THE EFFECTS OF SALT RESTRICTION ON THE RENAL CONCENTRATING OPERATION IN NORMAL, HYDROPENIC MAN

BY RICHARD M. STEIN,‡ BARRIE H. LEVITT, MARVIN H. GOLDSMITH,‡ JEROME G. PORUSH,‡ GILBERT M. EISNER,‡ AND MARVIN F. LEVITT

(From the Section of Renal Diseases, Department of Medicine, The Mount Sinai Hospital, New York, N. Y.)

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In the presence of antidiuretic hormone, the elaboration of a concentrated urine by the absorption of solute-free water depends upon the osmotic gradient established between collecting duct fluid and the hypertonic medullary interstitium (1-3). The quantity of solute deposited within the medulla depends, in large part, upon the rate at which sodium is presented to the ascending limb of the loop of Henle (2, 4, 5).

Considerable evidence indicates that prolonged salt restriction results in a decreased extracellular fluid volume and glomerular filtration rate (GFR) coincident with a sharp reduction in sodium excretion (6-8). It might be anticipated that such changes could affect medullary salt supply and thereby influence the renal concentrating operation. The reported effects of salt restriction on the concentrating operation appear to vary depending upon the species studied. Experiments in the dog have demonstrated that dietary salt restriction reduces maximal urine osmolality (9, 10), whereas similar studies in man (4) and the rat (11) have failed to reveal any such alteration.

The present studies were undertaken in order to elucidate further the effects of prolonged salt restriction on the concentrating operation in normal man under conditions of maximal hydropenia.

METHODS

Three experimental protocols were employed in maximally hydropenic subjects free of cardiovascular or renal disease. In the experiments of Group I, a solute diuresis was established with a hypertonic mannitol infusion in subjects maintained on both high and low salt diets. In those of Group II, subjects prepared as in Group I received intravenous aminophylline during a mannitol diuresis at high levels of solute clearance. In those of Group III, similarly prepared subjects received aminophylline at low levels of solute clearance during a mannitol diuresis.

Maximal hydropenia was established in all subjects by a 16-hour overnight fast. Twelve hours before the study, each subject received 5 U of vasopressin tannate in oil intramuscularly. Urine was collected in 11 female subjects by bladder catheterization, with emptying assured by double air washouts. In five male subjects, urine was obtained by spontaneous voiding. After priming doses of inulin and para-aminomethylpurpurate (PAH), an intravenous infusion was administered at a constant rate of 1.0 ml per minute with a Bowman constant infusion pump. This infusion contained aqueous vasopressin in a concentration adequate to deliver 50 mU per kg body weight per hour and sufficient quantities of inulin and PAH to produce satisfactory plasma levels. Urine specimens were collected at approximately 10- to 30-minute intervals. Heparinized blood specimens were obtained at 30- to 60-minute intervals throughout the study. The three experimental protocols of the present studies are described below.

Group I. Six subjects were studied after 7 days of a high salt diet containing at least 250 mEq of sodium per day, and again after 7 days of a low salt diet containing 25 mEq of sodium per day. In addition, three of these subjects were studied on a third occasion after a high salt diet had been reinstated. One hundred grams of protein per day were included in both diets. After 2 to 4 control urine collections were obtained, a solute diuresis was established by the infusion of a hypertonic (10 per cent) mannitol solution. The infusion was administered at increasing rates until a urine flow of 12 to 25 ml per minute was achieved.

Group II. In six salt-restricted subjects and in four subjects maintained on high salt diets, a hypertonic mannitol solution was infused until urine flow was stabilized at rates greater than 8 ml per minute, ranging from 8 to 20 ml per minute. After this steady state of urine flow was achieved, aminophylline was administered intravenously at the rate of 12.5 to 25 mg per minute for 20
Fig. 1. Effect of high and low salt diets on free water reabsorption ($T_{\text{H}_{2}O}$) and solute clearance ($C_{\text{osm}}$) during mannitol diuresis. All $C_{\text{osm}}$ and corresponding $T_{\text{H}_{2}O}$ values are grouped about successive 1-ml increments in $C_{\text{osm}}$ and represent the mean values for each group.

minutes. Urine collections were continued for the subsequent 45 minutes.

