Relative Influence of Acute Sodium and Volume Depletion on Aldosterone Secretion in Nephrectomized Man

By Robert E. McCaa, John D. Bower, and Connie S. McCaa

ABSTRACT

Plasma aldosterone concentration can increase in anephric man during hemodialysis despite the lack of kidneys to produce renin. Because the metabolic clearance rate of aldosterone does not change during hemodialysis, aldosterone secretion must increase in response to sodium depletion, volume depletion, or both. This study was designed to determine the relative influence of sodium and volume depletion by ultrafiltration and hemodialysis on plasma aldosterone concentration in anephric man. Fluid (547 ml) was removed from 13 anephric subjects during 4 hours of ultrafiltration in the absence of hemodialysis. Plasma sodium and potassium concentration did not change during ultrafiltration, but total body sodium and potassium decreased. Plasma aldosterone concentration did not change significantly. Each subject was then hemodialyzed for 8 hours. In 5 subjects, an additional liter of fluid was removed without a significant change in plasma sodium concentration. Plasma aldosterone concentration also did not change in response to the reduction in fluid volume. In 8 subjects, an additional liter of fluid was removed, and plasma sodium concentration decreased from 138.5 to 130.0 mEq/liter. Plasma aldosterone concentration increased from 8.3 to 19.6 ng/100 ml plasma. Three additional anephric subjects were hemodialyzed against a dialysate containing 125.0 mEq sodium/liter for 8 hours. Plasma potassium and total body fluid volume were held constant. Plasma sodium concentration decreased from 138.5 to 125.0 mEq/liter, and plasma aldosterone concentration increased from 7.4 to 24.3 ng/100 ml plasma. These data indicate that acute sodium depletion by hemodialysis accompanied by decreased plasma sodium concentration without a change in plasma potassium concentration or fluid volume can stimulate aldosterone secretion independently of the renal renin-angiotensin system.

KEY WORDS

-fluid volume
-ultrafiltration
-hemodialysis
-cortisol
-angiotensin II
-radioimmunoassay
-ACTH
-renin

Nephrectomized human beings maintained under stable conditions on chronic intermittent hemodialysis while awaiting kidney transplantation have been used by several investigators (1-3) to study the influence of acute stimuli on aldosterone secretion in the absence of an intact renin-angiotensin system. Several studies (2-4) have indicated that the plasma aldosterone concentration is within normal physiological limits in nephrectomized man despite the lack of kidneys to produce renin. Furthermore, we have demonstrated that plasma aldosterone concentration can increase in anephric subjects in response to hemodialysis, although plasma renin activity measured at the same time is undetectable (4). Simultaneous measurements of plasma aldosterone concentration and metabolic clearance rate of aldosterone before and during hemodialysis indicate that the increase in plasma aldosterone concentration in response to hemodialysis results from an increase in the rate of aldosterone secretion rather than from a decrease in the metabolic clearance rate of aldosterone (5). The increase in aldosterone secretion observed in these studies occurs in the absence of an intact renin-angiotensin system and without a concomitant increase in plasma cortisol concentration, indicating that increased pituitary secretion of...
adrenocorticotropic hormone (ACTH) does not account for the increase in aldosterone secretion. Also, there is a decrease in plasma concentration of sodium and potassium and a reduction in body fluid volume in response to hemodialysis.

Previous studies by other investigators (6) have indicated that decreased plasma sodium concentration has a direct stimulatory effect on the adrenal gland, causing an increase in aldosterone secretion. Therefore, the present study was designed to determine, quantitatively, the relative influence of decreasing body fluid volume by ultrafiltration and hemodialysis and decreasing plasma sodium concentration by hemodialysis on plasma aldosterone concentration in nephrectomized man. In addition, the influence of decreased plasma sodium concentration per se on plasma aldosterone concentration was determined in three nephrectomized subjects in whom body fluid volume and plasma potassium concentration were held constant.

