Observations on the Mechanism of Decreased Tubular Reabsorption of Sodium and Water during Saline Loading *

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It has been demonstrated by several recent studies that the regulation of sodium excretion involves factors other than the total filtered load of sodium and the renal tubular effects of mineralocorticoids. Contrary to earlier suggestions that an increase in the filtered load of sodium may be sufficient to account for the natriuresis of saline loading in the dog, de Wardener, Mills, Chapman, and Hayter (1) reported that the administration of saline to dogs receiving an exogenous mineralocorticoid results in an increased excretion of sodium that is not necessarily accompanied by an increased glomerular filtration rate. On the basis of this and other considerations, these authors suggested that natriuresis resulting from saline loading may be due largely to some unidentified circulating factor that affects tubular reabsorption. Similar observations that saline loading may result in natriuresis without a spontaneous increase in the filtered load of sodium have been made in this laboratory (2). Levinsky and Lalone (3), Blythe and Welt (4), and Rector, Van Giesen, Kiil, and Seldin (5) have demonstrated that hemodynamically induced reductions in the filtered load of sodium do not abolish the natriuresis of isotonic (3, 5) or hypertonic (4) saline loading. Thus, several recent investigations are consistent with the view that the excretion of sodium may be regulated in part by yet unidentified factors that alter net tubular reabsorption.

It was the purpose of the present studies to determine if specific changes in urinary composition may be associated with saline loading, under conditions of controlled urine flow. When the diuretic response to saline loading was prevented in one kidney by ureteral or aortic constriction, a clear effect of the saline load was evident, despite no change in the rate of urine flow. In hypopinic animals receiving vasopressin, saline loading with a constant urine flow was associated with decreased urinary osmolality, and urinary electrolyte concentrations (when initially low) were increased. These changes occurred as glomerular filtration rate decreased. The present results are consistent with the concept that saline loading in the dog results in decreased tubular reabsorption of electrolyte through a mechanism that also affects the urinary concentrating capacity.

Methods

Mongrel dogs, ranging in weight from 12.5 to 15.5 kg, received no food for 24 hours and no water for 48 hours before study. Twelve to 16 hours before experiment, the animals received by intramuscular injection 5 U of vasopressin, and 10 mg of desoxycorticosterone acetate (DOCA). In four experiments, additional injections of vasopressin and desoxycorticosterone were administered 2 hours before experimental measurements were begun. Under pentobarbital anesthesia each ureter was exposed retroperitoneally, and a cannula was tied tightly into each renal pelvis. In three experiments umbilical tape was placed around the aorta, above the left and below the right renal artery. The ends of this tape were carried out of the incision through a plastic tube, which allowed regulated and reversible constriction of the aorta between the renal arteries. A minimum of 45 minutes was allowed before beginning experimental measurements. Two hours before collections a constant infusion of saline was begun at 0.25 to 0.60 ml per minute. This contained creatinine and p-aminohippurate (PAH) in amounts necessary for clearance determinations. This maintenance infusion was acidified to pH 5.5 and delivered vasopressin at a rate of 50 to 125 mU per kg per hour and desoxycorticosterone at 20 μg per minute. Blood was collected into heparinized syringes at the midpoint of urine collections.

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In sixteen experiments, urine flow from one kidney during saline loading was controlled either by ureteral constriction or by constriction of the aorta between the renal arteries. In eleven experiments the effects of ureteral constriction were observed before saline loading, and in two experiments the effects of aortic constriction were observed before saline loading. To permit observations at varying rates of solute excretion and at low urinary electrolyte concentrations, a constant infusion of 15% mannitol in 50 mM Ringer solution was infused at 0.5 to 2.0 ml per minute in some experiments. These experimental designs are outlined in Table I.

Saline loading was accomplished by infusion of 1,000 to 1,750 ml of a modified Ringer's solution (Na, 140 or 145; K, 3.5; Cl, 128.5; and HCO₃, 15 or 20 mEq per L). After loading was complete, this infusion was continued at 10 to 15 ml per minute. This solution contained creatinine, PAH, and (in experiments employing mannitol) mannitol in amounts estimated to be the plasma concentrations of these substances. At the same moment the loading infusion was begun, adjustment of the ureteral or aortic constriction was initiated and continued during a 15- to 20-minute period so as never to stop the flow.

