Effects of flow rate and potassium intake on distal tubular potassium transfer

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Frequently the rate of urinary potassium loss increases with the augmentation of urinary flow rate and the excretion of larger than normal amounts of sodium into the urine. The kaliuresis observed after loading with sodium salts or after the administration of a variety of diuretics, particularly those acting at a site upstream of the distal tubule, are representative examples (3, 9, 10, 12, 18, 19, 25, 36). To explain the rise of potassium excretion under such conditions, it has been suggested that the delivery of larger than normal amounts of sodium to the distal tubule, the nephron site where most of potassium secretion normally takes place, is the key element and responsible for the observed stimulation of potassium secretion (3). However, the precise mechanism of the stimulating action of sodium upon potassium secretion has been elusive.

Normally, the amount of sodium entering the distal tubule and reabsorbed along this nephron site exceeds the rate of potassium secretion by at least an order of magnitude (12, 13, 31, 32). Distal tubular net sodium reabsorption should accordingly suffice to saturate the potassium transfer process if some obligatory tubular exchange mechanism were operative. However, it has been noted, first on the basis of indirect evidence (24), and more recently shown directly by micropuncture experiments in the rat (31, 32), that relatively small additional increments of distal sodium delivery passing the site of potassium secretion do provide a powerful stimulus to potassium secretion. The situation is further complicated by the finding that the induction of a distal tubular diuresis is not uniformly associated with kaliuresis. For instance, the excretion of larger than normal amounts of potassium fails to materialize during water diuresis (11) and, as shown in the present study, after dietary potassium deprivation (1, 2, 35, 39).

The present experiments were designed to explore the behavior of distal tubular potassium secretion during the delivery of progressively larger loads of fluid and sodium ions to the distal tubular epithelium. To this end the relationship between tubular fluid, sodium, and potassium transport during widely differing distal tubular volume flow rates was studied using free-flow and recollection micropuncture techniques. Rats were kept on varying regimes of potassium intake during graded expansion of the extracellular fluid volume by isotonic saline or urea-saline solutions, since extracellular volume expansion is known to decrease proximal tubular sodium reabsorption and to result in the delivery of a progressively larger fraction of the glomerular filtrate into the distal tubule.

Our results indicate that in animals on a normal and high-potassium intake distal tubular potassium secretion increased in direct proportion to flow rate. A different behavior was observed in animals on a low-potassium intake. Distal tubular transport rates of potassium remained constant and were not affected by changes in distal tubular flow rate. Furthermore, depending on dietary potassium intake, a widely varying pattern obtained between the rate of distal tubular sodium reabsorption and that of tubular potassium secretion.

METHODS

Experiments were performed on male Long-Evans rats weighing 250–315 g maintained on a Purina laboratory chow diet and tap water ad libitum. The animals were anesthetized by intraperitoneal injection of Inactin (80–100 mg/kg). The left jugular vein was exposed and two indwelling polychydrophil c catheters were inserted; one for the continuous infusion of the saline or urea-saline load, the other for intermittent injections of small amounts (about 0.05 ml) of a 5 or 10% Tris-buffered lissamine-green solu-
tion. The left femoral artery was cannulated for periodic collection of blood samples. A tracheotomy was performed. The left kidney was exposed by a subcostal incision, immobilized in a Lucite holder, and its surface was illuminated by means of a fiberoptic light source (American Optical Co.). Other aspects of the micropuncture technique were similar to those previously described (9, 29, 31, 32).

Three groups of rats were investigated. The first was kept on a diet of Purina laboratory chow (K: 0.72%, Na: 0.46%), the second on a potassium-deficient diet (General Biochemicals), and the third on a high-potassium diet (General Biochemicals, 15 g K/kg diet). The diets of low and high-potassium content were given for several weeks prior to the clearance and micropuncture experiments.

Diuresis was induced by the intravenous infusion of either an isotonic saline solution (300 mM) or of a slightly hyperosmotic urea-saline solution (200 mM urea, 100 mM NaCl). The latter solution was chosen to achieve a solute diuresis and yet prevent drastic dilution of the plasma sodium level. The choice of urea as a loading solute also allowed for the induction of a strong distal diuresis which, in contrast to that achieved by the administration of sodium chloride alone, progressed with the development of steeper transepithelial sodium concentration differences (23, 38).

Sodium chloride or sodium chloride-urea solutions were infused at three rates, 1.5, 8.0, and 25 ml/h, resulting in what shall be termed "low," "moderate," and "high" urine flow rates. Recollection of proximal and distal tubular fluid was carried out within timed urinary clearance periods. A priming dose of 100 μCi of inulin carboxyl-14C (New England Nuclear Corporation) was given and followed by a sustaining infusion delivered at a rate of 100 μCi/h. A period of 45 min was allowed for the equilibration of 14C labeled inulin before the beginning of tubular collections. During the first clearance periods (low urine flow rate) several collections of tubular fluid were made from superficial nephron segments, and late distal puncture sites. In addition, puncture sites were checked after the termination of each experiment by the method of least squares, mean values are given ± standard error, and standard tests using the t distribution were used to evaluate the significance of differences between mean values.