Group III. In six salt-restricted subjects, aminophylline was administered during the course of a mannitol diuresis before urine flow rates had reached 3 ml per minute. In separate control studies performed in these salt-restricted subjects, a solute diuresis was produced by the infusion of hypertonic mannitol alone. In two of

Fig. 2. Effect of high and low salt diets on sodium excretion ($U_{\text{Na}}V$) and solute clearance ($C_{\text{osm}}$) during mannitol diuresis. All $C_{\text{osm}}$ and corresponding $U_{\text{Na}}V$ values are grouped about successive 1-ml increments in $C_{\text{osm}}$ and represent the mean values for each group.
these subjects, an additional mannitol diuresis was established 1 week after the institution of a high salt diet. In another group of control studies, five salt-fed subjects received aminophylline during the course of a mannitol diuresis before urine flow rates had reached 3 ml per minute.

All urine and blood specimens were analyzed for osmolality and sodium, potassium, chloride, urea, inulin, and PAH concentrations. Osmalalities were determined with a Fiske osmometer. Other determinations were performed by methods previously described from this laboratory (4). GFR and effective renal plasma flow were measured as the clearances of inulin and PAH, respectively. Solute clearance (\(C_{\text{om}}\)) was calculated from the formula \(C_{\text{om}} = U_{\text{om}} V / P_{\text{om}}\), where \(U_{\text{om}}\) represents urine osmolality, \(V\) the rate of urine flow in ml per minute, and \(P_{\text{om}}\) plasma osmolality. The rate of free water reabsorption (\(T_{\text{H2O}}^*\)) was calculated as \(T_{\text{H2O}}^* = C_{\text{om}} - V\).