### Table I

<table>
<thead>
<tr>
<th>Exp’t</th>
<th>Control of urine flow</th>
<th>Ureteral constriction</th>
<th>Aortic constriction</th>
<th>15% mannitol infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V (ml/min)</td>
<td>GFR (ml/min)</td>
<td>C₉ (mEq/L)</td>
<td>Osmolarity (mOsm/kg)</td>
</tr>
<tr>
<td>13</td>
<td>40-60</td>
<td>0.4 ± 0.3</td>
<td>12 ± 3</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>60-80</td>
<td>0.4 ± 0.2</td>
<td>0.3 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>1.1 ± 0.1</td>
</tr>
</tbody>
</table>

### Table II

<table>
<thead>
<tr>
<th>Exp’t</th>
<th>V (ml/min)</th>
<th>GFR (ml/min)</th>
<th>C₉ (mEq/L)</th>
<th>Osmolarity (mOsm/kg)</th>
<th>Urea (mg/dl)</th>
<th>Sodium (mEq/L)</th>
<th>Chloride (mEq/L)</th>
<th>Plasma Osmality</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-185</td>
<td>5.0 ± 2.0</td>
<td>43 ± 7</td>
<td>1.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>5 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>195-205</td>
<td>4.5 ± 2.7</td>
<td>45 ± 0</td>
<td>1.1 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>1.3 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>5 ± 1</td>
<td>2 ± 1</td>
</tr>
</tbody>
</table>

### Footnotes

*V = urine flow; GFR = glomerular filtration rate; C₉ = para-aminohippurate clearance; R = right; L = left.
†15% mannitol in 50 mM sodium chloride infused at 2.0 ml per minute throughout this experiment.
‡13% mannitol in 50 mM sodium chloride infused at 0.5 ml per minute throughout this experiment.
This allowed comparison of the urinary composition at similar rates of urine flow, with and without ureteral constriction, and in the absence of saline loading.

Glomerular filtration rate was measured by the clearance of exogenous creatinine (6), and PAH was measured by a modification of the method of Smith, Finkelstein, Aliminoasa, Crawford, and Graber (7). Sodium and potassium were measured by internal standard flame photometry, chloride by amperometric titration (8), urea by a modification of the method of Fawcett and Scott (9), and osmolality by the freezing point depression.

**Results**

In sixteen experiments urine flow was kept at or near control rates by ureteral or aortic constriction during saline loading. The results of representative experiments are given in Table II. While urine flow was nearly constant in one kidney, the contralateral kidney underwent a diuretic response to the infusion of saline (Table II). In the experimental kidney, saline loading was associated with a fall in urine osmolality \(^3\) in every experiment, despite little or no change in urine flow (Figure 1). This was true both in experiments with relatively high control rates of solute (mannitol) excretion (experiments 1 through 9) and in those with relatively low control rates of solute excretion (experiments 10 through 16). Although the decreases in osmolality were associated with decreases in the concentration of urea, the major decrease was in the concentration of nonurea solute (Table II). Glomerular filtration was reduced 5 to 62% (average, 27%) during saline loading, when the flow of urine was little changed from control (Figure 1). At the same time glomerular filtration in the contralateral kidneys undergoing diuresis increased by an average of 13%.

In four experiments in which the urinary concentrations of electrolytes were high during the preloading control periods (experiment 13, Table II), the concentrations of sodium and chloride in the

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\(^3\)The urinary osmolalities observed in these animals before saline loading and during mannitol infusion were in most instances distinctly lower than those expected in the normal unanesthetized hydropenic dog. The influence of anesthesia and the surgical procedures on these control values cannot be assessed. However, maximal effects of hydropenia and vasopressin must have been present, and the conclusions based on the qualitative changes observed in these experiments would be independent of the exact degree of urinary hypertonicity as long as a maximal and constant permeability of the collecting duct is assumed.
urine decreased as urinary osmolality fell during saline loading. In experiments in which urinary electrolyte comprised a smaller fraction of the total urinary solute, electrolyte concentrations were usually increased during saline loading, despite decreases in urinary osmolality and little or no change in urine flow (Table II, Figure 2).