An approximation of absolute rates of net ion movement across the whole length of the distal tubular epithelium at a given tubular flow rate was obtained by estimating the rates of cation entry and leaving the distal tubule. Thus, in the case of potassium

\[ S_{Kd} = V_{100} [K^+]_{100} - V_0 [K^+]_0 \]

where \( S_{Kd} \) is the absolute amount of potassium secreted (nmol·min\(^{-1}\)), \( V_{100} \) and \( V_0 \) are the tubular volume flow rates (nl·min\(^{-1}\)), and \([K^+]_{100}\) and \([K^+]_0\) are the concentrations of potassium (meq/liter) in tubular fluid at 100 and 0 % tubular length.

Volume flow rates and solute concentrations at 100 and 0 % tubular length were calculated from the observed volume flow rate and solute concentrations at the puncture sites, the observed inulin and solute TF/P ratio at the puncture site, and the calculated inulin and solute TF/P ratios at 0 and 100 % distal tubular length. These latter values were derived by extrapolation, using the mean slopes relating inulin or solute TF/P concentration ratios to tubular length in the different experimental conditions and during the different infusion and urine flow rates (low, medium, and high). The calculation involved the following steps.

The absolute rate of fluid entry into the distal tubule was estimated from the observed rate of fluid collection at any point along the distal tubule and the fractional fluid reabsorption along the distal tubule to the same tubular site. It can be shown that

\[ V_{100} = V_0 (1 - V_{F 100}) \]

and

\[ V_0 = V_{100} (1 - V_{F 100})^{-1} \]

Similarly,

\[ V_0 = V_X (1 - V_{F X})^{-1} \]

where \( V_0 \) and \( V_{100} \) and \( V_X \) are the absolute volume flow rates at 0, 100, and X % distal tubular length and \( V_{F X} \) is the fraction of filtered water entering the distal tubule which is reabsorbed by the time the fluid reaches point X.

Fractional water reabsorption along the distal tubule...
can be expressed as the difference between the fractional amount of water entering and leaving the distal tubule, divided by the fraction of water present at zero distal tubular length. Thus

\[ V_{F100} = \frac{(P/TF)_{In0} - (P/TF)_{In100}}{(P/TF)_{In0}} \]  

(4)

\[ V_{FX} = \frac{(P/TF)_{In0} - (P/TF)_{InX}}{(P/TF)_{In0}} \]  

(5)

where \( V_{F100} \) and \( V_{FX} \) are the fractions of water entering the distal tubule which are reabsorbed along its total length (\( V_{F100} \)) or up to point \( X \) (\( V_{FX} \)), and \( (P/TF)_{In0} \), \( (P/TF)_{In100} \), and \( (P/TF)_{InX} \) are the fractions of filtered water present at the beginning, the end, and at point \( X \) along the distal tubule, respectively.

By substitution of \( V_{FX} \) as expressed in equation 5 into equation 3, an expression of the absolute flow rate at 0% distal tubular length was obtained. Thus,

\[ V_0 = V_X \left[ 1 - \frac{(P/TF)_{In0} - (P/TF)_{InX}}{(P/TF)_{In0}} \right]^{-1} \]  

(6)

and similarly, by substituting the expression \( V_{FX} \) as derived in equation 4 into equation 1, one obtains

\[ V_{100} = V_0 \left[ 1 - \frac{(P/TF)_{In0} - (P/TF)_{In100}}{(P/TF)_{In0}} \right] \]  

(7)

As pointed out above, inulin, potassium, and sodium concentrations at 0 and 100% distal tubular length were obtained from extrapolation using the linear plots of the regression lines relating these variables to distal tubular length. It was assumed that the observed linear relationships extend to 0% distal tubular length, i.e., beyond the earliest distal tubular sites accessible to surface punctures. We realize that \( V_0 \) and \( V_{100} \) could also have been derived by extrapolation utilizing a plot of \( V_X \) as a function of distal tubular length. A comparison of such estimates with those derived using the above-described method did not reveal significant differences. The use of inulin TF/P ratios ((TF/P)\(_{In0}\)) represents, in our opinion, an advantage, since this permits calculation of single-nephron glomerular filtration rates (SNGFR). Contamination of fluid samples by retrograde collection can be detected if the calculated SNGFR values are inordinately high.

RESULTS

This paper will center its attention on the properties of the potassium transport system during the development of different states of distal diuresis. Most of the data dealing with distal sodium transport are presented in another paper (23, 38).