**Table 1**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diet</th>
<th>Urine flow †</th>
<th>Urine max†</th>
<th>(U_{\text{om}} V) †</th>
<th>(U_{\text{om}} / U_{\text{om}})</th>
<th>(C_{\text{om}}) range</th>
<th>(T_{\text{H2O}}^*) Mean maximum</th>
<th>(C_{\text{inulin}}) Mean ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.D.</td>
<td>High salt I</td>
<td>0.9</td>
<td>1,384</td>
<td>207</td>
<td>0.25</td>
<td>3.6 - 33.4</td>
<td>7.7</td>
<td>101</td>
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<tr>
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<td>Low salt</td>
<td>0.4</td>
<td>1,380</td>
<td>2</td>
<td>0.40</td>
<td>1.7 - 25.9</td>
<td>5.4</td>
<td>85</td>
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<tr>
<td></td>
<td>High salt II</td>
<td>0.7</td>
<td>1,118</td>
<td>80</td>
<td>0.20</td>
<td>2.2 - 30.7</td>
<td>6.9</td>
<td>101</td>
</tr>
<tr>
<td>G.E.</td>
<td>High salt I</td>
<td>0.5</td>
<td>1,128</td>
<td>34</td>
<td>0.36</td>
<td>2.0 - 31.0</td>
<td>9.0</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>Low salt</td>
<td>0.6</td>
<td>922</td>
<td>2</td>
<td>0.46</td>
<td>1.7 - 27.3</td>
<td>4.6</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>High salt II</td>
<td>0.6</td>
<td>1,140</td>
<td>51</td>
<td>0.30</td>
<td>1.6 - 30.9</td>
<td>8.8</td>
<td>98</td>
</tr>
<tr>
<td>J.P.</td>
<td>High salt I</td>
<td>0.8</td>
<td>1,390</td>
<td>93</td>
<td>0.30</td>
<td>2.4 - 30.3</td>
<td>6.5</td>
<td>105</td>
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<tr>
<td></td>
<td>Low salt</td>
<td>0.6</td>
<td>1,123</td>
<td>4</td>
<td>0.39</td>
<td>1.9 - 24.7</td>
<td>5.1</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>High salt II</td>
<td>0.9</td>
<td>1,264</td>
<td>185</td>
<td>0.23</td>
<td>3.3 - 37.0</td>
<td>6.9</td>
<td>101</td>
</tr>
<tr>
<td>N.B.</td>
<td>High salt</td>
<td>1.3</td>
<td>1,350</td>
<td>222</td>
<td>3.8 - 30.7</td>
<td>7.3</td>
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<tr>
<td></td>
<td>Low salt</td>
<td>0.5</td>
<td>1,270</td>
<td>22</td>
<td>1.7 - 26.4</td>
<td>5.7</td>
<td>78</td>
<td></td>
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<tr>
<td>T.R.</td>
<td>High salt</td>
<td>0.8</td>
<td>812</td>
<td>126</td>
<td>2.1 - 20.2</td>
<td>6.1</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low salt</td>
<td>0.4</td>
<td>739</td>
<td>6</td>
<td>1.0 - 17.0</td>
<td>4.6</td>
<td>84</td>
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</tr>
<tr>
<td>B.L.</td>
<td>High salt</td>
<td>1.1</td>
<td>738</td>
<td>322</td>
<td>2.8 - 22.0</td>
<td>5.5</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low salt</td>
<td>0.3</td>
<td>743</td>
<td>3</td>
<td>0.9 - 15.6</td>
<td>3.4</td>
<td>65</td>
<td></td>
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<tr>
<td>G.C.</td>
<td>High salt</td>
<td>1.0</td>
<td>1,037</td>
<td>294</td>
<td>2.9 - 20.7</td>
<td>5.7</td>
<td>84</td>
<td></td>
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<tr>
<td></td>
<td>Low salt</td>
<td>0.4</td>
<td>1,086</td>
<td>34</td>
<td>1.5 - 18.2</td>
<td>4.5</td>
<td>84</td>
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<tr>
<td>F.M.</td>
<td>High salt</td>
<td>1.0</td>
<td>827</td>
<td>217</td>
<td>2.8 - 17.5</td>
<td>4.5</td>
<td>81</td>
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</tr>
<tr>
<td></td>
<td>Low salt</td>
<td>0.6</td>
<td>806</td>
<td>3</td>
<td>1.5 - 15.0</td>
<td>3.5</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>M.G.</td>
<td>High salt</td>
<td>0.9</td>
<td>1,115</td>
<td>210</td>
<td>3.4 - 22.4</td>
<td>5.9</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low salt</td>
<td>0.6</td>
<td>963</td>
<td>12</td>
<td>1.9 - 21.2</td>
<td>4.8</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>M.W.</td>
<td>High salt</td>
<td>0.7</td>
<td>790</td>
<td>192</td>
<td>1.9 - 13.6</td>
<td>4.0 ‡</td>
<td>64</td>
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</tr>
<tr>
<td></td>
<td>Low salt</td>
<td>0.4</td>
<td>871</td>
<td>8</td>
<td>1.3 - 11.2</td>
<td>4.0 ‡</td>
<td>70</td>
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</tr>
<tr>
<td>J.F.</td>
<td>High salt</td>
<td>1.0</td>
<td>646</td>
<td>175</td>
<td>2.1 - 13.1</td>
<td>4.4 ‡</td>
<td>120</td>
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<tr>
<td></td>
<td>Low salt</td>
<td>0.9</td>
<td>640</td>
<td>2</td>
<td>1.5 - 12.6</td>
<td>3.3 ‡</td>
<td>82</td>
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<tr>
<td>R.L.</td>
<td>High salt</td>
<td>0.6</td>
<td>771</td>
<td>146</td>
<td>1.7 - 14.0</td>
<td>4.6 ‡</td>
<td>73</td>
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<tr>
<td></td>
<td>Low salt</td>
<td>0.3</td>
<td>821</td>
<td>2</td>
<td>0.8 - 10.9</td>
<td>2.6 ‡</td>
<td>111</td>
<td></td>
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<tr>
<td>Mean</td>
<td>High salt</td>
<td>0.88</td>
<td>958</td>
<td>185</td>
<td>2.54</td>
<td>5.88</td>
<td>90.0</td>
<td></td>
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<tr>
<td></td>
<td>Low salt</td>
<td>0.50</td>
<td>949</td>
<td>8</td>
<td>1.45</td>
<td>4.29</td>
<td>83.5</td>
<td></td>
</tr>
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</table>

*Abbreviations: \(U_{\text{om}} V\) = rate of sodium excretion, \(U_{\text{om}} / U_{\text{om}}\) = fraction of urine solute composed of urea, \(C_{\text{om}}\) = solute clearance rate, \(T_{\text{H2O}}^*\) = rate of free water reabsorption, \(C_{\text{inulin}}\) = inulin clearance rate.
† Measurements obtained before the infusion of mannitol.
‡ The maximal \(T_{\text{H2O}}^*\) value derived from the plateau portion of the \(T_{\text{H2O}}^* - C_{\text{om}}\) curve in each study.
RESULTS

