Sodium Excretion in Volume-Expanded Dogs

I. Comparison of the Effects of Physiological Saline and 5% Glucose Solution

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Summary

Dogs were subjected to volume expansion with physiological saline and 5% glucose solution. During the infusion Na excretion was significantly increased only when saline was given. Maintenance of the volume expansion with 5% glucose solution immediately following saline infusion was ineffective in preventing the decline of Na excretion rate after the cessation of saline loading. Although the indices of hemodilution such as plasma total protein concentration and peripheral venous hematocrit were reduced along with natriuresis, these values also correlated with the total amount of Na retained during saline infusion. And this amount of retained Na has also a good correlation with the natriuresis. It is concluded that hemodilution is not the essential cause of natriuresis in the present volume expansion experiments, and that the amount of Na retained during saline loading determines the Na excretion rate in some unknown manner. The implication of regression coefficient between Na retention and Na excretion is discussed as a characteristic value in the Na homeostatic mechanism of the organism.

Additional Indexing Words:
Natriuresis Hemodilution Na homeostasis

In recent years there appeared several kinds of explanation for the renal mechanism of Na homeostasis and natriuresis after Na loading, namely: 1) glomerulo-tubular balance theory, 2) humoral regulation, particularly by the renin-angiotensin and aldosterone system, 3) physical or humoral third factors, 4) intrarenal redistribution of blood flow or glomerular filtrate, and 5) neural influences on tubular Na reabsorption. More recently, micropuncture and microperfusion studies were performed in various segments of the nephron, and it is now recognized that ionic flow characteristics are so com-
plexly differentiated that it is almost impossible to reorganize them quantitatively into a meaningful entity. It seems almost reasonable that Stein et al has decided to look only on the final segment of the nephron in regard to the regulation of Na excretion, in such a way as to revive glomerulo-tubular balance theory once more in another content.1)

We studied Na regulation under hypertonic saline infusion in dogs in previous publications, and found that plasma Na concentration and glomerular filtration rate (GFR) might have important roles in determining the amount of urinary Na excretion.2),3) In the present and following papers, we will deal with Na balance under volume expansion by physiological saline or other solutions. It was at first expected that different modes of regulatory mechanisms in Na homeostasis might be elucidated. However, it was found that very similar kinetics were operating in the renal Na handling under both types of Na loading. Since our principal aim of study at this moment is on the elucidation of Na regulatory process dynamics, so that we set aside to estimate the role of the Na regulatory systems in a narrow sense here, such as hemodynamic and humoral mechanisms. These aspects of Na regulation will be discussed in another place.

**METHODS**

Female mongrel dogs were anesthetized by pentobarbital and catheter was inserted into the urinary bladder. After the control period of about 1 hour, test solutions were infused intravenously at a rate of 500 ml/30 min. Blood samples were taken and urine were collected before beginning of the infusion and at each 30 min interval during and after the infusion.

Blood samples and urine were analyzed for Na, K, and creatinine, and blood samples were also determined for hematocrit and total plasma protein concentration. Na and K was analyzed by flame photometry. Creatinine was analyzed by Jaffé's reagent with pre-adsorption by Lloyd's reagent. Hematocrit was determined by micromethod and total protein concentration by refractometry.

**RESULTS**

Two groups of 5 dogs were infused intravenously with 1,500 ml of either physiological saline or 5% glucose solution for 90 min. The time course of the changes in plasma Na concentration (P_{Na}), plasma total protein concentration (TP), peripheral venous hematocrit (Ht), and urinary Na excretion rate (E_{Na}) were followed for the control period of around 1 hour and for 4 hours after the beginning of infusion. Average values of the 5 experiments for each group were shown in Fig. 1 (a and b). Comparing the effects of saline with that of glucose solution, it was apparent that the P_{Na} decreased only in the
Fig. 1 (a and b). Average courses of volume expansion in the dogs (physiological saline and 5% glucose solution: 1,500 ml/90 min).


case of glucose solution, while the TP and Ht were lowered by both infusions although the changes were a little milder after glucose solution than after saline. Large increments in E_Na were observed only by saline administration. The decreases in TP and Ht at the end of infusion were −28.9% and −21.8% in the average in cases of saline, and −16.5% and −1.2% after glucose solution, respectively. During the whole experimental period, the GFRs were fluctuated but without any definite directions in each dog.