Urinary Excretion Data

Table 1 provides a summary of glomerular filtration rates, urine flow rates, and urinary excretion rates of potassium during varying diuretic states in animals on different intakes of potassium. There were no marked effects of intravenous saline or saline-urea loading upon GFR, and the increase of the urine flow rates was of similar magnitude in rats on control, low-K, and high-K diet. The administration of the saline-urea load at the two higher infusion rates was less diuretic than when an isotonic

<table>
<thead>
<tr>
<th>TABLE 1. Summary of glomerular filtration rates, urinary flow rates, and urinary excretion rates of potassium in animals on different diets undergoing progressive saline or urea-saline diuresis</th>
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<tbody>
<tr>
<td>Control</td>
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<tr>
<td>--------</td>
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<tr>
<td></td>
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<tr>
<td>GFR, ml/min(^{-1})-kg(^{-1})</td>
</tr>
<tr>
<td>±SE</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>U(_{V}), ml/min(^{-1})-kg(^{-1})</td>
</tr>
<tr>
<td>±SE</td>
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<tr>
<td>U(_{K}), meq/min(^{-1})-kg(^{-1})</td>
</tr>
<tr>
<td>±SE</td>
</tr>
<tr>
<td>(U/P)(_{KIn})</td>
</tr>
<tr>
<td>±SE</td>
</tr>
<tr>
<td>(U/P)(_{Naln})</td>
</tr>
<tr>
<td>±SE</td>
</tr>
</tbody>
</table>

Table headings show diet, infused substance, and infusion rate. Mean plasma potassium values in animals on a control diet (saline infusion): 4.4 ± 0.1 meq/liter (n = 26), control diet (urea-saline infusion): 4.5 ± 0.2 meq/liter (n = 8), low-potassium diet (urea-saline infusion): 2.7 ± 0.2 meq/liter (n = 15), high-potassium diet (urea-saline infusion): 5.4 ± 0.3 meq/liter (n = 14). Compared to values obtained in animals on a control diet, the plasma potassium levels of animals on a low- or high-potassium intake are significantly different (p < 0.005). The following values are as compared with control (urea saline): *NS. †p < 0.05. ‡p < 0.01.
saline load was administered, a difference probably due to the larger volume of distribution of the former. Since the urea-saline load is less effective in expanding the extracellular fluid volume, it would depress proximal tubular fluid and sodium transport to a smaller degree than would a comparable sodium chloride load (4, 27). According to this interpretation, a larger fraction of tubular fluid escapes proximal tubular reabsorption during sodium chloride loading than during urea-saline loading and, not being completely reabsorbed during its passage through the distal nephron and collecting ducts, escapes into the urine.

Inspection of Table 1 also indicates that, depending on the dietary regime of the animals, widely different urinary excretion patterns of potassium were observed. In addition, different potassium excretion patterns were observed depending on whether the animals received saline or saline-urea infusions. In animals on a control diet, the infusion of a saline load is more effective in inducing urinary potassium loss than is the administration of an urea-sodium load given at the identical rate of infusion. This difference manifests itself by the lower absolute and fractional potassium excretion rates at low, moderate, and high urine flow rates in the saline-urea-loaded animals.

A second important finding concerns the very marked differences regarding the magnitude of the kaliuresis which obtained in low- and high-potassium animals. The kaliuresis induced by the very substantial intravenous saline loading is severely blunted in potassium-deprived rats with peak urinary excretion rates of potassium at the highest saline infusion rates not exceeding some 4% of the filtered load. In sharp contrast, the peak kaliuresis in animals on a control or a high-potassium intake is significantly greater, reaching values of some 36 and 73% of the filtered potassium load, respectively. Similarly, the urinary potassium excretion is consistently less in low-potassium rats at the low and moderate infusion rates as well, varying between 1 and 2.5% in low-potassium animals. These values are at least one order of magnitude less than comparable potassium excretion rates in control and high-potassium animals.

It should be noted that in animals on a control diet the lower potassium excretion in urea-saline-loaded animals as compared to saline-loaded animals is associated with lower sodium excretion rates. As described in detail elsewhere (38), the fractional sodium excretion was 1.00 ± 0.005% and 4.71 ± 0.08% of the filtered load during moderate and high urine flow rates in urea-saline-loaded animals as contrasted to fractional excretion rates of 3.80 ± 0.01% and 9.3 ± 0.01% in saline-loaded animals. On the other hand, the highly significant differences in potassium excretion which were observed in low- and high-potassium animals receiving increasing urea-saline loads were not associated with major differences in urinary sodium excretion.

**Microperfusion Data**

**Proximal convoluted tubule.** In the course of our investigation, the effect of saline loading upon proximal tubular potassium transport in animals on a control diet was evaluated. Table 2 summarizes relevant results. Confirming previous data from this laboratory (31, 32), a small but significant transepithelial potassium concentration difference was observed during low and moderate saline infusions, whereas at the highest tubular flow rates this concentration difference was obliterated. Also confirming previous evidence from this (27) and other laboratories (4, b), the expansion of the extracellular fluid volume by saline led to progressive inhibition of proximal tubular fluid reabsorption. This manifested itself by the marked decrease of end-proximal inulin concentration differences. It is also apparent that the fraction of filtered potassium remaining in the lumen of late proximal convolutions increases in rough proportion to the fall in fluid reabsorption.