1. Mannitol diuresis in subjects on high and low salt diets. Maximal $T^{c}H_{2}O$ was diminished by dietary salt restriction in 11 of 12 subjects. The mean maximal $T^{c}H_{2}O$ in the salt-restricted subjects was 4.3 ml per minute and that in the high salt subjects 5.9 ml per minute. Composite curves from all studies performed on each diet are shown in Figure 1, where $T^{c}H_{2}O$ has been plotted against $C_{osm}$. As $C_{osm}$ increased beyond 4 ml per minute, the difference in $T^{c}H_{2}O$ between the two groups became apparent. In subjects on high salt diets, $T^{c}H_{2}O$ values increased progressively until $C_{osm}$ approached 17 ml per minute, whereas $T^{c}H_{2}O$ in salt-restricted subjects increased more slowly and became stabilized at a $C_{osm}$ of 14 ml per minute. Thereafter, $T^{c}H_{2}O$ values in both groups remained maximal over a wide range of $C_{osm}$, but showed a slight tendency to fall as $C_{osm}$ increased beyond 25 ml per minute.

Despite the difference in $T^{c}H_{2}O$, maximal urine TABLE II

<table>
<thead>
<tr>
<th>Subject</th>
<th>$C_{osm}$</th>
<th>$T^{c}H_{2}O$</th>
<th>$U_{Na}V$</th>
<th>$C_{erin}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.W.</td>
<td>11.0 †</td>
<td>4.0</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>14.1</td>
<td>3.9</td>
<td>6.7</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>20.7</td>
<td>3.2</td>
<td>1,360</td>
<td>122</td>
</tr>
<tr>
<td>J.F.</td>
<td>11.8 †</td>
<td>3.3</td>
<td>248</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>16.0</td>
<td>3.4</td>
<td>655</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>26.1</td>
<td>2.8</td>
<td>1,560</td>
<td>116</td>
</tr>
<tr>
<td>R.L.</td>
<td>10.5 †</td>
<td>2.6</td>
<td>400</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>12.6</td>
<td>2.3</td>
<td>815</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>18.1</td>
<td>1.7</td>
<td>1,570</td>
<td>151</td>
</tr>
<tr>
<td>T.R.</td>
<td>16.6 †</td>
<td>4.6</td>
<td>613</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>22.9</td>
<td>4.9</td>
<td>1,120</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>30.8</td>
<td>3.8</td>
<td>1,940</td>
<td>108</td>
</tr>
<tr>
<td>B.L.</td>
<td>15.4 †</td>
<td>3.4</td>
<td>316</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>24.5</td>
<td>3.7</td>
<td>749</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>30.7</td>
<td>2.9</td>
<td>1,330</td>
<td>89</td>
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<td>M.G.</td>
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<td>4.6</td>
<td>859</td>
<td>96</td>
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<td>1,250</td>
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<tr>
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<td>30.4</td>
<td>4.4</td>
<td>1,540</td>
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</table>

* Abbreviations as in Table I. † Mean of 3 collection periods obtained in a steady state before the administration of aminophylline.

FIG. 3. Effects of aminophylline superimposed on a mannitol diuresis at high levels of solute clearance. Typical experiments performed in Subject B.L. on high and low salt diets are depicted.
osmolalities were comparable in both groups of subjects, averaging 958 and 949 mOsm per kg on
high and low salt diets, respectively. Plasma osmolalities were also comparable. However, con-
trol V, C\textsubscript{osm}, and T\textsubscript{H\textsubscript{2}O}, before the administration of mannitol, were lower in the salt-restricted
subjects.

Control rates of sodium excretion in the salt-restricted subjects averaged 8 \( \mu \text{Eq} \) per minute,
compared to 185 \( \mu \text{Eq} \) per minute in the group maintained on a high salt diet. A composite curve
relating sodium excretion to \( C\text{osm} \) for all subjects on both dietary regimens is presented in Figure 2.
As \( C\text{osm} \) rose from control levels to 7 to 11 ml per minute, the rate of sodium excretion in both groups
of subjects increased only modestly, but thereafter rose at a more rapid rate. In the salt-restricted
subjects, sodium excretion remained lower at every level of \( C\text{osm} \). At high levels of solute clear-
ance, however, sodium excretion in the salt-restricted group exceeded the control rates of excretion noted in the subjects on a high salt diet. No significant differences in plasma sodium concentra-
tions were noted in the subjects maintained on the two diets.