In order to determine whether the kidney was able to reduce the urinary concentration of electrolyte to minimal values during saline loading, additional ureteral constriction was applied in two experiments to reduce urine flow approximately 50%. The concentration of sodium promptly fell to 3 and 4 mEq per L in the two experiments, and this fall in the concentration of sodium was accompanied by a fall in the concentrations of chloride and potassium. Thus, the presence of saline loading did not prevent the attainment of minimal urinary electrolyte concentrations when the flow of urine was slowed sufficiently.

Since it was not possible to control the flow of urine at precisely the control rates in all of the above experiments, the changes in urinary sodium concentration and osmolality have been compared to the changes in total solute excretion (osmolal clearance) in Figures 2 and 3. In the control experiments in which urine flow was reduced by ureteral or aortic constriction, before saline loading, urinary osmolality increased, and urinary sodium concentration decreased, as osmolal clearance was decreased. In contrast, similar decreases in osmolal clearance during saline loading were associated with decreases in urinary osmolality in all experiments, and in most experiments (in the presence of mannitol) urinary sodium concentration increased (Figure 2).

When the ureteral or aortic constriction was released during saline loading, the excretion of sodium and water and the glomerular filtration rate increased immediately to values approaching those of the contralateral kidney undergoing diure-
During the periods of control ureteral or aortic constriction (before saline loading) shown in Figures 1, 2, and 3, urine flow was reduced to values ranging from 35 to 56% of preconstriction values, whereas with similar constriction during saline loading urine flow was intentionally kept near the preconstriction value. Although under the two conditions the changes in urinary osmolality and sodium concentration were qualitatively opposite with similar decreases in glomerular filtration and osmolar clearance (Figures 1 and 2), it appeared necessary to establish whether ureteral constriction in the absence of saline loading, and without a reduction in urine flow, also would be associated with changes in osmolality and electrolyte concentration opposite to those observed during saline loading, and without a reduction in urine flow. In three experiments frequent collection periods were made during increasing hypertonic mannitol diuresis. The flow of urine was then reduced by ureteral constriction to some lower value observed during the increasing diuresis. This allowed comparison of glomerular filtration and urinary composition at equal rates of urine flow, with and without ureteral constriction. In the presence of ureteral constriction glomerular filtration was reduced 20, 31, and 36% (reductions entirely comparable to those observed during saline loading with controlled urine flow). At the same time urinary sodium and chloride concentrations were strikingly reduced, and urinary osmolality (and urine/plasma osmolality) was increased to the same values observed at the lower urine flow during the increasing diuresis before ureteral constriction. Details of one of these control experiments are given in Table III. Thus, reductions in glomerular filtration by ureteral constriction in the absence of saline loading produced changes in osmolality and electrolyte concentrations qualitatively opposite to those observed during saline loading, even when the same rates of urine flow are compared in both situations.