**Distal convoluted tubule.** Figure 1 summarizes distal tubular data from experiments in rats on a control diet. The data are divided into three groups according to the rate of saline infusion. In the upper set of panels, from left to right, the progression of potassium TF/P ratios ((TF/P)K) is plotted as a function of distal tubular length at low, moderate, and high infusion rates of saline. Confirming previous data from this (29, 31, 32, 45) and other laboratories (5, 28, 42), we observed an increase along the distal tubule of (TF/P)K from values less than unity to values exceeding 2.0. It is also apparent that the delivery of progressively larger fractions of proximal tubular fluid into the distal tubule does not substantially affect the relationship between (TF/P)K and tubulur length. Accordingly, despite some scatter, during widely different distal tubular volume flow rates, the values of early and late distal tubular (TF/P)K fall into a similar range. The slopes relating potassium concentration ratios to tubular length are statistically not different from each other. Thus, an important conclusion from these findings is that the tubular potassium concentration is remarkably constant over a wide range of tubular volume flow rates. Table 3 provides a summary of distal tubular flow rates resulting from the sequence of saline or urea-saline loading in control, high-, and low-potassium animals.

Since the tubular potassium concentrations remain constant over the experimental range of flow rates, it is to be expected that the delivery of larger fractions of the glomerular filtrate into the distal tubule would effect an increase in net potassium secretion. Indeed, it can be seen (Fig. 1) that an amount equivalent to some 20% of the filtered potassium load is present at the end of the distal

| TABLE 2. Summary of end-proximal potassium data in animals on control diet undergoing progressive saline diuresis |
|---------------------------------|-------------------|-------------------|
| Infusion Rate of Isotonic Saline (iv) | 1.5 ml-h⁻¹ (low) | 8.0 ml-h⁻¹ (moderate) | 25.0 ml-h⁻¹ (high) |
| (TF/P)K | 0.84± ± 0.03 (n = 40) | 0.84± ± 0.05 (n = 19) | 1.03± ± 0.06 (n = 16) |
| (TF/P)1a | 1.98± ± 0.06 1.51± ± 0.06 1.24± ± 0.04 |
| (TF/P)K/1a | 0.43± ± 0.02 0.38± ± 0.03 0.72± ± 0.00 |

Proximal tubular flow rate increased more than threefold from 15 to 54 ml/min during the transition from lowest to highest infusion rates. * Significantly different from unity (P < 0.01).
† P < 0.01 (low infusion rates compared with moderate and moderate infusion rates with high, respectively).
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FIG. 1. Progression of distal (TF/P)K and (TF/P)Kx, in animals on a normal potassium diet receiving isosmotic sodium chloride solutions at increasing rates. Data obtained at 3 different distal tubular flow rates are summarized. Left panel: data at a mean distal flow rate of 4.0 nl/min. Middle panel: mean flow rate 8.6 nl/min. Right panel: mean flow rate 23.0 nl/min. Urinary potassium concentration ratios and data on fractional potassium excretion are also included.

Table 3. Mean distal tubular flow rates at low, moderate, and high infusion rates in rats on control, high-K, and low-K diet

<table>
<thead>
<tr>
<th></th>
<th>Control Diet</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Saline infusion</td>
<td>4.0 ± 0.4</td>
<td>8.6 ± 1.3*</td>
<td>23.0 ± 2.9*</td>
<td></td>
</tr>
<tr>
<td>rates</td>
<td>(29)</td>
<td>(18)</td>
<td>(25)</td>
<td></td>
</tr>
<tr>
<td>Urea-saline</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>infusion rates</td>
<td>3.1 ± 0.4</td>
<td>7.6 ± 1.2*</td>
<td>24.7 ± 2.7*</td>
<td></td>
</tr>
<tr>
<td>Flow rates, nl min⁻¹</td>
<td>(13)</td>
<td>(9)</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Urea-saline</td>
<td>2.8 ± 0.3</td>
<td>6.7 ± 0.6*</td>
<td>10.9 ± 0.9*</td>
<td></td>
</tr>
<tr>
<td>infusion rates</td>
<td>(15)</td>
<td>(20)</td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td>Flow rates, nl min⁻¹</td>
<td>(16)</td>
<td>(17)</td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Urea-saline</td>
<td>3.2 ± 0.6</td>
<td>7.7 ± 0.7*</td>
<td>17.1 ± 2.0*</td>
<td></td>
</tr>
<tr>
<td>infusion rates</td>
<td>(16)</td>
<td>(17)</td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td>Flow rates, nl min⁻¹</td>
<td></td>
<td></td>
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</tbody>
</table>

Numbers in parentheses are numbers of observations. * P < 0.005 (low infusion rates compared with moderate and moderate infusion rates with high, respectively).

