during Days 1–4 of the recovery period. Kaliuresis was more prominent in the adrenalectomized dogs during the recovery period. In these animals urinary potassium excretion exceeded intake by an average of 2 to 10 mEq/day, and this response persisted throughout the entire recovery period.

Plasma Sodium Concentration, Plasma Potassium Concentration, Plasma Protein Concentration, and Hematocrit

In both groups of dogs, there was a statistically significant fall in plasma sodium concentration and a statistically significant increase in plasma potassium concentration after 2 weeks of sodium depletion (fig. 3); the changes in plasma sodium concentration were relatively small, whereas the hyperkalemia was rather marked, particularly in the adrenalectomized dogs. After 1 and 2 weeks of sodium depletion, plasma sodium concentration fell 2 ± 1 and 3 ± 1 mEq/liter (to 98% of control), respectively, in the intact dogs. The corresponding values for the adrenalectomized dogs were −4 ± 1 and −7 ± 1 mEq/liter (to 95% of control), respectively. Plasma potassium concentration increased 0.1 ± 0.1 and 0.5 ± 0.2 mEq/liter (to 111% of control) in the intact dogs and 0.6 ± 0.1 and 0.9 ± 0.3 mEq/liter (to 119% of control) in the adrenalectomized dogs after 1 and 2 weeks of sodium depletion respectively. The changes in plasma sodium concentration and plasma potassium concentration at 1 and 2 weeks of sodium depletion were significantly greater in the adrenalectomized dogs.
Changes in plasma protein concentration and hematocrit that occurred during sodium depletion were similar in both groups of dogs. After 2 weeks of sodium depletion, plasma protein concentration increased to 112% ± 3% and 116% ± 3% of control in the intact and adrenalectomized dogs respectively; the difference between the means was not statistically significant. Hematocrit was unchanged after 2 weeks of sodium depletion in both intact and adrenalectomized dogs.

Renal Function — GFR and ERPF

As can be observed in figure 4, changes in renal function were similar in the intact and adrenalectomized dogs throughout the entire experiment. Changes in GFR were not statistically significant during sodium depletion or during the recovery period. In contrast, ERPF fell to 91% ± 2% and to 93% ± 1% of control in the intact and adrenalectomized dog, respectively; the difference between the means was not statistically significant. Unexpectedly, ERPF apparently fell even further in the dogs during the recovery period, especially in the intact dogs.

Discussion

In the light of the multitude of effects of glucocorticoids and mineralocorticoids on water and electrolyte metabolism, renal function, and arterial pressure, it seems very important in a study of this nature that the blood levels of aldosterone and cortisol achieved by infusion of exogenous hormones in adrenalectomized dogs match the blood levels of these steroids present when the dogs have actively secreting adrenals. As is evident from the measured blood levels of aldosterone and cortisol (table 1), this objective, in fact, was accomplished. Moreover, it is also clear from table 1 that having accomplished this basic objective, all other measured variables relating to arterial pressure, water and electrolyte metabolism, and renal function were similar in the dogs when intact and, subsequently, when the dogs were maintained in the adrenalectomized state.

It is probably fair to say that the consensus of opinion supports the concept that aldosteronism — that is, the marked increase in aldosterone secretion — plays by far the dominant role in the maintenance of sodium balance and arterial pressure during sodium depletion. The present data do not support this contention. The data do indicate that failure of plasma aldosterone concentration to increase to above normal levels during sodium restriction is not associated with major disturbances in water and electrolyte metabolism, renal function, or arterial pressure. In fact, in comparing the adrenalectomized dogs with normal plasma levels of aldosterone to the intact dogs where plasma aldosterone concentration increased 14-fold during sodium depletion, there were no statistically significant differences in either the net loss of sodium or the fall in extracellular fluid volume (sodium-iothalamate space) which occurred during the 2 weeks of dietary sodium restriction. And, throughout the entire second week of sodium restriction, sodium balance was achieved (urinary sodium excretion was less than 3 mEq/day) in all intact and adrenalectomized dogs irrespective of the plasma concentration of aldosterone. It is also significant that, in the adrenalectomized dogs, sodium balance was achieved during sodium restriction without abnormal changes in renal function.