The relationships of E_Na to P_Na, TP, and Ht are shown in Fig. 2 (a, b, and c), a chain of connected points representing 1 experiment. From the figures, it is apparent that after saline infusion the E_Na can increase in the absence of increases in P_Na, and even when the P_Na is in the hyponatremic range. The TP and Ht are inversely proportional to E_Na after some threshold values are reached. These relationships are found only in the cases of saline infusion, and which values are differing among dogs. The variety
of threshold values may imply the adaptation of dogs to the fluctuation of blood compositions in achieving Na homeostasis. However, in another experiment (Fig. 3), where the volume expansion was sustained with glucose solution after saline infusion had been finished, although the TP and the Ht remained lowered, the $E_{Na}$ declined as in the former series. This result is interpreted as relatively minor roles are played by TP and Ht in determining the level of $E_{Na}$.

Since only saline load was found to be effective in causing large increases in $E_{Na}$, the amounts of Na retained (Na overload, $\Delta Q_{Na}$) was suspected to have a decisive influence on $E_{Na}$. $\Delta Q_{Na}$ was calculated as a mid-point value of re-

![Fig. 2 (a, b, and c). Relationships between $E_{Na}$ and $P_{Na}$, TP, Ht. Each connected point represents 1 experiment.](image-url)
Fig. 3. Effect of sustained hemodilution by 5% glucose solution after saline expansion in a dog.

Fig. 4. Relationships between the amount of Na retained ($\Delta Q_{Na}$) and TP and Ht.

tained Na obtained at each of neighboring times of blood and urine sampling. When $\Delta Q_{Na}$ was related to TP and Ht (Fig. 4, a and b), it was found that there were again inversely proportional relationships. So, it is inferred that TP and Ht were in fact dummy variables, because they represented the effect of the
Fig. 5. Relationship between $\dot{Q}_{\text{Na}}$ (abscissa) and $E_{\text{Na}}$. An experiment with a longer duration (4 hr) and a greater load (4 L) is included. Closed circles represent points during saline infusion and open circles those after cessation of infusion. \( r = 0.76. \)

**Table I. Coefficients of Regression Equation ($E_{\text{Na}} = a\dot{Q}_{\text{Na}} + b \pm e$)**

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>e</th>
<th>$T = 1/a$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DOG 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.0011</td>
<td>0.3096</td>
<td>0.2243</td>
<td>909.1</td>
</tr>
<tr>
<td>3</td>
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<td>-0.3755</td>
<td>0.1406</td>
<td>166.7</td>
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<tr>
<td>4</td>
<td>0.0116</td>
<td>-0.7105</td>
<td>0.1586</td>
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<tr>
<td>5</td>
<td>0.0037</td>
<td>-0.1127</td>
<td>0.2576</td>
<td>270.3</td>
</tr>
<tr>
<td>6</td>
<td>0.0021</td>
<td>-0.0744</td>
<td>0.0891</td>
<td>476.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.0044</td>
<td>-0.1460</td>
<td>0.2701</td>
<td>227.3</td>
</tr>
</tbody>
</table>

Total: coefficients for an equation rendering all points in ensemble. a and b: coefficients, e: residual error, T: time constant.

The amount of water retained which would have a close relationship to the amount of Na retained, during the physiological saline infusion.

Finally, the relation between $Q_{\text{Na}}$ and $E_{\text{Na}}$ was investigated and it was found that there was also a good linear relationship between the two (Fig. 5). An experiment where 4 L of physiological saline was infused for 4 hours is included in the same figure. A linear regression analysis was performed for each of the 6 experiments and for all points assembled as a whole. The regression coefficients are shown in Table I. Since the extracellular fluid volume (or osmotic volume) can be regarded as a single compartment, as shown in a previous publication, and the reciprocal of rate constant (a) as a time constant (T) in such a situation, their estimated values are also shown in the table.
DISCUSSION

The role of physical factors in regulating Na reabsorption of the renal tubules were in recent years extensively investigated and reviewed. There was also a large body of micropuncture and microperfusion studies at various segments of the nephron both in vivo and in vitro. And, now, it is recognized almost unequivocally that, although physical factors can affect Na excretion after volume expansion, the precise mode of effect and the way of organization are hardly identifiable in a satisfactory manner at the present time.

