Evidence for a Splanchnic Sodium Input Monitor Regulating Renal Sodium Excretion in Man
Lack of Dependence upon Aldosterone

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SUMMARY Eight normal male subjects were placed on a constant 10 mEq sodium, 60 mEq potassium diet for 5 days. At 8:00 a.m. on the 4th day, the subjects were given a standard dose of 100 mEq of sodium orally or intravenously. Subjects receiving oral sodium also received 200 ml of 5% dextrose in water intravenously, and those receiving intravenous sodium also received placebo capsules orally. Water intake and posture were controlled. The subjects then returned to a free diet for 1 month and subsequently were restudied by using the opposite route of sodium administration. The subjects given the oral sodium load excreted greater quantities of sodium in their urine than those repleted intravenously. The differential natriuresis was significant as early as 2 hours after sodium loading. Plasma aldosterone concentration was similar irrespective of the route of sodium administration. Six patients with primary adrenocortical insufficiency and documented hypoaldosteronism were studied with the same protocol after 5 days of 50 mEq sodium, 60 mEq potassium intake. They also had significantly greater natriuresis after oral than intravenous sodium administration. The data suggest the presence of a splanchnic input monitor for sodium which partially regulates renal sodium excretion and is not dependent upon a turn-off mechanism for aldosterone secretion.

DIETARY sodium depletion in man is followed by rapid conservation of sodium by the kidneys.1 When man in sodium balance at a fixed level of sodium intake shifts abruptly to lower intake, urinary sodium excretion decreases exponentially. Approximately one-half of the original sodium intake is excreted within the first 24 hours of the new low dietary sodium intake, and a new balance state is achieved within 3–5 days. Early physiological adjustment to varying levels of dietary sodium intake suggests that the gastrointestinal tract may sense the quantity of sodium presented to it and contribute to the control of renal sodium excretion by unknown mechanisms. Recent studies in sodium-depleted conscious rabbits have supported this concept: gastric sodium loading produced a greater natriuresis than intravenous sodium administration.2–9 Similar differences, although more variable, have been reported for man as early as 8 hours after oral sodium loading.4

Subsequent to the discovery of the potent sodium-retaining hormone, aldosterone, in 1953,8 it became apparent that increased secretion of this hormone plays an important role in renal sodium conservation during dietary sodium restriction.8 Under these conditions, the renin-angiotensin system is an important stimulus to aldosterone secretion. Whether or not other mechanisms also increase aldosterone secretion during sodium restriction is uncertain.7,8

The purpose of our investigation was to define further the difference in renal sodium excretion after oral and intravenous sodium repletion in man. The early phase of renal sodium excretion after the two routes of sodium repletion and the role of aldosterone in mediating this response were studied.

Methods

Eight normal male volunteer subjects, from 20 to 30 years old, were studied. The subjects were placed on a constant diet containing 100 mEq of sodium, 60 mEq of potassium, and 2860 calories per day for 3 days. At the end of this time, they were placed on a constant diet containing 10 mEq of sodium, 60 mEq of potassium, and 2860 calories per day for 5 days. All meals were prepared and consumed in the research dietary facility of the Clinical Research Center, but the subjects continued their usual daily activities during each 8-day study period. Twenty-four-hour urine collections for measurement of sodium, potassium, and creatinine were obtained daily.

At 8:00 a.m. on the morning of the 6th day of the 10 mEq sodium diet, before breakfast, the subjects were given a standard dose of 100 mEq of sodium. They received this sodium load either orally in the form of sodium chloride in gelatin capsules or intravenously as 200 ml of hypertonic sodium chloride (500 mEq/liter) infused over a 10-minute period. The selection of subjects for oral or intravenous route was random. In order to equalize the volume of fluid given to the subjects, those who received their sodium load orally also received an intravenous infusion of 200 ml of 5% dextrose in water.
During the ensuing period from 8:00 a.m. to 11 p.m., the subjects maintained a constant oral water intake of 150 ml/hour and were ambulatory. After 11 p.m., no water was ingested and the subjects were supine until completion of the experiment at 8:00 a.m. the next day. Urine was collected at 1, 2, 4, 8, and 24 hours after the sodium load while the subjects continued their constant low sodium diets. Blood was collected via indwelling heparin lock for serum sodium and potassium and plasma aldosterone measurements at the same time intervals following sodium load.