In the control collection periods, before the infusion of mannitol, the fraction of urine solute
composed of urea (\( U_{\text{urea}}/U\text{osm} \)) was consistently higher in the salt restricted subjects (Table I). Because of the lower control rates of urine flow in these subjects, rates of urea excretion (\( U_{\text{urea}}V \)) were similar in both dietary groups. During the ensuing mannitol diuresis, urine urea concentra-
tions fell markedly and the difference noted between the two groups at control rates of urine flow
tended to disappear.

GFR in subjects fed a low salt diet averaged 7 per cent less than that noted in salt-fed subjects

\begin{figure}
\centering
\includegraphics{figure4}
\caption{Effects of aminophylline administered at low levels of solute clearance during a mannitol di-
uresis to a salt-restricted subject. Control T\textsubscript{H\textsubscript{2}O}–C\textsubscript{osm} curves obtained in this subject on high and low salt diets after infusions of mannitol alone are also presented.}
\end{figure}
TABLE I

Three subjects, however, demonstrated little or no change in GFR and in two others it was somewhat higher after salt depletion.

Control rates of potassium excretion were variable, but somewhat lower in the salt-restricted subjects. As $C_{osm}$ rose to 8 to 10 ml per minute, the rate of excretion increased in both groups, but thereafter tended to become stable.

II. The administration of aminophylline at high levels of solute clearance. In six salt-restricted subjects, aminophylline was administered after the mannitol diuresis became stabilized at a $C_{osm}$ averaging 14 ml per minute, with a range from 11 to 21 ml per minute. An abrupt increase in GFR averaging 38 per cent, with a range from 24 to 58 per cent, was noted. With the increment in GFR, $C_{osm}$ rose an average of 12 ml per minute, with a range from 8 to 15 ml per minute. Although the calculated increment in filtered sodium

TABLE III

<table>
<thead>
<tr>
<th>Subject</th>
<th>$C_{osm}$</th>
<th>$T_HO$</th>
<th>$U_{NaV}$</th>
<th>$C_{inj}$</th>
<th>$C_{inj}$</th>
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<tr>
<td>M.W.</td>
<td>13.2†</td>
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<td>72</td>
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<td>1,000</td>
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</tr>
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<td>25.8</td>
<td>4.9</td>
<td>2,040</td>
<td>89</td>
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<td>J.F.</td>
<td>12.8†</td>
<td>4.3</td>
<td>485</td>
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<tr>
<td>24.6</td>
<td>4.6</td>
<td>1,900</td>
<td>174</td>
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<td>T.R.</td>
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<td>30.9</td>
<td>6.5</td>
<td>2,520</td>
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<td>B.L.</td>
<td>21.0†</td>
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<td>1,760</td>
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<tr>
<td>Aminophylline</td>
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<td>1,990</td>
<td>99</td>
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</tr>
<tr>
<td>27.4</td>
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<tr>
<td>28.3</td>
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<td>113</td>
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</tr>
</tbody>
</table>

*Abbreviations as in Table I.
† Mean of 3 collection periods obtained in a steady state prior to the administration of aminophylline.
load averaged 4,800 μEq per minute, mean sodium excretion increased only 1,100 μEq per minute. Despite the increments in GFR, filtered sodium, and solute and water excretion induced by aminophylline, no measurable increase was recorded in T^\text{H}_2\text{O} (Table II, Figure 3). In five of these subjects, T^\text{H}_2\text{O} fell somewhat as C_{osm} exceeded 20 to 25 ml per minute.

In four subjects studied on high salt diets, aminophylline was administered when C_{osm} became stabilized at a rate greater than 13 ml per minute, ranging from 13 to 21 ml per minute. Under these conditions, as in the salt-restricted subjects, no significant rise in T^\text{H}_2\text{O} was observed (Table III, Figure 3). However, the slight fall in T^\text{H}_2\text{O} noted in the salt-free subjects at higher levels of C_{osm} was less evident.