TABLE 3. Mean distal tubular flow rates at low, moderate, and high infusion rates in rats on control, high-K, and low-K diet

In animals receiving the smallest saline load, whereas some 40% are present in the animals receiving the highest saline load. It should be noted that some potassium may be reabsorbed along the collecting ducts in the animals during low-urine flow rates (left panel), since the fractional amounts of potassium in the final urine are frequently less than at the late distal tubular level. We have previously made similar observations in hydropenic rats (29, 31). In contrast, at the two higher flow rates the amount of potassium is not affected in a major way by the activity of the collecting duct epithelium.

Table 4 provides a summary of regression lines of (TF/P)In, (TF/P)K, and (TF/P)Kx, as a function of distal tubular length. Data from animals on different dietary potassium intake and undergoing different degrees of diuresis are included. The following should be noted. In animals on a control and high-K diet, the induction of a moderate or high urine flow rates by saline or urea-saline infusions and, concomitantly, the very dramatic increase in distal tubular flow rate do not significantly affect the magnitude of distal transepithelial concentration differences. Thus, at normal or high-potassium intake, despite the fact that the zero-intercept TF/P inulin values as well as the slopes relating the (TF/P)In to distal tubular length decline with the augmentation of flow rates, the slopes of TF/P potassium ratios remain, in general, similar at low, moderate, and high distal tubular flow rates. Accordingly, in these animals distal tubular potassium secretion increased in proportion to distal flow rate. This is apparent from the progressive elevation of the zero intercept (TF/P)Kx, with distal flow augmentation and the corresponding enhancement of distal tubular potassium secretion. It should be realized that similar (TF/P)Kx, slopes originating from progressively higher zero (TF/P)Kx, values
TABLE 1. Regression lines of distal tubular inulin, potassium, and potassium/inulin TF/P ratios as function of percent distal tubular length in rats on control, low-K⁺, and high-K⁺ intake receiving saline or urea-saline intravenously at low (I), moderate (II), and high (III) infusion rates

<table>
<thead>
<tr>
<th>(TF/P) I</th>
<th>(TF/P) K</th>
<th>(TF/P) K/I</th>
<th>P &lt; *</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>y = 4.91 + 0.125x</td>
<td>y = 0.52 + 0.017x</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(±0.12) (±0.002)</td>
<td>(±0.05) (±0.005)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>y = 2.74 + 0.068x</td>
<td>y = 0.32 + 0.019x</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(±0.42) (±0.003)</td>
<td>(±0.04) (±0.007)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>y = 5.02 + 0.120x</td>
<td>y = 0.23 + 0.016x</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(±0.31) (±0.006)</td>
<td>(±0.03) (±0.003)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>y = 0.79 + 0.006x</td>
<td>y = 0.26 + 0.001x</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>(±0.74) W (±0.001)</td>
<td>(±0.014) (±0.002)</td>
<td></td>
</tr>
</tbody>
</table>

Control diet, saline

Control diet, urea saline

High-K⁺ diet, urea saline

Low-K⁺ diet, urea saline

NS

* Significantly different from a slope of zero.

represent, on a semilogarithmic plot, larger absolute secretion rates. It should also be noted that the progressive increase of distal tubular potassium concentration ratios along the distal tubule is accentuated in high-potassium rats. Hence, potassium secretion along the distal tubule, expressed as the slope of (TF/P) K/I, also exists in this group of animals that observed in animals on a control potassium intake. It is also apparent that in animals on a control or high-potassium intake with increasing flow rate a progressively larger fraction of filtered potassium enters the distal tubule as evidenced by the lowering of zero-intercept values of (TF/P) K/I, with high distal tubular flow rates. Inspection of Table 4 also shows that the situation is different in the group of animals pretreated with a low-potassium diet. It has already been referred to that the kaliuresis of such rats is much smaller when they are volume expanded (see Table 1). This is also reflected by a different behavior at the distal tubular level. Whereas in animals on a normal or high-potassium intake the distal tubular potassium concentration is largely independent of tubular flow rate, the concentration of potassium in potassium-deprived rats falls with increasing tubular flow rate. This manifests itself in a decline of a slope relating tubular potassium concentrations to distal tubular length. The finding of a progressive lowering of the distal tubular potassium concentration with increasing volume flow rate accounts for the unchanged pattern of distal tubular potassium transport, despite the induction of a distal diuresis which exceeds normal flow rates by as much as an order of magnitude. This is apparent from the lack of any changes in the slopes relating (TF/P) K/I, to distal tubular length with increasing distal flow rate. Significant net secretion was absent at all flow rates, and only some 5–6% of the filtered potassium load was present at both the early and the late distal tubular level at the different flow rates achieved. The fact that a moderate increase of urinary potassium excretion, from less than 1% at the lowest to some 4% of the filtered load at the highest flow rates, was observed in the low-K group of animals can be accounted for by the progressively less effect reabsorption of potassium across the collecting duct epithelium as tubular volume flow rate increased. Diezi et al. (10) have previously shown by puncture of single collecting ducts in potassium-deprived rats that active potassium reabsorption is a consistent finding at this site. The present study indicates that this process becomes less effective with an increase in tubular flow rate into the collecting duct system.