**Discussion**

The observations that glomerular filtration may not spontaneously increase during saline diuresis...
(1, 2), and that hemodynamically induced reductions in glomerular filtration may not abolish the natriuresis of saline loading (3–5), provide strong evidence that saline loading in the normal dog is associated with a decrease in the net tubular reabsorption of sodium, which is not prevented by the administration of mineralocorticoids (1–3, 5). The present studies provide additional evidence that expansion of the extracellular volume by saline infusion decreases tubular reabsorption, since in the present experiments sodium excretion increased during saline loading as urinary sodium concentrations increased in the presence of a reduced glomerular filtration rate and unchanged flow. In addition, striking natriuresis occurred without an increased filtered load of sodium as ureteral constrictions were partially released during saline loading. The present studies also demonstrate that a decrease in the reabsorption of water accompanies the decreased reabsorption of sodium, since urine volumes were kept constant as the total filtered volume was decreased. The most consistent change produced by saline loading (as urine flow was kept constant) was a decrease in urinary osmolality. Regardless of the control osmolality, the concentration of total solute, as well as nonurea solute, decreased during saline loading, despite no increase in urine volume or total solute excretion. When urinary sodium concentrations were initially high, saline loading with constant urine flow was associated with a fall in sodium concentration (and sodium excretion) as osmolality decreased. When electrolyte comprised a smaller fraction of urinary solute (during mannitol diuresis), the fall in urinary osmolality was accompanied by an increased concentration of sodium and an increased excretion of sodium when urine flow was constant during saline loading. These changes occurred despite pretreatment with, and the constant infusion of, vasopressin and desoxycorticosterone. Reduction of glomerular filtration rate by ureteral or aortic constriction in the absence of saline loading was always associated with increased urinary osmolality and decreased urinary electrolyte concentrations, as others have previously reported (10–13). Even when reductions in glomerular filtration were produced by ureteral constriction during increasing mannitol diuresis, electrolyte concentrations were reduced and osmolality was not decreased when comparison was made with similar rates of urine flow before ureteral constriction.

On the basis of the present observations it may be suggested that the decreased net tubular reab-

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**TABLE III**

*Effects of ureteral constriction during mannitol diuresis on urinary composition*

<table>
<thead>
<tr>
<th>Time</th>
<th>V ml/min</th>
<th>GFR ml/min</th>
<th>Urine Osmolality mOsm/kg</th>
<th>Urea mmol/L</th>
<th>Sodium mEq/L</th>
<th>Chloride mEq/L</th>
<th>Plasma Osmolality mOsm/kg</th>
<th>Sodium mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–70</td>
<td></td>
<td></td>
<td>15% mannitol in 50 mM sodium chloride, 1 ml per minute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.58</td>
<td>30</td>
<td>633</td>
<td>56</td>
<td>34</td>
<td>34</td>
<td>331</td>
<td>149</td>
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<tr>
<td>10–20</td>
<td>1.90</td>
<td>28</td>
<td>600</td>
<td>48</td>
<td>35</td>
<td>35</td>
<td>334</td>
<td>147</td>
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<tr>
<td>20</td>
<td>2.2</td>
<td>28</td>
<td>579</td>
<td>40</td>
<td>35</td>
<td>37</td>
<td>339</td>
<td>144</td>
</tr>
<tr>
<td>30–40</td>
<td>2.4</td>
<td>27</td>
<td>573</td>
<td>35</td>
<td>35</td>
<td>33</td>
<td>340</td>
<td>143</td>
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<tr>
<td>84–94</td>
<td>3.3</td>
<td>27</td>
<td>555</td>
<td>25</td>
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<td>357</td>
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<tr>
<td>94–108</td>
<td>2.9</td>
<td>24</td>
<td>564</td>
<td>28</td>
<td>28</td>
<td>30</td>
<td>357</td>
<td>149</td>
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<tr>
<td>108–120</td>
<td>3.0</td>
<td>25</td>
<td>588</td>
<td>30</td>
<td>17</td>
<td>19</td>
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<td>120</td>
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</tr>
<tr>
<td>120–130</td>
<td>2.2</td>
<td>19</td>
<td>600</td>
<td>29</td>
<td>9</td>
<td>11</td>
<td>359</td>
<td>143</td>
</tr>
<tr>
<td>130–140</td>
<td>2.0</td>
<td>18</td>
<td>606</td>
<td>28</td>
<td>7</td>
<td>10</td>
<td>360</td>
<td>144</td>
</tr>
</tbody>
</table>