In contrast to the intact dogs, MAP did fall in every adrenalectomized dog during sodium depletion but this fall was moderate (2–12 mm Hg). Further, there was no indication that MAP would have fallen more if the duration of sodium deprivation had been extended beyond 2 weeks: During the second week of sodium deprivation, all adrenalectomized dogs were in sodium balance and MAP, if anything, tended to increase slightly. Presumably, since aldosterone concentration could not increase in the adrenalectomized dogs, the modest hypotension that occurred during sodium depletion was due to a slightly greater loss of sodium and water and, therefore, a slightly greater reduction in blood volume. Although not achieving statistical significance, the net loss of sodium and reduction in extracellular fluid volume that occurred in the adrenalectomized dogs during sodium depletion were greater than that observed in the dogs when their adrenals were intact. Thus, in the adrenalectomized

---

**Table 1. Control Values for Dogs while Intact and while Maintained in the Adrenalectomized State by Infusion of Aldosterone and Cortisol**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intact</th>
<th>Adrenalectomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>96 ± 3</td>
<td>97 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>56 ± 5</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>PAC (µg/dl)</td>
<td>5.8 ± 2.0</td>
<td>6.1 ± 1.9</td>
</tr>
<tr>
<td>PCC (µg/dl)</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>PRA (ng AI/ml/hr)</td>
<td>0.6 ± 0.2</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>FNa (mEq/l)</td>
<td>146 ± 1</td>
<td>146 ± 1</td>
</tr>
<tr>
<td>FK (mEq/l)</td>
<td>4.6 ± 0.1</td>
<td>4.8 ± 0.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42 ± 1</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>Fpea (g/dl)</td>
<td>6.5 ± 0.1</td>
<td>6.7 ± 0.2</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>69 ± 4</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>ERPF (ml/min)</td>
<td>179 ± 8</td>
<td>173 ± 6</td>
</tr>
<tr>
<td>UNaV (mEq/24 hrs)</td>
<td>45 ± 3</td>
<td>45 ± 3</td>
</tr>
<tr>
<td>UkV (mEq/24 hrs)</td>
<td>49 ± 3</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>Na iothalamate space (ml)</td>
<td>6527 ± 115</td>
<td>6727 ± 200</td>
</tr>
<tr>
<td>Body weight (Kg)</td>
<td>23.3 ± 1.2</td>
<td>23.0 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SEM for n = 5.

Abbreviations: MAP = mean arterial pressure; PAC = plasma aldosterone concentration; PCC = plasma cortisol concentration; PRA = plasma renin activity; PNa = plasma sodium concentration; FK = plasma potassium concentration; Fpea = plasma protein concentration; GFR = glomerular filtration rate; ERPF = effective renal plasma flow; UNaV = urinary sodium excretion; UkV = urinary potassium excretion.

---
dogs where plasma aldosterone concentration could not increase during sodium restriction, there was only a slight deficiency in the ability to regulate water and electrolyte metabolism, and arterial pressure during sodium deficiency.

Recent studies in which angiotensin II competitive antagonists or angiotensin I converting enzyme inhibitors have been administered chronically to sodium-depleted dogs provide further insight relating to the importance of the renin-angiotensin-aldosterone system in the control of arterial pressure during sodium depletion. It should be emphasized that such studies in which these blocking agents are administered actiely reveal information only about the direct vasoconstrictor effects of angiotensin II and do not provide information about the more long-term arterial pressure effects of the renin-angiotensin-aldosterone system which relate to salt and water balance. Thus, for quantitative information pertinent to the importance of the renin-angiotensin-aldosterone system in the long-term control of arterial pressure, one must look at the chronic as well as the acute effects of these blocking agents. McCaa, in infusion the angiotensin I converting enzyme inhibitors, SQ 20,881 and SQ 14,225, as well as the angiotensin II competitive antagonists, [Sar1, Ala9] angiotensin II and [Sar1, Ile8] angiotensin II, for up to 2 weeks in sodium-depleted dogs. In their studies, PRA increased to 3.6 ng Al/ml/hr (six times control) after 3 weeks of dietary sodium restriction. Then, subsequent long-term infusion of either SQ 20,881 or SQ 14,225 produced a sustained fall in MAP of 32 to 36 mm Hg, which was associated with a fall in plasma aldosterone concentration to almost sodium replete levels. In the sodium-depleted dogs chronically infused with one of the two angiotensin II antagonists, MAP fell 17-20 mm Hg, but plasma aldosterone concentration did not fall (because of the agonistic effects of the blocking drug on the adrenal cortex). Our present data, taken together with that of McCaa, indicate that, quantitatively, the renin-angiotensin-aldosterone system plays an extremely important role in the control of arterial pressure during sodium depletion and that a major component of this control system involves actions of angiotensin II which are unrelated to the regulation of aldosterone secretion. It is also relevant that the changes in aldosterone concentration that accompany chronic angiotensin II infusion in the dog have very little influence on the severity of the ensuing hypertension.