**Methods**

Thirteen nephrectomized human beings maintained on chronic intermittent hemodialysis while awaiting kidney transplantation were used in this study. Dietary sodium intake for each subject was restricted to 34 mEq/day, and dietary potassium intake was 60 mEq/day. All of the anephric subjects were normotensive; none was taking medication during the week prior to this study. Each subject reported to The Artificial Kidney Unit every 4 days for a regularly scheduled 12-hour period of hemodialysis. Each subject was required to remain supine for 1 hour before control blood samples were collected. After control blood samples were drawn, each subject was connected to the Kiil hemodialyzer via indwelling arteriovenous shunts. During the first 4 hours, fluid was removed from each subject by ultrafiltration in the absence of dialysate flow. Blood samples were collected each hour during the 4-hour period of ultrafiltration. At the end of 4 hours of ultrafiltration, the volume of ultrafiltrate collected was measured and a portion of the ultrafiltrate was used for determination of sodium and potassium concentration. Ten ml of the ultrafiltrate was frozen for subsequent analysis of aldosterone and cortisol concentration. After 4 hours of ultrafiltration, dialysate flow was started and each subject was hemodialyzed for 8 hours against a dialysate containing 130.0 mEq sodium/liter and 4.0 mEq potassium/liter. An infusion of potassium chloride was maintained throughout the study to prevent variation in plasma potassium concentration during the experiment. An infusion of 5% glucose solution was used to maintain constant weight throughout the experiment. Blood samples were collected at 4 hours and at 8 hours for determination of aldosterone and cortisol concentration.

At the end of 8 hours on the experimental dialysate, the dialysate was changed and the subject was hemodialyzed for 4 hours against a dialysate containing 130.0 mEq sodium/liter and 3.0 mEq potassium/liter. Blood samples were collected before the subject was disconnected from the Kiil hemodialyzer. All blood samples were stored as described previously until determination of plasma aldosterone and cortisol could be performed.

**Plasma Electrolyte Determination.**—A portion of each blood sample collected throughout the experiment was used for the determination of plasma sodium and potassium concentration. Plasma electrolyte concentrations were determined using a flame photometer (Instrumentation Laboratory, Inc., model 343).

**Plasma Aldosterone Determination.**—Plasma aldosterone concentrations were determined using a rapid radioimmunoassay procedure for aldosterone previously described by McCaa et al. (4).

**Results**

The results of changes in body weight and plasma concentrations of sodium, potassium, aldosterone, and cortisol observed in 13 nephrectomized human subjects in response to 4 hours of ultrafiltration followed by 8 hours of ultrafiltration and hemodialysis are summarized in Table 1. After 4 hours of ultrafiltration in the absence of dialysate flow, there was an average weight loss of 0.6 kg. Fluid loss (ultrafiltrate) averaged $547 \pm 205$ (SE) ml in these subjects. Plasma concentration of sodium and potassium did not change during 4 hours of ultrafiltration; however, total body sodium and potassium decreased during this period since the concentration of sodium and potassium in the ultrafiltrate collected from each subject was the...
TABLE 1

Summary of Changes in Body Fluid and Plasma Concentrations of Sodium, Potassium, Aldosterone, and Cortisol in 13 Nephrectomized Subjects in Response to 4 Hours of Ultrafiltration followed by 8 Hours of Hemodialysis

<table>
<thead>
<tr>
<th>Status of subjects</th>
<th>Plasma sodium (mEq/liter)</th>
<th>Plasma potassium (mEq/liter)</th>
<th>Plasma aldosterone (ng/100 ml)</th>
<th>Plasma cortisol (µg/100 ml)</th>
<th>Decrease in body fluid (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control: immediately before hemodialysis; fluid and electrolyte excess</td>
<td>135.0 ± 1.3</td>
<td>4.2 ± 0.1</td>
<td>9.4 ± 1.4</td>
<td>13.4 ± 1.3</td>
<td>547 ± 205*</td>
</tr>
<tr>
<td>After 4 hours of ultrafiltration with removal of isotonic fluid</td>
<td>135.0 ± 1.3</td>
<td>4.2 ± 0.1</td>
<td>11.5 ± 1.3</td>
<td>10.1 ± 2.2</td>
<td>547 ± 205*</td>
</tr>
<tr>
<td>After 8 hours of hemodialysis</td>
<td>131.0 ± 0.9*</td>
<td>3.2 ± 0.1*</td>
<td>16.0 ± 3.4*</td>
<td>11.3 ± 2.2</td>
<td>1010 ± 258*</td>
</tr>
<tr>
<td>Total change after ultrafiltration and hemodialysis</td>
<td>-4.0 ± 1.1</td>
<td>-1.0 ± 0.1</td>
<td>6.6 ± 2.3</td>
<td>-2.1 ± 1.9</td>
<td>-157 ± 380</td>
</tr>
</tbody>
</table>