Table 5 provides a summary of distal tubular recollection data during saline loading in the different experimental group. Data from control experiments are also shown. In this group of animals the saline infusion at the lowest rate (1.5 ml/h) was continued throughout the experiment, and the same distal tubule was repunctured over a time course of 30–60 min. The finding that the (TF/P) K/I remains at a value not significantly different from unity indicates that the recollection method is applicable under the experimental conditions of this study.

The data shown in Table 5 confirm that dietary potassium
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TABLE 5. Summary of distal tubular recollection data

<table>
<thead>
<tr>
<th>Diet Infusion</th>
<th>Control Diet</th>
<th>High K Diet</th>
<th>Low K Diet</th>
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<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>Urea-Saline</td>
<td>Urea-Saline</td>
</tr>
<tr>
<td>(TF/P)K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.93 ± 0.009* (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate flow</td>
<td>1.89 ± 0.12* (12)</td>
<td>1.32 ± 0.23* (9)</td>
<td>0.66 ± 0.12§ (13)</td>
</tr>
<tr>
<td>High flow</td>
<td>1.27 ± 0.32* (12)</td>
<td>1.53 ± 0.44* (11)</td>
<td>0.50 ± 0.12§ (9)</td>
</tr>
<tr>
<td>(TF/P)K/in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.15 ± 0.11* (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate flow</td>
<td>1.22 ± 0.29* (12)</td>
<td>1.85 ± 0.27* (9)</td>
<td>0.90 ± 0.20* (15)</td>
</tr>
<tr>
<td>High flow</td>
<td>2.86 ± 0.88§ (12)</td>
<td>3.59 ± 0.83§ (13)</td>
<td>1.01 ± 0.19* (14)</td>
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Numbers in parentheses are number of observations. The following are significantly different from 1.0 as follows: *NS. †P < 0.05. ‡P < 0.01. §P < 0.005.

intake has a marked effect upon distal tubular potassium transport. In animals receiving the control and high-potassium diet, administration of a saline or urea-saline load and the resulting distal tubular diuresis does not greatly affect transepithelial potassium concentration ratios. None of the experimental (TF/P)K is significantly different from control values with the exception of one group ((TF/P)K/In: moderate diuresis/control, control diet) in which a significant increase was observed. We have no explanation for this occurrence. It is safe to conclude from these data that the very dramatic increase of distal tubular flow rate does not interfere with the maintenance of essentially constant tubular potassium concentration values. In sharp contrast, the tubular potassium concentration falls during urea-saline loading in animals on a low-K diet. The respective potassium TF/P recollection ratios (TF/P experimental/TF/P control) were 0.66 and 0.50, respectively, indicating a progressive fall of the tubular potassium concentration as distal tubular flow rate increased.

Potassium secretion along the distal tubule increased in animals on a normal and high-potassium intake with delivery of larger fractions of glomerular filtrate into this nephron segment. This is documented by the augmentation of (TF/P)K/in ratios during both moderate and high urine flow rates which becomes highly significant at the higher flow rates. Again, a different behavior is typical of the animals maintained on a low-K diet. As evidenced by the constancy of the (TF/P)K/in ratios during all diuretic states, the fraction of potassium found at each site along the distal tubule remains unchanged despite a more than 10-fold increase in distal tubular flow rate.

A comparison of the absolute secretion rates of potassium in the several experimental conditions confirms the conclusions derived from consideration of fractional transport rates. Figure 2 provides a summary of potassium secretory rates, normalized to total distal tubular length, as a function of distal tubular flow rate. In potassium-loaded rats, distal secretion of potassium increased linearly with flow rate. Even at the highest distal flow rates no evidence of saturation was obtained. A similar behavior is typical of the animals on a control diet, although the stimulation of potassium secretion with augmented distal flow rate is less marked. In sharp contrast, in animals on a low-potassium diet, distal tubular potassium transport was not affected by flow augmentation. As pointed out before, this is due to the fact that the increase in distal flow rate is accompanied by a proportionate decrease in tubular potassium concentrations. Accordingly, the enhancement of distal flow rate is ineffective in stimulating distal tubular potassium secretion.

Figure 3 contains further data on distal tubular potassium secretion during different types of distal tubular solute diuresis. In the upper part the absolute rates of potassium secretion, normalized to total distal tubular length, are plotted as a function of tubular flow rate as the latter is increased by the intravenous infusion of isotonic saline. The lower part summarizes similar data of a series of experiments in which a urea-saline solution was used to increase fluid delivery into the distal tubule. Since the slope relating absolute potassium secretion to flow rate during saline infusion was significantly greater than that in the urea-saline group (P < 0.05), it can be concluded that the latter loading solution is less effective in stimulating distal tubular potassium secretion. It is of interest that at similar distal volume flow rates the induction of diuresis with a urea-saline solution is also less effective than a saline solution to augment both the luminal sodium concentration as well as absolute rate of distal tubular sodium reabsorption (23, 38). This relationship between distal tubular potassium secretion and sodium transport is consistent with a large body of evidence supporting the view that distal tubular sodium delivery stimulates potassium secretion.
The data summarized in Figs. 4–6 further underscore the importance of distal tubular sodium delivery, sodium reabsorption, and distal tubular sodium concentrations with respect to the rate of transepithelial potassium transfer.