One mechanism to account for the long-term, non-aldosterone effects of angiotensin II on arterial pressure and one that we favor as being especially important is that angiotensin II acts directly on the kidney to regulate sodium and water excretion. Similar observations were made by Kimbrough et al. in conscious, intact, sodium-depleted dogs during intrarenal infusion of either [Sar1, Ala8] angiotensin II or SQ 20,881. Finally, in unilaterally nephrectomized dogs we infused angiotensin II intrarenally at a very low rate (1 ng/kg/min) that did not cause a measurable immediate rise in MAP. Ten days of intrarenal angiotensin II infusion produced chronic sodium retention and a sustained elevation of MAP. Cessation of intrarenal angiotensin II infusion on Day 10 was associated with an immediate and a marked natriuresis and diuresis, and MAP fell only after several hours of fluid loss. Collectively, these data indicate that endogenous angiotensin II acts directly on the kidney to regulate sodium and water excretion and, thus, arterial pressure.

The data in this study are also consistent with several observations made in patients with Addison's disease. Our suggestion is that, due to the quantitative importance of the intrarenal effects of angiotensin II in regulating sodium excretion and, thus, arterial pressure, the control of sodium balance and arterial pressure is not critically dependent upon changes in aldosterone secretion, provided there is a minimal (sodium-replete) amount of aldosterone present in the circulating blood. In our present study, sodium balance was achieved in the adrenalectomized dogs during sodium depletion with only approximately a 50% greater increase in PRA than was observed in the intact dogs where plasma aldosterone concentration increased 14-fold. Similarly, patients with adrenal insufficiency on a fixed dosage of both mineralocorticoids and cortisol maintain sodium balance despite an inability to regulate secretion of these hormones. Additionally, patients with the rare syndrome of selective aldosterone deficiency associated with defective renin secretion present marked derangements in electrolyte metabolism and renal function. In contrast, only a minority of Addisonians with cortisol as the sole replacement therapy develop such disturbances, presumably because the renin-angiotensin system is functional. Apparently, in the absence of aldosteronism, gross disturbances in sodium balance and arterial pressure control are not observed in dog or man during sodium depletion, provided there is a minimal amount of aldosterone present, provided renal function is normal, and provided the renin-angiotensin system is intact.

In the absence of adrenals, how then can angiotensin II decrease sodium excretion, and, thus, maintain sodium balance during sodium restriction? Angiotensin II can impair the ability of the kidneys to excrete sodium by decreasing GFR, and in the present study GFR was unchanged from control levels in both intact and adrenalectomized dogs during sodium depletion. Therefore, enhanced tubular reabsorption of sodium and water must have been the primary mechanism responsible for establishing sodium balance during the 2 weeks of sodium restriction. In accordance with the known effects of angiotensin II on the renal artery of conscious, adrenalectomized, sodium-depleted dogs and observed increased sodium and water excretion. More recently, we infused the angiotensin II blocker, [Sar1, Ala8] angiotensin II, directly into
renal blood flow, and effective renal plasma flow was reduced in both intact and adrenalectomized dogs during sodium depletion and, thus, the increased filtration fraction would indicate alterations in the Starling forces across the peritubular capillaries in a direction that would favor enhanced tubular reabsorption of filtrate. In the adrenalectomized dogs, however, the reduction in effective renal plasma flow during sodium depletion and, thus the resulting increase in filtration fraction, was no greater than in the intact dogs in spite of the fact that PRA was higher in the former. Therefore, our measurements of GFR and ERPF do not support the conclusion that angiotensin II-induced changes in renal hemodynamics were more important in mediating sodium retention in the adrenalectomized than in intact dogs.