III. The administration of aminophylline at low levels of solute clearance to subjects maintained on both high and low salt diets. During a mannitol diuresis in salt-restricted subjects, the administration of aminophylline at low levels of C_{osm} resulted in an abrupt increase in GFR averaging 42 per cent. During the period of the sustained increase in GFR, the rise in C_{osm} was associated with T^\text{H}_2\text{O} levels appreciably higher than those noted in the same subjects when the diuresis was produced solely by mannitol (Figures 4, 5). In both salt-restricted and salt-fed subjects, the administration of aminophylline resulted in T^\text{H}_2\text{O}–C_{osm} curves that were very similar (Figure 5).

DISCUSSION

These data indicate that dietary salt restriction diminished the maximal T^\text{H}_2\text{O} in man. This concentrating defect was corrected by the administration of aminophylline at a low C_{osm}.

Goldsmith and co-workers (10), studying the effect of salt restriction on the concentrating operation in the dog, have also noted a decrease in maximal T^\text{H}_2\text{O}. Several of their findings, however, differ from those reported here in man. First, rates of sodium excretion at varying levels of C_{osm} were similar in dogs maintained on high and low salt diets. In addition, dogs maintained on a salt-poor diet showed a decrease in maximal U_{osm} and excreted hypotonic urine at urine flow rates of approximately 9 ml per minute. These workers postulated that salt restriction reduced tubular permeability to water so that distal tubular fluid failed to reattain isotonicity despite the presence of antidiuretic hormone (10). When GFR was increased in the salt-depleted dog by the prolonged administration of glucocorticoids, the concentrating defects were corrected. It was suggested that an increase in GFR in the dog might indirectly enhance distal tubular permeability to water (10).

In addition to the species differences between man and dog noted above, evidence is available to suggest that in the normal hydropenic dog (12), in contrast to the rat (3) and probably to man, distal tubular fluid may fail to reattain isotonicity at a relatively low C_{osm}. During a solute diuresis in the normal dog, T^\text{H}_2\text{O} often fails to rise as C_{osm} increases from 4 to 10 ml per minute, and U_{osm} tends to fall towards or below isotonicity as C_{osm} approaches 15 ml per minute (12–14). In both normal and salt-restricted man, however, T^\text{H}_2\text{O} rises progressively as C_{osm} approaches 15 ml per minute and remains relatively stable at this maximal plateau as C_{osm} increases from 15 to 25 ml per minute (Figure 1). Thereafter, as C_{osm} continues to rise, T^\text{H}_2\text{O} may fall below peak levels (15).

In addition, studies with chlorothiazide also unmask a species difference in the capacity for distal tubular fluid to reattain isotonicity. When this drug was administered to the dog after maximal T^\text{H}_2\text{O} levels had been achieved, the resulting block in late distal salt absorption was associated with a sharp increase in T^\text{H}_2\text{O} (14). The administration of chlorothiazide in man at levels of C_{osm} between 11 and 20 ml per minute produced no increase in T^\text{H}_2\text{O} (16, 17). When distal tubular fluid fails to reattain isotonicity, a block in late distal salt absorption would be expected to raise the tonicity of the fluid entering the collecting duct towards isotonicity and increase the measured T^\text{H}_2\text{O}.

The proposal that a low salt diet reduces distal tubular permeability to water (10) is difficult to reconcile with the findings reported here in man. As mentioned above, it seems unlikely that distal tubular fluid fails to reattain isotonicity in hydropenic man, particularly at modest levels of C_{osm}. Moreover, when aminophylline was administered to salt-restricted man at a low C_{osm}, the T^\text{H}_2\text{O} defect was corrected (Figures 4, 5). The administration of this agent at a high C_{osm}, where the consequences of persistent distal tubular fluid hypo-
tonicity would be more manifest, failed to over-

come the $T_{s}^{H_{2}O}$ defect (Table II, Figure 3). If
aminophylline were capable of increasing tubular
permeability to water, the effects of its administra-
tion on $T_{s}^{H_{2}O}$ would be most pronounced at a high
$C_{om}$. The capacity for aminophylline to correct
the $T_{s}^{H_{2}O}$ defect does not appear, therefore, to be
mediated through any influence on tubular perme-
ability to water. Consequently, it is difficult to
implicate diminished distal tubular permeability
as the factor limiting $T_{s}^{H_{2}O}$ in salt-depleted man.