Figure 4 summarizes data obtained during saline loading which were derived from measurements of tubular flow rate and of tubular potassium and sodium concentrations. It is apparent that with the enhancement of sodium delivery into the distal tubule, the absolute rate of potassium secretion along the distal tubule increases. We have not observed any saturation of the latter process, even at the highest sodium loads achieved.

An assessment of the relationship between distal tubular sodium reabsorption and potassium secretion in animals on different potassium intakes reveals significant differences in the tubular exchange ratio of these ions. Figure 5 summarizes relevant data on potassium secretion in control, potassium-fed, and potassium-deprived rats. As shown in Fig. 2 these maneuvers greatly modify the response of the distal tubular potassium secretory system to an increase in tubular flow rate. Net addition of potassium to the distal tubular lumen receives a powerful stimulus from distal fluid delivery in animals on a control or high-potassium intake, whereas this augmentation is absent in low-potassium rats. In sharp contrast to the situation with respect to potassium, the dietary pretreatment had no major effects upon the sodium transport pattern across the distal tubule. The exchange ratio of potassium secreted/sodium reabsorbed is high in high-K animals and declines with falling potassium intake. Thus, a sliding exchange ratio of K/Na exists, its magnitude being primarily related to the strength of the stimulus for potassium secretion.

Inspection of Fig. 6 demonstrates that there also obtains a fairly linear relationship between the amount of potassium secreted and the tubular concentration of sodium when the latter is varied by increasing the solute delivery into the distal tubule. As pointed out in other papers from this laboratory (23, 28), the tubular sodium concentration along the distal tubule, particularly its later part, increases in proportion to the increment of fluid delivered to this nephron site. Thus, the delivery of larger fractions of the glomerular filtrate into the distal tubule is followed by an increase in tubular sodium concentration, in net tubular sodium reabsorption, and in net potassium secretion.
FLOW RATE AND TUBULAR POTASSIUM TRANSFER

The most important finding of our experiments is the dramatic increase in distal tubular net potassium secretion which occurs in all but the potassium-deprived animals subsequent to the delivery of larger than normal amounts of fluid into the distal tubule. Figure 7 summarizes the effects of increasing distal tubular volume flow rate upon distal tubular potassium secretion. Two points should be noted. First, augmenting distal tubular fluid delivery enhances potassium secretion in rats on a normal and on a high-potassium intake. In contrast, net potassium secretion was absent in animals kept on a low-potassium diet. In these animals, increasing fluid delivery to the distal tubule was conspicuously ineffective in stimulating potassium secretion: net potassium secretion remained absent at even the highest distal flow rates. Second, it is also clear from inspection of Fig. 7 that the magnitude of the stimulatory effect of distal flow rate upon potassium secretion was affected by the state of the potassium secretory system. Similar increments in fluid delivery are much more effective in inducing augmented potassium secretion in high-K animals than in animals kept on a normal potassium intake. It should also be noted that in animals on a control potassium diet loading with saline was moderately more effective in inducing distal kaliuresis than a urea-saline solution.

The augmentation of distal tubular potassium secretion following the various loading maneuvers was associated with essentially constant tubular potassium concentrations at all distal tubular flow rates. This finding extends to the highest range of distal tubular flow rates and supports previous observations that free-flow potassium concentrations are generally close to steady-state values as measured in stop-flow microperfusion experiments (33). Morgan and Berliner (34), using continuous microperfusion techniques of single distal tubules, also observed that the concentration of potassium was almost unaffected by changes in flow rate. If the concentration of potassium in distal tubular fluid is independent of flow rate, tubular secretion rate varies directly and proportionately with distal volume flow rate. Net secretion of potassium into the distal tubule is thus flow limited. Accordingly, other factors remaining constant, the rate of volume flow past the secretory site of potassium constitutes a major factor determining the magnitude of the secretory process. We have previously provided evidence that the increase in potassium excretion following the administration of diuretics acting at a nephron site upstream of the distal tubule is primarily due to the delivery of larger than normal fluid loads to the distal tubule (35). These observations strongly implicate distal volume flow as an important factor regulating potassium secretion.

There are important exceptions to the described flow dependence of distal tubular potassium secretion. Thus, the induction of a water diuresis is not kaliuretic (1, 2, 11, 35, 39). Similarly, as shown in the present study, when urinary potassium excretion is initially low after dietary potassium deprivation, potassium excretion rate is not much affected by the administration of large saline loads, a maneuver which increases both the delivery of fluid and of sodium to the distal tubule. Under these conditions, the concentration of potassium in distal tubule fluid progressively falls as distal volume flow rate is increased. Hence, potassium excretion remains constant over a wide range of volume flow rates, and the rate of potassium influx into the distal tubule is transfer limited rather than flow limited. A fixed amount of potassium is transferred from cell to lumen per unit time independent of the rate of volume flow past the secretory site.