After completion of this part of the study, the subjects returned to a free diet for a period of 3 weeks to 2 months. Each subject was then restudied by the same protocol except that the opposite route of sodium administration was employed. Thus, paired data on the response of all parameters measured to oral and intravenous sodium load were obtained for each subject.

Six (21- to 55-year-old) patients with documented primary adrenocortical insufficiency also were studied. These patients had markedly subnormal values for urinary 17-hydroxycorticosteroid excretion, plasma cortisol, and aldosterone concentrations basally and in response to intravenous ACTH, 40 U, over 8 hours for each of 3 consecutive days. They discontinued their 9α-fluorohydrocortisone replacement therapy 3 days prior to admission to the Clinical Research Center. On admission, they continued cortisone acetate, 25 mg, at 10:00 a.m. daily and began a constant diet containing 50 mEq of sodium and 60 mEq of potassium. After approximate sodium balance was achieved (within 3-5 days), the same protocol was repeated as for normal subjects except that urine was also collected at 4 p.m. and there was an interlude of only 48 hours between the oral and intravenous sodium load experiments.

Plasma and urinary sodium and potassium concentrations were measured by atomic emission spectrophotometry. Plasma aldosterone was measured by the radioimmunoassay of Buhler et al.9 Statistical evaluation of the data was conducted by paired Student's t-test and Wilcoxon’s signed rank test. All results are expressed as mean ± SEM.

Results

Normal Subjects

On the 3rd day of the 100 mEq sodium diet, the eight subjects were in sodium balance with a urinary sodium excretion of 103.5 ± 5.6 mEq of sodium per day, as shown in Figure 1. Within the first 24 hours of the new low sodium intake (10 mEq/day), sodium excretion decreased by 40% of the control value. During the ensuing 4 days, sodium excretion continued to decrease, but compared to each previous 24-hour period, the decrement was less on each successive day. At 5 days, approximate sodium balance was achieved with a 24-hour urine sodium excretion of 12.9 ± 1.0 mEq. At this point, their cumulative sodium deficit was 114.1 ± 23 mEq.

A comparison of the cumulative sodium excretion of the eight sodium-depleted subjects after oral and intravenous sodium load is shown in Figure 2. The control urinary sodium excretion during the 24 hours prior to sodium repletion was 10.1 ± 1.6 mEq for the subjects subsequently repleted orally and 10.5 ± 1.4 mEq for those subsequently repleted intravenously [P = not significant (NS)]. After intravenous sodium loading, urinary sodium excretion increased logarithmically. By 24 hours after
TABLE 1  Comparison of Factors which Might Influence Urinary Sodium Excretion after Oral or Intravenous Sodium Repletion

<table>
<thead>
<tr>
<th>Method of repletion</th>
<th>Oral (mEq)</th>
<th>NS</th>
<th>Intravenous (mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour urine Na</td>
<td>10.1 ± 1.6</td>
<td></td>
<td>10.5 ± 1.4</td>
</tr>
<tr>
<td>Cumulative Na deficit</td>
<td>162.6 ± 21.7</td>
<td>NS</td>
<td>130.8 ± 16.1</td>
</tr>
<tr>
<td>8hrs</td>
<td>418 ± 45</td>
<td>NS</td>
<td>343 ± 62</td>
</tr>
<tr>
<td>16hrs</td>
<td>817 ± 96</td>
<td>NS</td>
<td>857 ± 135</td>
</tr>
<tr>
<td>24hrs</td>
<td>1130 ± 108</td>
<td>NS</td>
<td>1314 ± 721</td>
</tr>
<tr>
<td>Cumulative K excretion</td>
<td>36.8 ± 3.1</td>
<td>NS</td>
<td>35.1 ± 2.7</td>
</tr>
<tr>
<td>8hrs</td>
<td>66.4 ± 6.4</td>
<td>NS</td>
<td>64.0 ± 6.6</td>
</tr>
<tr>
<td>24hrs</td>
<td>81.5 ± 7.5</td>
<td>NS</td>
<td>82.4 ± 6.4</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± se. NS = not significant.