*Significant difference from control (P < 0.05).
Values are means ± SE.

same as the plasma concentration in that subject. Plasma aldosterone concentration averaged 9.4 ± 1.4 ng/100 ml plasma before ultrafiltration and 11.5 ± 1.3 ng/100 ml plasma after ultrafiltration (not statistically significant [NS], P > 0.05); plasma cortisol concentration averaged 13.4 ± 1.3 µg/100 ml plasma before ultrafiltration and 10.1 ± 2.2 µg/100 ml plasma after ultrafiltration (NS, P > 0.05). During the next 8 hours, the subjects were hemodialyzed against a dialysate containing 130.0 mEq sodium/liter and 3.0 mEq potassium/liter. There was an additional average weight loss of 1.0 kg. In response to 8 hours of ultrafiltration and hemodialysis, plasma sodium concentration decreased from 135.0 ± 1.3 mEq/liter to 131.0 ± 0.9 mEq/liter (P < 0.05), and plasma potassium decreased from 4.2 ± 0.1 mEq/liter to 3.2 ± 0.1 mEq/liter (P < 0.05), resulting in an increase in the ratio of sodium to potassium from 32.8 to 40.5. Plasma aldosterone concentration averaged 11.5 ± 1.3 ng/100 ml plasma before hemodialysis and 16.0 ± 3.4 ng/100 ml plasma (NS, P > 0.05) after hemodialysis, and plasma cortisol concentration averaged 10.1 ± 2.2 µg/100 ml plasma before hemodialysis and 11.3 ± 2.2 µg/100 ml plasma (NS, P > 0.05) after hemodialysis.

The plasma aldosterone concentration at the end of a 4-hour period of ultrafiltration and an 8-hour period of ultrafiltration and hemodialysis was significantly elevated (P < 0.05) compared with the plasma aldosterone concentration in control samples before ultrafiltration. The subjects were divided into two groups. The criteria used for this division was the concentration of plasma sodium determined immediately before ultrafiltration and hemodialysis. Group 1 included five subjects who began the study with plasma sodium concentrations averaging 131.5 mEq/liter. Because the sodium concentration in the dialysate was 130.0 mEq/liter, plasma sodium concentration did not decrease in this group in response to hemodialysis. Group 2 included eight subjects who began the study with plasma sodium concentrations averaging 138.5 mEq/liter. Plasma sodium concentration was significantly decreased by hemodialysis in this group (P < 0.01).

Effect of Volume Reduction on Plasma Aldosterone Concentration in Nephrectomized Subjects.—The response of plasma aldosterone concentration to 4 hours of ultrafiltration and 8 hours of hemodialysis in five anephric subjects is illustrated in Figure 1. Plasma sodium concentration averaged 131.5 ± 1.5 mEq/liter in these subjects before ultrafiltration and hemodialysis. After 4 hours of ultrafiltration, an average of 605 ± 196 ml of ultrafiltrate had been collected. Plasma concentration of sodium and potassium did not change during the 4-hour period of ultrafiltration, but total body sodium and potassium decreased since the concentration of sodium and potassium in the ultrafiltrate was the same as the plasma concentration of sodium and potassium. Plasma aldosterone concentration did not increase significantly in response to removal of fluid by ultrafiltration (9.4 ± 2.5 ng/100 ml plasma to 11.2 ± 3.6 ng/100 ml plasma, NS, P > 0.10). In addition to the fluid removed by ultrafiltration, an additional loss of 895 ± 210 ml of fluid occurred during 8 hours of hemodialysis. After 8 hours of hemodialysis, plasma sodium concentration remained unchanged at 131.0 ± 1.1 mEq/liter, and plasma potassium concentration decreased from 4.6 ± 0.3 mEq/liter to 3.4 ± 0.3 mEq/liter. The decrease in plasma potassium concentration resulted in a significant

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increase in the ratio of sodium to potassium. Plasma aldosterone concentration did not change significantly in response to volume reduction (9.4 ± 2.5 ng/100 ml plasma to 10.9 ± 2.1 ng/100 ml plasma, NS, P > 0.10). Plasma cortisol concentration averaged 13.4 ± 3.4 µg/100 ml plasma before ultrafiltration and 8.6 ± 4.2 µg/100 ml plasma (NS, P > 0.10) after ultrafiltration and hemodialysis.