* Values shown are those from the left kidney only.
sorption of sodium, chloride, and water which accompanies extracellular volume expansion in the dog occurs through a mechanism that also decreases the ability to concentrate the urine. Under the conditions of the present experiments, the decreases in urinary osmolality cannot be attributed to either a decreased availability of vasopression or to an increased total solute excretion. It also appears unlikely that the availability of sodium reaching the transport site of the ascending limb of Henle's loop limited the concentrating capacity in the present studies, since urinary sodium concentration and sodium excretion were usually increased during saline loading. However, the possibility cannot be excluded that the reduction in glomerular filtration (during controlled urine flow) limited the delivery of sodium to the ascending limb to such an extent that the concentrating capacity was diminished. This would require, however, that sufficient sodium and chloride still escaped reabsorption in Henle's loop, only to be rejected from reabsorption at some more distal site, in order that sodium excretion could still be increased. Likewise, the possibility cannot be excluded that saline loading through some unidentified pathway directly affects the transport system of the ascending limb. If sodium reabsorption at this site were slowed, then urinary osmolality should decrease as the excretion of sodium increased. Since less water would be reabsorbed by the collecting duct, it would be possible to have a reduced glomerular filtration rate without a reduction in urine flow under these circumstances. However, Rectro and associates (5) have reported that during water diuresis urinary dilution may increase with saline loading and reduced glomerular filtration, and on the basis of this observation these authors have suggested that the decreased tubular reabsorption occurs at some site proximal to the ascending limb of Henle's loop.

An additional factor that may influence urinary osmolality is the rate of medullary blood flow, since an inverse relationship must exist between medullary blood flow and the degree of medullary hypertonicity (14-16). This factor could be of importance in producing the decreased urinary osmolality observed in the present studies, and it is entirely possible that changes in medullary blood flow may indirectly influence sodium reabsorption and sodium excretion. Under conditions of antidiuresis the isotonic tubular fluid entering Henle's loop is progressively concentrated during passage through the descending limb (17). This increased concentration very likely occurs as the result of a passive loss of tubular water to the hypertonic medullary interstitium and perhaps to a lesser extent as the result of a gain in solute. Therefore, the concentration of sodium (chloride) in the fluid reaching the ascending limb is increased above isotonicity. Probably the same qualitative situation obtains during water diuresis, since medullary interstitial (nonurea) hypertonicity may persist to some degree during water diuresis (18-20). If medullary blood flow is increased, the degree of medullary hypertonicity will decrease, and secondarily the volume of water lost from the descending limb would be diminished. Therefore, the rate of flow through the ascending limb would be increased, and the concentration of sodium in the fluid reaching this latter segment would be decreased. It is entirely possible that the net transport of sodium by the ascending limb would be diminished under such conditions. Even if this transport site could achieve the same minimal concentration of sodium in the tubular fluid, net reabsorption would be decreased as an increased rate of flow of less concentrated fluid entered the ascending limb. Little direct information is available that bears on the relationships between substrate (sodium) concentration and rate of flow, and net reabsorption by the ascending limb of Henle's loop. However, Lassiter, Mylle, and Gottschalk (21) and Giebisch, Kloese, and Windhager (22) have reported that during saline loading in the rat, fractional reabsorption by the proximal tubule is unchanged, whereas the tubular fluid to plasma inulin ratio in the early part of the distal convolution of cortical nephrons may be decreased (21). This latter observation is consistent with the view that volume reabsorption within Henle's loop is diminished during saline loading, and unless the concentration of sodium in the fluid leaving the ascending limb is decreased (in comparison with antidiuresis) then less sodium must be reabsorbed within the loop. Such changes could be even more marked in juxtamedullary nephrons with long loops of Henle.

Likewise, there is very little direct information bearing on the factors that may influence medul-
lary blood flow. Maude and Wesson have suggested that the fall in renal concentrating capacity 
\( T_{\text{H}_2\text{O}} \) which sometimes accompanies saline loading may be due to an increased medullary blood
flow (23). In this laboratory \( T_{\text{H}_2\text{O}} \) has been found to be distinctly lower in mineralocorticoid-
treated dogs during massive expansion with isotonic saline than at similar rates of solute excretion
during hypertonic mannitol or hypertonic saline diuresis (24). These observations indicate that
the concentrating mechanism is less efficient during expansion of the extracellular volume, and
this could be due to an increased medullary blood flow. Thurau, Deetjen, and Kramer (25) have
reported that the circulation time of medullary blood flow is decreased during hypotonic saline
loading.

