Sodium Flux into the Renal Tubular Lumen During Saline Loading[1] (36108)

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(Introduced by Ewald E. Selkurt)

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When the extracellular fluid (ECF) volume of normal experimental animals is expanded with saline solutions, a diuresis occurs due to decreased net reabsorption by the renal tubule. In the small intestine as well, net absorption of sodium and water is decreased during ECF expansion and becomes negative, resulting in secretion into the gut lumen (1, 2). Studies of unidirectional sodium transport by the small intestine have shown that this movement of fluid from the extracellular space into the gut lumen occurs because of large increases in the unidirectional serosal to mucosal (toward the lumen) flux of sodium; sodium flux in the opposite direction, mucosal to serosal, does not appear to be changed by extracellular volume expansion (2). These findings suggest, by analogy, that a similar process may take place in other sodium-transporting epithelia, and the following studies were carried out to determine whether some of the decrease in renal tubular net sodium reabsorption, which occurs during volume expansion, might be due to an increase in unidirectional sodium flux into the tubular lumen. The sodium precession method of Chinard and Enns (3), which demonstrates flux of sodium into the renal tubule, has been used to document increased sodium excretion by a nonglomerular, transtubular route in the saline-loaded dog.

Materials and Methods. Eight adult mongrel dogs of both sexes, fasted overnight, were anesthetized with pentobarbital (30 mg/kg), the trachea was intubated, and the dog was suspended feet-down by the loose skin of the back. A retroperitoneal flank incision was made and the renal vein, artery, and ureter were exposed and the ureter was cannulated. A 20-gauge hook-shaped needle was inserted into the renal artery for injections of $^{22}Na^+$ and inulin which exited from the needle via side-holes to insure mixing. An intravenous infusion of either 5% dextrose or 0.9% NaCl was begun and the infusion rate was varied to achieve as many different rates of urine flow and sodium excretion as possible. Several timed urine collections were made for determination of flow and sodium excretion rates. When the desired rates were attained, $^{22}Na^+$, 5 μCi; and inulin, 10 mg, in 0.1 ml of saline was injected rapidly as a bolus into the renal artery. Eight dogs received a total of 24 such injections, with each dog receiving 2 to 4 injections. Urine collections were begun instantaneously with injection and continued at 15 sec intervals. The counts per minute from the first two intervals were averaged and subtracted as background from the number of counts at the peak of $^{22}Na^+$ excretion.

Sodium-22 was counted in a well-type scintillation counter. Inulin in each urine specimen was determined by the anthrone reaction (4) and sodium and potassium were assayed by flame photometry.

Results. Figure 1 illustrates a typical sodium precession pattern as originally described by Chinard and Enns (3). As inulin marks the appearance in the urine of substances filtered through the glomerulus, it can be seen that the $^{22}Na^+$ has preceded inulin into the urine via a transtubular, nonglomerular route. Figure 2 illustrates the fractional excretion of $^{22}Na^+$, *i.e.*, the fraction of $^{22}Na^+$ counts injected that were excreted into the urine at the peak excretion of $^{22}Na^+$, plotted against the simultaneous urinary sodium excretion rate of that kidney. As shown, there is a high degree of correlation, with a greater

[1] Investigation supported by U.S. Public Health Service Grants HE-11638 and HE-06308 and by a grant from the Marion County Chapter of the Indiana Heart Association.

[2] Recipient of U.S. Public Health Service Research Career Development Award HE-42403.

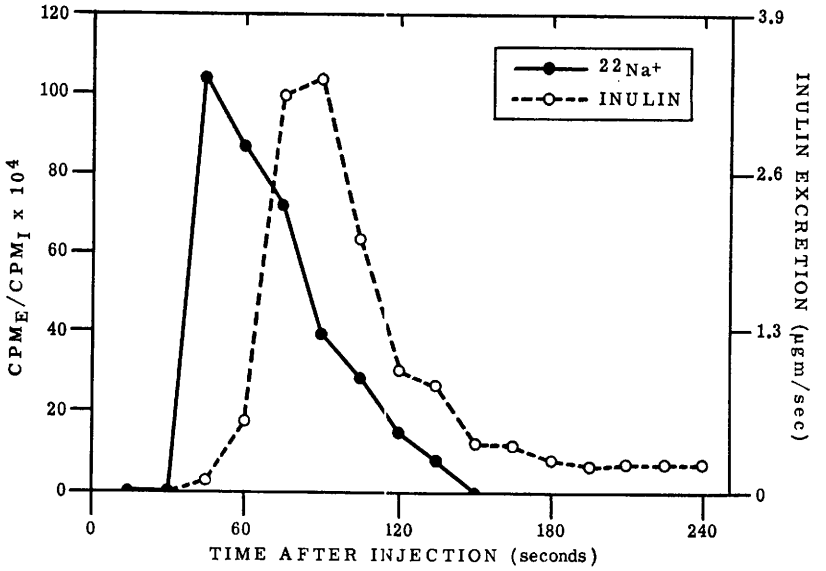

FIG. 1. Precession of $^{22}Na^+$ before inulin in ureteral urine after simultaneous injection into the renal artery: (left ordinate) the fraction of the injected $^{22}Na^+$ which was excreted during each collection period.