Finally, although providing no direct evidence, our data is consistent with the findings that angiotensin II exerts a direct effect on the renal tubule to increase sodium reabsorption of sodium and water. It should also be stated that in no way does our data exclude the possibility that other mechanisms unrelated to the renin-angiotensin system may have played an important contributory role in reducing renal sodium excretion in both intact and adrenalectomized dogs during sodium restriction. An obvious possibility is enhanced renal nerve activity secondary to hypovolemia, but the importance of this mechanism and others in the control of sodium excretion during chronic sodium depletion remains to be determined.

The changes in plasma electrolyte concentration which occurred in the intact and adrenalectomized dogs were expected. Aldosterone is not a primary controller of plasma sodium concentration, and accordingly, after 2 weeks of sodium depletion plasma sodium concentration was only slightly lower (3%) in the adrenalectomized than in the intact dogs. In both groups of dogs, hyponatremia during sodium depletion reflected sodium loss in excess of water loss: sodium balance was negative; water intake was fixed by intravenous infusion of 5% dextrose and, therefore, could not be decreased (the dogs drank little or no additional water); vasopressin secretion was probably elevated due to the hypovolemia, with or without attendant hypotension; and delivery of tubular fluid to the diluting segments of the distal nephron was probably decreased due to enhanced proximal reabsorption of filtrate.

Absence of aldosteronism during sodium depletion was associated with more pronounced derangements in potassium than in sodium metabolism. Although a low sodium intake attenuates the effects of aldosterone on potassium concentration, there was, nevertheless, considerably more potassium retention and an 8% greater hyperkalemia during sodium depletion in the adrenalectomized dogs than in the intact dogs where plasma aldosterone concentration increased markedly. In fact, hyperkalemia is the most prominent electrolyte disturbance in Addison's disease, although frequently a contributing factor to the hyperkalemia in this syndrome is depressed renal function. Nonetheless, in patients with hyporeninemic hypoaldosteronism, hyperkalemia is disproportionate to the degree of renal insufficiency. In addition, in the present study hyperkalemia was more severe during sodium depletion in the adrenalectomized than in the intact dogs in spite of the fact that renal function was similar in the two groups of animals. In light of the pronounced effects of aldosterone on plasma potassium concentration as shown by this study and others, and, reciprocally, in light of the marked stimulatory effects of small increases in plasma potassium concentration on aldosterone secretion, it is apparent that an important role of aldosteronism during sodium depletion is the control of plasma potassium concentration. Again, in the present study, there was a greater disturbance in potassium than sodium metabolism in dogs that were unable to secrete enhanced amounts of aldosterone during sodium depletion.

In summary, during sodium restriction, relatively small disturbances in sodium and water metabolism were observed in the adrenalectomized dogs maintained on basal amounts of aldosterone and cortisol; perturbations in potassium metabolism were more prominent. When the dogs were intact, sodium balance was achieved with a 10-fold increase in PRA and a 14-fold increase in plasma aldosterone concentration, and MAP was virtually unchanged. In the adrenalectomized dogs where plasma aldosterone concentration could not increase significantly during sodium depletion, establishment of sodium balance was associated with a 50% greater increase in PRA and a small decrease (8 mm Hg) in MAP (fig. 3). Thus, the data from the 2-week period of sodium restriction indicate that the conservation of sodium and the maintenance of arterial pressure during sodium depletion is not critically dependent upon enhanced aldosterone secretion.

Acknowledgments

The authors are grateful to Wesley C. Emfinger for his invaluable assistance with the animals, to Sheryl Holton and Marianne LaCour for their outstanding work in the radioimmunoassay laboratory, and to the Upjohn Company for generously supplying Solu-Cortef.

References

Is aldosteronism important in the maintenance of arterial blood pressure and electrolyte balance during sodium depletion?

T E Lohmeier, P R Kastner, M J Smith and A C Guyton

_Hypertension_. 1980;2:497-505
doi: 10.1161/01.HYP.2.4.497

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://hyper.ahajournals.org/content/2/4/497.citation