Effect of Volume Reduction and Decreased Plasma Sodium Concentration on Plasma Aldosterone Concentration in Nephrectomized Subjects.—The response of plasma aldosterone concentration to 4 hours of ultrafiltration and 8 hours of ultrafiltration and hemodialysis in eight anephric subjects is illustrated in Figure 2. Plasma sodium concentration averaged 138.5 ± 1.5 mEq/liter in these subjects before ultrafiltration and hemodialysis. After 4 hours of ultrafiltration, an average of 511 ± 185 ml of ultrafiltrate had been collected. Plasma sodium and potassium concentration did not change during the period of ultrafiltration, but total body sodium and potassium decreased because the concentration of sodium and potassium in the ultrafiltrate was the same as the plasma concentration of sodium and potassium. Plasma aldosterone concentration was not significantly altered (8.3 ± 2.1 ng/100 ml plasma to 13.1 ± 3.2 ng/100 ml plasma, NS, P > 0.10) in response to 4 hours of ultrafiltration. After 4 hours of ultrafiltration, dialysate flow was started and these subjects were hemodialyzed for 8 hours against a dialysate containing 130.0 mEq sodium/liter and 3.0 mEq potassium/liter. After 8 hours of ultrafiltration and hemodialysis, plasma sodium concentration decreased from 138.5 ± 1.7 mEq/liter to 131.0 ± 1.8 mEq/liter and plasma potassium concentration decreased from 4.3 ± 0.1 mEq/liter to 3.1 ± 0.1 mEq/liter. The removal of sodium and potassium by hemodialysis resulted in an increase in the ratio of sodium to potassium from 32.2 to 42.3. Plasma aldosterone concentration increased from 13.1 ± 3.2 ng/100 ml plasma to 19.2 ± 3.4 ng/100 ml plasma (P < 0.05) in response to 8 hours of hemodialysis. Plasma cortisol concentration averaged 12.4 ± 3.5 µg/100 ml plasma before ultrafiltration and hemodialysis and 12.0 ± 4.1 µg/100 ml plasma after hemodialysis. An additional 1249 ± 306 ml of fluid was removed from these subjects during the 8-hour period of hemodialysis.

Effect of Decreased Plasma Sodium Concentration Per Se on Plasma Aldosterone Concentration in Nephrectomized Subjects.—The effect of decreasing plasma sodium concentration per se on plasma...
aldosterone concentration in nephrectomized subjects is illustrated in Figure 3. The plasma sodium concentration was lowered from 138.5 ± 1.0 to 125.0 ± 1.0 mEq/liter in these subjects by hemodialysis against a dialysate containing 125.0 mEq sodium/liter and 4.0 mEq potassium/liter. Plasma potassium concentration and body weight were monitored continuously during the study. Variation in body weight was prevented by infusion of 5% glucose solution. Plasma potassium concentration was maintained during hemodialysis by adjusting the dialysate potassium concentration to 4.0 mEq/liter and by infusing potassium chloride during the study. After 8 hours of hemodialysis, plasma sodium concentration decreased from 138.5 ± 1.0 mEq/liter to 125.0 ± 1.0 mEq/liter (P < 0.001). Plasma aldosterone concentration increased from 7.4 ± 1.3 ng/100 ml plasma in the predialysis samples to 24.3 ± 3.5 ng/100 ml plasma in the 8-hour samples. At the end of 8 hours, the experimental dialysate was discontinued and the subjects were hemodialyzed for 4 hours against a dialysate containing 130.0 mEq sodium/liter and 3.0 mEq potassium/liter. At the end of 4 hours, plasma sodium concentration averaged 130.0 ± 1.0 mEq/liter, plasma potassium concentration averaged 3.3 ± 0.5 mEq/liter, and plasma aldosterone concentration remained elevated above control levels, averaging 19.0 ± 1.5 ng/100 ml plasma. Plasma cortisol concentration averaged 7.8 µg/100 ml plasma in these three subjects before hemodialysis and 9.2 µg/100 ml plasma after 8 hours of hemodialysis (NS, P > 0.05). In the postdialysis samples, plasma cortisol concentration averaged 9.0 µg/100 ml plasma.