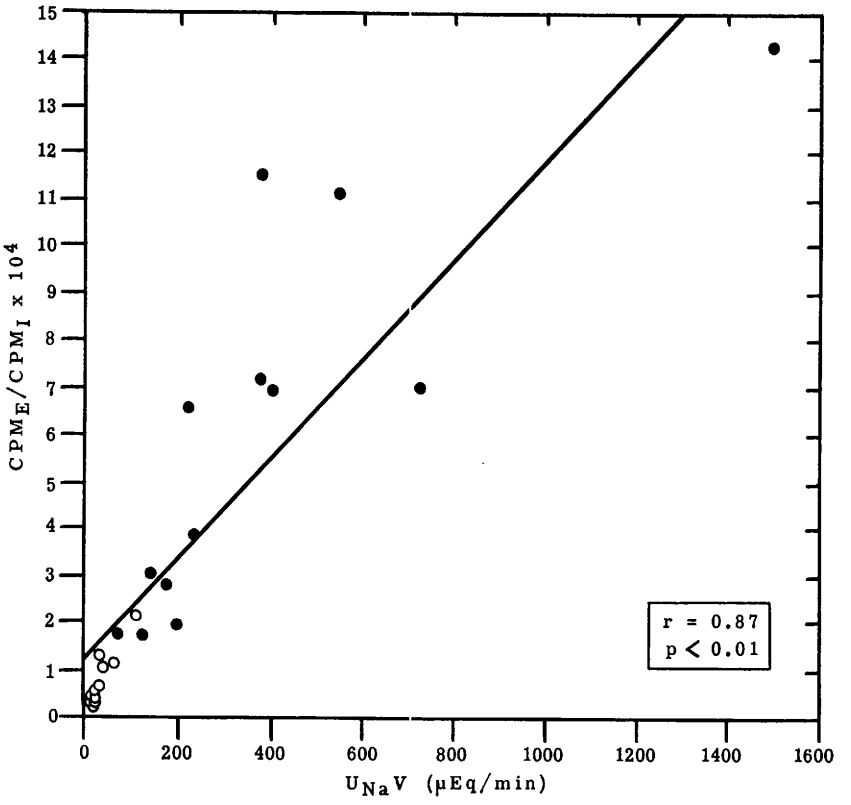

FIG. 2. Fractional excretion of $^{22}Na^+$ in precession peak plotted against the simultaneous Na excretion rate for saline-loaded (●); and water-loaded dogs (○). Correlation coefficient r and statistical significance p are indicated.

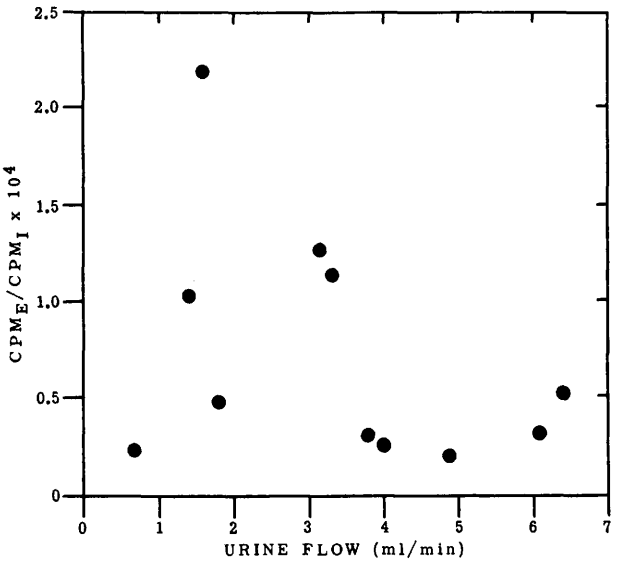

FIG. 3. Fractional excretion of $^{22}Na^+$ in precession peak plotted against simultaneous urine flow, showing no correlation in dogs infused with glucose and water.

excretion fraction of $^{22}Na^+$ counts appearing in the urine at high rates of sodium excretion. This appears to be true whether the urinary sodium excretion rate was examined during saline infusion or during dextrose and water infusion. The fact that the excretion fraction of $^{22}Na^+$ does not correlate with the urine flow alone is shown in Fig. 3, where the excretion fraction is plotted against the urinary flow rate during intravenous infusion of dextrose and water.