The difference in $T_{s}^{H_{2}O}$ in the two groups of
subjects may be explained by the hypothesis that
$T_{s}^{H_{2}O}$ is limited by a maximal rate of sodium trans-
port at the ascending limb. In this view, it would
follow that salt depletion depresses this tubular
maximum. This hypothesis would require that
sodium transport at the ascending limb be de-
creased while total sodium reabsorption is en-
hanced throughout the renal tubule. Moreover,
these studies would imply that aminophylline could
restore a normal tubular maximum for sodium
only when administered at a low $C_{om}$. Further-
more, in both groups of subjects, when the filtered
sodium load was abruptly increased by aminophyl-
line administration at a high $C_{om}$, only a modest
fraction of this additional load appeared in the
urine. It is unlikely that at such a high $C_{om}$ all
of the increase in sodium reabsorption took place
within the proximal tubule. It is therefore ap-
parent that total sodium transport in the distal tu-
bulc, if not specifically at the ascending limb, could
be augmented even at a high $C_{om}$. In addition,
micropuncture analyses have failed to demonstrate
a tubular maximum for sodium at the ascending
limb during a salt or mannitol diuresis (3, 18).
Admittedly, the possibility of a maximal rate for
sodium transport at the ascending limb cannot be
excluded; the data presented here, however, do
not support the hypothesis that prior salt restric-
tion depresses the capacity for sodium transport
at this site.

An alternative that might explain the difference
in $T_{s}^{H_{2}O}$ in the two groups of subjects would as-
sume that salt depletion reduces the rate of de-
ivery of sodium to the ascending limb. Consis-
tent with this hypothesis is the observation that
salt excretion was sharply reduced per unit of
$C_{om}$ in the salt-free group, particularly at lower
levels of $C_{om}$ (Figure 2). This finding indicates
that the capacity for tubular salt absorption against
the osmotic gradient established by the non-ab-
sorbed solute was augmented by previous salt re-
striction. It is likely that this enhanced salt ab-
sorption occurred, in part, within the proximal
tubule. Such a change in proximal tubular func-
tion would diminish the percentage of absorbable
solute (salt) per unit of mannitol presented to the
ascending limb. In support of this hypothesis,
when the quantity of salt delivered to the ascend-
ning limb during a mannitol diuresis was increased
by the administration of aminophylline, at a low
$C_{om}$, the $T_{s}^{H_{2}O}$ defect was corrected (Table IV,
Figures 4, 5).

The precise cause of the enhanced tubular salt
reabsorption noted after salt restriction remains
to be established. It might result in part from the
modest and variable reduction in GFR pro-
duced by salt depletion.

The observation that maximal urine osmolalities
were comparable in both groups of subjects does
not invalidate the assumption that salt restriction
diminishes medullary salt supply and content.
Control V and $T_{s}^{H_{2}O}$ before the infusion of manni-
itol were lower in the salt-restricted subjects (Table
I, Figure 1). In this fasting state, the quantity of
fluid presented to the collecting duct and coursing
through the medulla was diminished after salt de-
pletion. It appears reasonable that a smaller
quantity of medullary solute might achieve com-
parable medullary (and urinary) concentrations
if a reduced quantity of water dilutes the medulla.
In fact, when urine concentration was plotted
against V, salt-free subjects demonstrated a con-
sistently lower $U_{om}$ at each V (Figure 6).

Another factor that may obscure a difference in
maximal $U_{om}$ between both groups is the rela-
tively greater role of urea in defining $U_{om}$ at a low
V (22, 23). The enhanced tubular salt and water
reabsorption in salt-restricted subjects caused the
fraction of urine solute composed of urea to rise

---

2 Available data suggest that the administration of
aminophylline sharply increases salt supply at the as-
cending limb (19, 20). To what extent this change may
be a consequence of an increase in GFR or an inhibition
of proximal salt absorption is not clear (21). The ef-
eft of this agent during a mannitol diuresis would
therefore increase the percentage of absorbable solute
(salt) presented to the ascending limb, compared to the
percentage delivered by a comparable mannitol diuresis
alone.
above that noted in the salt-fed subjects (Table 1). In the hydropenic state, urea is highly dif-
mosus, so that an increase in urine urea concen-
tration will be reflected in an increased medullary concentration (24). This factor may tend to ob-
secure the reduction in $U_{\text{osm}}$ imposed by the de-
creased medullary salt content. As the solute di-
uresis supervenes, the fraction of medullary solute com-
posed of urea diminishes (5) and the influence of the decreased medullary salt content be-
comes manifest.