Relationship between Plasma Concentration of Sodium and Aldosterone in Nephrectomized Subjects.—Further evidence that decreased serum sodium concentration is a factor in the acute stimulation of aldosterone secretion can be obtained by comparing changes in plasma sodium concentration with changes in plasma aldosterone concentration observed in three anephric subjects during hemodialysis. Figure 4 illustrates the relationship between the plasma concentration of sodium and aldosterone in nephrectomized subjects. In this figure, plasma sodium concentration was lowered by hemodialysis while fluid volume and plasma potassium concentration were held constant. Vertical and horizontal lines indicate the mean ± se, and N indicates the number of subjects studied.
sodium and that of aldosterone in three nephrectomized subjects. Plasma sodium concentration was lowered from 138.5 to 125.0 mEq/liter by hemodialysis while plasma potassium concentration and total body fluid volume were maintained constant. Plasma aldosterone concentration increased threefold in response to decreasing plasma sodium concentration. Plasma cortisol concentration did not increase significantly during hemodialysis.

Discussion

Despite intensive investigations during the past 15 years, considerable controversy still exists concerning the processes by which the aldosterone control mechanisms are evoked, the interrelationships between the control mechanisms, and the mode of action of each on the adrenal production of aldosterone. The regulatory mechanism that determines the rate of aldosterone secretion is influenced by a number of factors. In addition to the four known control mechanisms, the renal renin-angiotensin system, the plasma concentration of sodium, the plasma concentration of potassium, and the pituitary secretion of ACTH, experimental evidence has suggested that some unknown factor or undefined mechanism (8-10) may also be involved in the regulation of aldosterone secretion.

The renal renin-angiotensin system is generally considered to be the primary mechanism responsible for increasing the rate of aldosterone secretion and plasma aldosterone concentration in response to upright posture and sodium and volume depletion. Recent studies from our laboratory (11) and studies by Cooke et al. (12) have demonstrated that plasma aldosterone concentration does not increase significantly in response to postural variation in nephrectomized human subjects, but plasma aldosterone concentration and plasma renin activity increase in response to upright posture in kidney allograft recipients. These observations indicate that an intact renal renin-angiotensin system is necessary for an increase in aldosterone secretion in response to upright posture. Whether decreased plasma sodium concentration per se can stimulate aldosterone secretion in human subjects in the absence of an intact renal renin-angiotensin system as has been observed in experimental animals (6) is less certain.

The complications involved in controlling several interrelated variables have made it difficult to separate the influence of sodium concentration from the influence of fluid volume on aldosterone secretion in intact man or experimental animals. Alterations in body sodium content and fluid volume are usually in the same direction. Sodium depletion, a potent stimulus of aldosterone secretion, reduces the amount of extracellular sodium and diminishes the extracellular fluid volume. Yet, plasma sodium concentration is only slightly altered in response to sodium depletion. Hyponatremia may result in increased aldosterone secretion in intact man, but under usual experimental conditions its effect is masked by the suppressant effect of volume expansion that occurs during water loading or administration of vasopressin. Bartter et al. (13) demonstrated that aldosterone secretion decreased when extracellular fluid volume increased regardless of whether plasma sodium concentration increased, remained unchanged, or decreased and that aldosterone secretion increased when extracellular fluid volume decreased regardless of whether serum sodium concentration remained unchanged or increased.

In the present study, we have determined the influence of reduction in body fluid volume and plasma sodium concentration by ultrafiltration and hemodialysis on plasma aldosterone concentration in nephrectomized human subjects. Our results indicate that removal of approximately 600 ml of fluid (ultrafiltrate) by ultrafiltration fails to significantly increase the plasma aldosterone concentration. In five anephric subjects used in this study, hemodialysis resulted in the removal of an additional 895 ml of fluid without a significant increase in plasma aldosterone concentration. In addition to the removal of fluid by ultrafiltration, total body sodium and potassium decreased in all subjects during ultrafiltration and hemodialysis. Our results suggest that volume depletion of this magnitude (1500 ml) has little effect on aldosterone secretion in the absence of the renal renin-angiotensin system. In eight anephric human subjects, plasma aldosterone concentration increased an average of 4 ng/100 ml plasma in response to 4 hours of ultrafiltration that resulted in a decrease in total body fluid volume of 511 ml. Although the increase in plasma aldosterone concentration in response to ultrafiltration was consistent in each of the 8 subjects, it did not represent a statistically significant increase from control levels. Perhaps the difference would have been significant had a larger number of subjects been used in the study. An additional 8 hours of ultrafiltration and hemodialysis, resulting in the removal of another 1200 ml of fluid and a decrease in plasma sodium concentration of 8.0 mEq/liter, caused a significant increase.