SODIUM INPUT MONITOR/Carey

intravenous sodium repletion, cumulative sodium excretion had risen progressively to 15.5 ± 2.4 mEq. Similarly, after oral sodium repletion, cumulative urinary sodium excretion increased. At 1 hour after sodium repletion, the difference in sodium excretion between the two routes of sodium administration was not significant. However, beginning at 2 hours after sodium repletion, the subjects had significantly greater natriuresis after oral than intravenous sodium repletion: 2.0 ± 0.6 vs. 1.0 ± 0.2 mEq of sodium (P < 0.05) at 2 hours, 5.5 ± 1.3 vs. 2.9 ± 0.7 mEq (P < 0.005) at 4 hours, 12.1 ± 3.5 vs. 6.1 ± 1.4 mEq (P < 0.01) at 8 hours, and 29.4 ± 4.6 vs. 15.5 ± 2.4 mEq (P < 0.005) at 24 hours. Thus, at 24 hours the orally repleted subjects excreted approximately twice as much sodium as after intravenous repletion.

A comparison of some other factors which might influence urinary sodium excretion in this experimental protocol is shown in Table 1. There was no significant difference between the oral or intravenous routes of sodium administration in the cumulative sodium deficit or the cumulative urine volume or potassium excretion after repletion. The sodium load, whether intravenous or oral, produced no change in serum sodium or potassium concentration at 1, 2, 4, 8, 16, or 24 hours after sodium loading. No change in creatinine clearance was observed for the 24 hours after the sodium dose.

During sodium depletion, plasma aldosterone concentration rose from 5.3 ± 1.2 ng/100 ml to 33.6 ± 4.4 ng/100 ml (P < 0.001). As shown in Figure 3, control plasma aldosterone was 35.3 ± 4.5 ng/100 ml for the subjects subsequently repleted orally and 30.8 ± 5.0 ng/100 ml for subjects subsequently repleted intravenously. In response to both oral and intravenous sodium load, aldosterone decreased to less than 50% of the control value at 1 hour (P < 0.001) then rose toward control values at 4 hours (P = NS). Plasma aldosterone concentration decreased by approximately 50% at 8 hours (P < 0.01), then returned toward control values by 24 hours (P = NS). No significant difference in plasma aldosterone concentration was observed between the oral and intravenous groups at any time after sodium repletion.

Subjects with Adrenocortical Insufficiency

As shown in Figure 4, after 5 days of sodium intake (50 mEq/day), six subjects with documented primary adrenocortical insufficiency had urinary sodium excretion of 72.3 ± 9.8 mEq/24 hours. There was no significant difference in control 24-hour urine sodium excretion between the oral and intravenous groups. After oral sodium repletion, cumulative urinary sodium excretion increased logarithmically. Sodium excretion also increased after intravenous sodium repletion. At 1 hour following sodium repletion, there was no difference in sodium excretion between the oral and intravenous routes. However, similar to the results in normal subjects, subjects with adren-
Evidence in support of this hypothesis indicates that, in sodium-deficient animals or man, oral sodium loading is followed by greater natriuresis than intravenous sodium loading.\(^2\)\(^-\)\(^4\)

The present study was designed to examine the early phase of renal sodium excretion in response to oral and intravenous sodium loading in sodium-deficient man. The results show that, as early as 2 hours following oral sodium administration, a 2-fold greater natriuresis is present compared to intravenous sodium repletion. This differential natriuresis cannot be explained by differences in distention of the gut, fluid load, posture, serum sodium concentration, urinary volume, or potassium excretion because these factors were not significantly different with the two methods of sodium administration. The rapidity of the differential natriuresis with oral compared with intravenous sodium intake demonstrated in this study enhances the attractiveness of the hypothesis of a splanchnic or gastrointestinal input monitor for sodium.

According to the concepts of Straus et al.,\(^1\) the reduction in urinary sodium excretion which occurs on dietary sodium restriction is due to sodium depletion, which increases as long as output exceeds intake. In the present study, a cumulative sodium deficit of 114 mEq was required to reduce urinary sodium excretion to approximately 10 mEq/day, a new steady state value. Straus et al. stated that the new steady state total body sodium content would be the same irrespective of the rapidity with which the deficit developed. The inverse of this concept is that if sodium is administered to a sodium-deficient individual in a steady state, thus reducing the degree of deficiency, some of the administered sodium should be excreted. In the present study, it was not feasible to give physiological saline containing an equivalent amount of sodium because of the large fluid load that would have taken longer to administer than was desirable for study of the early phase of sodium excretion.