It has been proposed that salt restriction reduces sodium supply, but not the capacity for
transport at the ascending limb. At a high $C_{\text{osm}}$, however, particularly after the administration of
aminophylline, salt-restricted subjects demon-
strate an appreciable increase in sodium excretion
(Tables II, III, Figure 2). At such a high $C_{\text{osm}}$ it
appears that sodium supply at the ascending limb
is no longer limited. Therefore, a proposal must
be sought to explain the failure of this increasing
sodium supply to be incorporated within the medulla.

On the basis of direct studies, it has been con-
cluded that a progressive increase in effective
medullary blood flow develops during the course of a solute diuresis (25). This proposal is sup-
ported by the observation that medullary solute content is reduced under these conditions (26).
Such a change in medullary hemodynamics, when
sufficient in magnitude, might prevent further re-
tention of medullary solute and limit $T_{\text{H}_{2}O}$ despite
increasing sodium transport at the ascending limb.
If it is assumed that a comparable increase in
medullary blood flow develops in salt-depleted
subjects during a solute diuresis, this hyperemia

**TABLE IV**

*Aminophylline administered to subjects on a low salt diet at low levels of solute clearance*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Aminophylline plus mannitol</th>
<th>Mannitol</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{osm}}$</td>
<td>$T_{\text{H}_{2}O}$</td>
</tr>
<tr>
<td></td>
<td>ml/min</td>
<td>ml/min</td>
</tr>
<tr>
<td>C.R.</td>
<td>5.5</td>
<td>3.0</td>
</tr>
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</tr>
<tr>
<td></td>
<td>8.3</td>
<td>4.5</td>
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</tr>
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<td></td>
<td>17.1</td>
<td>5.8</td>
</tr>
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<td>E.M.</td>
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<td>2.4</td>
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</tr>
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<td></td>
<td>12.6</td>
<td>4.4</td>
</tr>
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</tr>
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<td>11.6</td>
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<td>F.M.</td>
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<tr>
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<tr>
<td></td>
<td>17.0</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*Abbreviations as in Table I.
† $T_{\text{H}_{2}O}$ value obtained from the $T_{\text{H}_{2}O}/C_{\text{osm}}$ curve produced by mannitol alone at that $C_{\text{osm}}$ recorded in the aminophylline plus mannitol study.
might reach critical levels while sodium supply at the ascending limb is still relatively diminished. Thereafter, any further increase in sodium supply or transport at the ascending limb might not increase the quantity of solute retained within the medulla, nor increase the calculated $T_{\text{H}_{2}\text{O}}$.

The cause of this alleged increase in medullary blood flow is unknown. It is likely that the rate of outflow of blood from the medulla might be enhanced by the diffusion of solute-free water into the medullary interstitium from the collecting duct ($T_{\text{H}_{2}\text{O}}$). Inasmuch as $T_{\text{H}_{2}\text{O}}$ was lower in salt-restricted subjects, the proposal that a progressive and comparable increase in medullary blood flow occurs in both groups of subjects implies that factors in addition to back-diffusion of water at the collecting duct may provoke this change in medullary hemodynamics.

The hypothesis that salt restriction reduces medullary salt content is consistent with the observation that in salt-depleted subjects, $T_{\text{H}_{2}\text{O}}$ levels reach a plateau at a lower $C_{\text{osm}}$ and reveal a greater tendency to fall from peak levels (Tables II, III, Figure 1). A medulla containing less solute would be more likely to be vulnerable to any factor which dissipates medullary solute content and thus limits $T_{\text{H}_{2}\text{O}}$. Whether progressive medullary hyperemia represents the responsible factor, as alleged, remains to be established.

**SUMMARY**

1. Data have been presented demonstrating that salt restriction in man diminishes the maximal rate of free water reabsorption ($T_{\text{H}_{2}\text{O}}$) without changing maximal urine osmolality.

2. Aminophylline was capable of correcting the $T_{\text{H}_{2}\text{O}}$ defect only when administered at low levels of solute clearance.

3. These findings are best explained by the hypothesis that reduced $T_{\text{H}_{2}\text{O}}$ in salt-depleted man...
results from a reduced medullary salt content secondary to a reduced rate of sodium delivery to the ascending limb at every level of solute clearance.

REFERENCES