It may appear unlikely that an increased flow through Henle’s loop could have occurred in the
present studies at a time when glomerular filtration was reduced, unless a simultaneous decrease
in proximal reabsorption occurred. However, the decreased urinary osmolality (and presumably,
medullary interstitial osmolality) would be associated with decreased water reabsorption by both
the descending limb and the collecting duct. This total decreased volume reabsorption could be
reflected by an equivalent decrease in glomerular filtration as urine flow is kept constant. As a
consequence of the diminished loss of water from the descending limb, a similar or even increased
volume could be still delivered to the ascending limb and more distal parts of the nephron. The
actual increases in sodium excretion observed in these studies were small and occurred only if the
relative concentration of sodium in the urine was initially low. However, any influence that flow
rate and substrate concentration may have on reabsorption by the ascending limb should be much
greater if glomerular filtration were not depressed and the kidney allowed to undergo diuresis.

The clearance of PAH increased during saline loading as glomerular filtration was depressed by
ureteral constriction, but aortic constriction was associated with a decreased clearance of PAH.
This latter observation may not be inconsistent with the suggestion that medullary blood flow is
increased. The studies of Thurau and Deetjen are consistent with the view that medullary and
cortical blood flow may vary independently (26), and Carriere, Thorburn, O’Morchoe, and Barger,
utilizing the krypton technique, have suggested that during hemorrhage medullary blood flow may
not decrease despite large falls in cortical blood flow (27). In this laboratory we have found that
during saline loading the extraction ratio for PAH is decreased 5 to 25% (28). This observation
indicates that the clearance of PAH becomes a smaller fraction of total renal blood flow during
saline loading, and furthermore, the decreased extraction ratio may indicate that a redistribution
of blood away from the cortex occurs during saline loading.

The suggestion that medullary blood flow may indirectly alter sodium excretion requires the
assumption that net reabsorption by the ascending limb is influenced by the rate of intratubular flow,
or the concentration of substrate electrolyte, or both. Confirmation of this hypothesis will de-
pend upon the demonstration that this transport system does indeed have such characteristics and
that medullary flow is increased during saline loading. This concept is not inconsistent with the
findings of others who observed that during water diuresis, saline loading and a reduction in glomeru-
lar filtration were associated with increased urinary dilution as sodium excretion increased (5). Since
significant medullary hypertonicity may persist during water diuresis, water will be lost from the
descending limb and a hypertonic fluid delivered to the ascending limb, even though the final urine
is dilute. If this passive loss of water from the descending limb is diminished as a consequence of
increased medullary blood flow during saline loading, then urinary dilution could be enhanced by
the delivery of a larger volume of less concentrated fluid to the more distal “water-imperme-
able” segments of the nephron.

Summary

The effects of saline loading on tubular reabsorption were studied in the dog by maintaining a
constant rate of urine flow by ureteral or aortic constriction during saline loading. Under these
conditions of unchanged urine flow, saline loading was associated with a decreased glomerular filtra-
tion, decreased urinary osmolality (despite hydropenia and vasopressin infusion), and usually in-
creased urinary electrolyte concentrations. Similar reductions in filtration rate by ureteral or aortic constriction in the absence of saline loading were associated with increases in urinary osmolality and decreases in electrolyte concentration. Decreased tubular reabsorption during saline loading was evident by 1) increased sodium and chloride excretion with a decreased filtered load of electrolyte and 2) an unchanged rate of urine flow in the presence of a reduced filtration rate. This decreased tubular reabsorption was associated with decreased urinary osmolality despite a constant infusion of vasopressin, no increase in solute excretion, and maintained or increased sodium excretion. To account for this combination of changes, we suggest that saline loading may result in a primary increase in medullary blood flow. As a consequence of the decreased medullary interstitial hypertonicity, passive water reabsorption from the descending limb of Henle’s loop could be decreased. The resulting increased rate of flow of fluid with a lower concentration of sodium may then lead to a decrease in the net reabsorption of sodium by the ascending limb and more distal portions of the nephron.

Acknowledgment

We are indebted to Miss Deborah Lufkin for her assistance with these studies.

References