Discussion

In 1885, Carl Ludwig\(^1\(^9\)\) first reported that when man, in balance at a fixed normal dietary sodium intake, suddenly shifts to a lower sodium intake, a new steady state develops within 3–5 days in association with a lower total body sodium content. Subsequently, Straus et al.\(^1\) observed that, when the shift from normal to low sodium intake is made, renal sodium excretion decreases exponentially until urinary sodium output matches sodium intake. In man, renal sodium conservation is rapid with an approximate 60% decrease in urinary sodium excretion during the first 24 hours of low sodium diet. In other species, the decrease in urinary sodium excretion during the first day of sodium restriction is as great as 80%.\(^5\) This early decrease in renal sodium excretion in response to dietary sodium deprivation suggests that the gastrointestinal tract may monitor the quantity of sodium presented to it and in some way signal the kidneys to conserve sodium.
Similarly, other nongastrointestinal routes (such as peritoneal or subcutaneous) were not practical for these experiments in man.

The mechanism of the differential natriuresis originally was thought possibly to be related to "turn-off" of aldosterone secretion or possibly to target organ refractoriness to aldosterone. In the present study, plasma aldosterone concentrations were nearly identical, irrespective of the route of sodium administration. The plasma aldosterone concentrations were increased appropriately in the sodium-restricted state and decreased dramatically 1 hour following sodium loading, probably due to acute plasma volume expansion with suppression of aldosterone secretion, as described by Espiner et al. Four hours after sodium loading, plasma aldosterone concentrations had recovered their original values but decreased in the afternoon as a result of normal diurnal variation. Twenty-four hours after sodium loading, plasma aldosterone concentration was somewhat lower than control, possibly reflecting mild volume expansion at that time. In a previous study, plasma aldosterone values were significantly lower at 24 hours after oral compared to intravenous sodium administration. The reason for this discrepancy with the results of the present study is uncertain. The similarity of plasma concentrations of aldosterone between oral and intravenous sodium administration does not rule out differences in secretory rate and/or target organ response. However, the adrenalectomized subjects, maintained on a fixed slightly restricted sodium intake and cortisone acetate and documented to be aldosterone deficient, had a differential natriuresis similar to that of normal subjects in response to oral and intravenous sodium administration. Thus, the present study offers good evidence that in man, as in other species, the differential natriuresis is not mediated by an aldosterone-dependent mechanism.

There are few previous studies of the role of the gastrointestinal tract or splanchic circulation in the regulation of sodium excretion. From time to time, evidence has been presented that the liver may be important in the control of sodium excretion. Miles showed that a concentrated extract of liver perfusate caused sodium secretion or possibly to target organ refractoriness to aldosterone. In the present study, plasma aldosterone secretion or possibly to target organ refractoriness to aldosterone. In the present study, plasma aldosterone concentrations were increased appropriately in the sodium-restricted state and decreased dramatically 1 hour following sodium loading, probably due to acute plasma volume expansion with suppression of aldosterone secretion, as described by Espiner et al. Four hours after sodium loading, plasma aldosterone concentrations had recovered their original values but decreased in the afternoon as a result of normal diurnal variation. Twenty-four hours after sodium loading, plasma aldosterone concentration was somewhat lower than control, possibly reflecting mild volume expansion at that time. In a previous study, plasma aldosterone values were significantly lower at 24 hours after oral compared to intravenous sodium administration. The reason for this discrepancy with the results of the present study is uncertain. The similarity of plasma concentrations of aldosterone between oral and intravenous sodium administration does not rule out differences in secretory rate and/or target organ response. However, the adrenalectomized subjects, maintained on a fixed slightly restricted sodium intake and cortisone acetate and documented to be aldosterone deficient, had a differential natriuresis similar to that of normal subjects in response to oral and intravenous sodium administration. Thus, the present study offers good evidence that in man, as in other species, the differential natriuresis is not mediated by an aldosterone-dependent mechanism.

At present, the mechanism for the differential natriuresis following oral and intravenous sodium loading in man is unknown. It is possible that alteration of glomerular filtration rate, renal plasma flow, or renal vascular resistance may account for this phenomenon. These parameters of renal function were not monitored in the present study because of the large volumes of fluid required. However, gross changes in glomerular filtration rate as quantified by creatinine clearance did not occur. Other possible mechanisms include a neural reflex arising in the gut wall or direct osmotic stimulus to the liver or portal circulation. Also, the differential natriuresis could involve release of a natriuretic hormone from the gastrointestinal tract. For example, glucagon in physiological quantities can be a natriuretic hormone in experimental animals and man. Studies of these potential mechanisms should provide fruitful avenues for future investigation.

References

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