Knox et al reviewed the experimental data and pointed out that the end-distal tubule and collecting duct might have decisive role for the natriuresis after the volume expansion by saline infusion. Also owing to such a difficulty, Stein et al proposed that the same last segments of nephron might be eventually responsible for the final and facultative elaboration of urinary Na excretion. After these considerations, they investigated and discussed intensively the effects of physical factors on these segments. However, there seems to be no conclusion to date, whether this new version of glomerulotubular balance theory could well account for the natriuresis of volume expansion or not.

Although sufficient parameters were not measured in the present experiments, circumstantial evidences show that the effects of those physical factors, such as oncotic pressure and hematocrit, on the responsive segments of the nephron are thought to be not so much different between the saline and 5% glucose solution loading. The urinary compositions are only discriminated in their Na content. In addition, the maintenance of hemodilution by 5% glucose solution after saline expansion (Fig. 3) could not apparently prevent the decline of natriuresis. Therefore, the decreases in TP and Ht can not be considered as sufficient causes for natriuresis induced by the infusion of physiological saline.

Furthermore, there are clinical situations where hyperglobulinemia or anemia is not accompanied by any signs of Na retention or wastage. These facts again cast reasonable doubt on the decisive role of such physical factors determining natriuresis. Adaptations may have occurred in these situations after sufficient lapses of time. In our present experiment, hyponatremia was also not shown to reduce natriuresis. However, there are some evidences that acute and chronic hyponatremia would curtail natriuresis during volume expansion. This point will be dealt with in more detail in our future publication.

It will be argued, as Wasserman et al has reported, that there would be difference in the changes of plasma or blood volume during and after volume
expansion with saline or glucose solution.\textsuperscript{9) They demonstrated that there was a plasma volume expansion after saline infusion but not after glucose solution administration. Simple calculations based on the changes in TP and Ht suggested that similar tendency was apparent in our experimental series. However, even in cases of saline infusion, it was found that the degree of plasma volume expansion was not uniform, and large Na excretion rates were observed with minimal plasma volume expansion (Fig. 2). So, it is considered that the difference in plasma volume expansion between saline and glucose solution infusion is not an important determinant of natriuresis. Kramer et al\textsuperscript{10,11) and Knight et al\textsuperscript{12)} have demonstrated that anesthesia could change the distribution of expanded volume and that infused saline would be more readily retained in the interstitial space with leaked plasma protein in anesthetized animals. However, although we did not perform experiments without anesthesia, the same simple calculations have not proved such protein leakage but rather a gain. This consideration does not seem to influence our conclusion.

Lastly, Papper et al have reported that Na excretion rates were quite similar when the same amounts of NaCl were infused even in different concentrations.\textsuperscript{13) In our experiments, it was found that the rate constants or time constants of Na excretion were distributed in a similar range with isotonic and hypertonic saline loadings (Fig. 6). Some years ago, McCance et al presented an evidence that a coefficient derived as GFR normalized by total body water is a stable figure during wide range of developmental year of ages and among individuals.\textsuperscript{14) This coefficient has some correspondence to the rate constant of the present experiment in which the organism is regarded as a single compartment model. It is interesting to note here that the time constants of our dogs which are obtained by hypertonic and physiologic saline loading are also not so much different from those in humans which are cal-

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig6.png}
\caption{Time constants of Na excretory function in the dog during isotonic and hypertonic saline loading. Time constant calculated by assembling all points of Fig. 5 in one is shown by broken line. Points for hypertonic saline are taken from Ref. 2.}
\end{figure}
culated in an oral NaCl loading experiments. The reciprocal of McCance's constant is analogous to the time constant of a single compartment model and his original intention on this coefficient has been to express the efficiency of renal excretory function.

REFERENCES

3. ibid: Constant infusion of hypertonic saline in the dog. V. The relative importance of plasma Na concentration and GFR as the determinants of renal Na excretion. Jap Heart J 11: 541, 1970