Discussion. There has been an enormous amount of work done in the past decade on control of sodium excretion with special emphasis on the changes in tubular net sodium reabsorption which lead to greater fractional excretion of filtered sodium (5, 6). Although Chinard and Enns (3), and Morel and Lechene (7) demonstrated that sodium can be excreted by a nonglomerular route, *i.e.,* transtubular flux into the tubular lumen, and despite the fact that Maude (8) and DeRouffignac and Morel (9) showed significant bidirectional fluxes of sodium in the renal tubule, the possibility for a significant contribution of sodium flux into the tubular lumen during natriuresis has been offered as an explanation only in studies of the effect of hypernatremia on sodium excretion (10, 11). Most investigators appear to have assumed that tubular reabsorption of sodium during extracellular fluid expansion is controlled exclusively by changes in the rate of active transport out of the tubules.

For the purposes of this discussion, unidirectional sodium transport from the tubular lumen into the extracellular fluid is defined as luminal to basal flux, and flux in the opposite direction as basal to luminal flux, analogous to mucosal to serosal flux and serosal to mucosal flux in the intestine.

The present studies demonstrate that, when $^{22}Na^+$ is injected directly into the renal artery, a greater percentage of the counts appears in the sodium precession peak when the animal is saline loaded, and the fractional excretion of counts shows a significant correlation with the sodium excretion rate. An estimate of the quantity of sodium which is excreted via basal to luminal flux in the renal tubule cannot be made from the present data because the fraction of the blood entering the kidney which reaches the tubules without passing first through glomeruli is unknown. It is assumed that this nonglomerular portion represents only a small fraction of the total renal blood flow (12), and this is the only blood which provides the counts of $^{22}Na^+$ seen in the precession peak. Almost all of the blood entering the kidney ultimate-

ly perfuses the renal tubules after it leaves the glomeruli, and if one extrapolates to this large blood flow the same basal to luminal flux seen from the nonglomerular peritubular blood, it is evident that a significant amount of sodium could be excreted by this nonglomerular transtubular route. This question might be resolved by determination of unidirectional sodium fluxes in the renal tubule utilizing micropuncture techniques.

There are several possible mechanisms for the increased fractional excretion of injected $^{22}Na^+$ counts in the precession peak. It is possible that there is a change in permeability allowing a leak of sodium into the tubular lumen. It is also possible that a change in distribution of renal blood flow leads to a greater delivery of $^{22}Na^+$ directly to the renal tubules bypassing the glomeruli. Finally, decreased sodium reabsorption in the distal tubule would allow the appearance in the urine of a greater proportion of the $^{22}Na^+$ counts which have reached the tubular lumen by transtubular basal to luminal flux in more proximal segments of the tubule.

It has been postulated that some of the abnormalities of renal function seen in patients with chronic renal disease might occur by the same mechanisms operative in the salt-loaded normal animal. Alhough it is highly speculative, one might wonder whether such a phenomenon as skewing of the glucose threshold curve might not be explained by similar backflux routes as are demonstrated for sodium in the present studies.

A physiologically significant role of nonglomerular sodium excretion via a transtubular basal to luminal route remains to be established, but the present studies suggest that unidirectional sodium fluxes must be taken into consideration in any attempt to explain control of sodium excretion by changes in net tubular sodium reabsorption.

Summary. Expansion of the extracellular fluid by saline infusion causes a decrease in net sodium reabsorption from the renal tubule and in net sodium absorption by the small intestine. The decreased net transport by the small intestine appears to be due to increased unidirectional flux of sodium from the extracellular fluid into the lumen, suggesting a similar mechanism in the renal tubule. Sodium-22 injected simultaneously with inulin into the renal artery appears in the urine before the inulin ("sodium precession"), demonstrating nonglomerular excretion of sodium via flux into the tubular lumen, and this method was used here to investigate this route of sodium excretion in dogs undergoing saline or water diuresis. A high degree of correlation was found between fractional excretion of $^{22}Na^+$ in the precession peak and the rate of sodium excretion during saline loading. There was no correlation of fractional excretion of $^{22}Na^+$ with urine flow rate during water diuresis. It is postulated that transtubular flux of sodium into the tubular lumen may contribute significantly to the renal Na excretion during salt loading.

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Received June 14, 1971. P.S.E.B.M., 1972, Vol. 139.