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in plasma aldosterone concentration. These data suggest that acute reduction in plasma sodium concentration by hemodialysis can stimulate aldosterone secretion in anephric subjects and that this response is not mediated by the renal renin-angiotensin system. However, it was difficult to ascertain whether hyponatremia alone had a stimulatory effect on aldosterone secretion, since it was associated with a further 1200-ml reduction in fluid volume.

Total body fluid volume and plasma potassium concentration were maintained constant in an additional group of nephrectomized subjects while plasma sodium concentration was lowered from 138.5 mEq/liter to 125.0 mEq/liter by hemodialysis. Plasma aldosterone concentration increased markedly in these three anephric subjects in the absence of a significant increase in plasma cortisol concentration, which indicates that increased pituitary secretion of ACTH does not account for the increase in aldosterone secretion. These subjects were carefully monitored to ensure that plasma potassium concentration did not change during the study. At the beginning of hemodialysis, the plasma concentration in the subjects was above the potassium concentration in the dialysate (4.0 mEq/liter). The increase in plasma aldosterone concentration was independent of any increase in plasma potassium concentration which actually decreased slightly (0.5 mEq/liter).

The increase in plasma aldosterone concentration observed in nephrectomized human subjects in response to acute reduction in plasma sodium concentration apparently is transient. In a previous study (1), we observed that the plasma aldosterone concentration decreased within 24 hours after hemodialysis, although plasma sodium concentration did not change significantly. In addition, the increase in plasma aldosterone concentration observed in the present study may be correlated more closely with the rate of decrease in plasma sodium concentration than it is with the plasma sodium concentration alone.

Several investigators (14-17) have used in vitro models to study the influence of various factors known to stimulate adrenal steroidogenesis. In vitro stimulation of aldosterone biosynthesis by ACTH, angiotensin II, increased potassium concentration, and decreased sodium concentration has been observed in rat adrenal tissue (14) and beef adrenal tissue (17). Although relatively small changes in potassium concentration in the incubation medium significantly increase aldosterone production, marked decreases in sodium concentration in the incubation medium are either ineffective or produce only small increases in aldosterone production.

Other investigators have also observed the influence of alterations in plasma sodium concentration on aldosterone secretion in experimental animals and man. Davis et al. (6) have demonstrated that an infusion of 5% glucose solution into the arterial supply of isolated adrenals in hypophysectomized, nephrectomized dogs, lowering local plasma sodium concentration by 20 mEq/liter, results in a significant increase in aldosterone secretion. Blair-West et al. (18) have demonstrated that local alterations in sodium and potassium within physiological ranges in adrenal arterial blood of sheep with adrenal autotransplants to the neck significantly influence aldosterone secretion. In anephric man, Bayard et al. (2) have observed no correlation between serum sodium concentration and plasma aldosterone concentration on the first, third, and fourth days after hemodialysis. In a preliminary communication, Sanders et al. (19) have reported that dietary sodium restriction of anephric subjects causes a four- to fivefold increase in the estimated aldosterone production rate. These studies, together with the present study, suggest that an acute decrease in plasma sodium concentration alone or in association with volume reduction may acutely stimulate aldosterone secretion in nephrectomized man.

In conclusion, this study demonstrates several facts that will be significant in the final understanding of the regulation of aldosterone secretion. First, reduction in fluid volume fails to stimulate aldosterone secretion in the absence of an intact renal renin-angiotensin system unless the decrease in fluid volume is accompanied by a decrease in plasma sodium concentration. Second, a reduction in plasma sodium concentration without a significant change in fluid volume, plasma potassium concentration, or pituitary secretion of ACTH can stimulate aldosterone secretion in the absence of a functional renal renin-angiotensin system. Finally, although sodium concentration has an alternate stimulatory pathway to the adrenal gland through some mechanism that excludes the renal renin-angiotensin system, whether this mechanism is due only to a direct stimulatory effect of decreased sodium concentration on the zona glomerulosa (6) or is, in addition, mediated by some undefined factor (9, 10) remains to be determined.
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References


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