Kunau (26) has recently confirmed the flow dependence...
of distal tubular potassium secretion. Distal potassium tubular fluid/plasma concentration ratios remained constant during the dramatic augmentation of distal flow rate by volume expansion with saline (animals on a high-K diet) or after mannitol loading (cell dehydration). Accordingly, net secretion rate increased with volume flow rate. In animals excreting only some 8% of the filtered potassium load, the increase in flow rate was proportionately larger than the moderate fall in tubular potassium concentration and resulted still in a significant enhancement of distal tubular potassium secretion. This situation is intermediate between that seen in our low-potassium and control animals. We observed no fall in tubular fluid/plasma potassium concentration ratios in our control group excreting some 13% of the filtered potassium at low urine flow rates but noticed a fall in potassium tubular fluid/plasma concentration ratios in rats on a low potassium diet excreting less than 1% of the filtered potassium load at low urine flow rates. It was also confirmed by Kunau (26) that at a given distal tubular flow rate the greatly differing rates of distal tubular potassium secretion occurred with no significant modification of the simultaneously measured rates of sodium reabsorption.

In the following an attempt will be made to explain the different response of the distal potassium secretory mechanism to volume flow changes within the framework of what is presently known about distal tubular function. Figure 8 provides a summary of some essential features of distal tubular potassium transport. Also included are the possible modifications of the transport system which we consider responsible for the conversion of “flow-limited” into “transfer-limited” properties.

Several lines of evidence support the view that the variable net transfer rate of potassium ions across the distal tubule can be accounted for by two pump-leak systems in series, residing within an electrically asymmetrical tubule cell (12-15, 17). Across the peritubular cell membrane, a sodium-potassium exchange pump regulates potassium uptake into the tubule cell (7, 12, 17), but from the observation that the rates of net sodium reabsorption and net potassium secretion across the distal tubular epithelium can be dramatically dissociated from each other (12, 17, 31, 32, 45), it is unlikely that a fixed relationship exists between active potassium uptake and sodium extrusion. Across the luminal cell membrane, another pump-leak system modulates potassium transfer. Potassium diffuses from the cell into the lumen across the partly depolarized cell membrane (pd lumen < pd peritubular). This secretory flux component is opposed by an active potassium pump which we have shown to be ouabain sensitive (7, 33). In the rat on a normal or high-potassium intake, the luminal pump-leak system is poised toward net secretion, i.e., the potassium flux from cell to lumen exceeds that in the opposite direction.

In animals on a normal or high-potassium intake, the capacity of the “peritubular” potassium pump in the steady state must be large enough to compensate effectively for the significant egress of cellular potassium into the lumen which results from the increase in distal tubular flow rate. We consider the following to be the likely stimulus for increased peritubular potassium transport: 1) pump-driven peritubular potassium uptake is sensitive to the transmucobrane potassium concentration difference such as to maintain the cellular potassium concentration at near-normal levels by increasing its activity as the cellular potassium concentration begins to decline. It is the large adaptive increase in peritubular potassium uptake which prevents the cellular potassium concentration to decline below the critical level necessary to maintain the luminal potassium concentration at virtually unchanged levels despite the large increase in tubular flow rate. 2) An additional factor which would favor distal tubular secretion of potassium with increased flow rates and with the associated rise in luminal sodium concentration and sodium reabsorption is the increase in distal luminal negativity. We have shown in previous studies that the magnitude of the transmucosal potential difference across the distal tubule (lumen negative) is partly dependent on the luminal sodium concentration (16, 30). Accordingly, as the sodium concentration rises with increasing distal tubular flow rate, the electrical driving force favoring translocation of potassium into the tubular lumen increases. We have recently demonstrated that the sodium-induced increase in luminal negativity is largely due to peritubular hyperpolarization (40). This observation localizes the electrogenic effect on potassium of changing luminal sodium concentration at this cell site. The increase in cell negativity would lead to an increase in passive peritubular uptake of potassium.

Evidence based on 1) the magnitude of the electrical potential difference across the peritubular cell membrane of single distal tubule cells (44), on 2) tracer flux studies across single amphibian (41) and mammalian distal tubules (7), and on 3) intracellular measurements with potassium-sensitive microelectrodes (22) is consistent with the view that the effective intracellular potassium concentration declines in rats kept on a low-potassium diet. In kinetic studies on potassium transport in potassium-deprived rats, it can be shown that this phenomenon is due to a fall in peritubular potassium uptake (7). As a consequence, net secretion of potassium either ceases or is even changed to net potassium reabsorption as the unidirectional influx of potassium from cell to lumen drops below a critical level and leaves largely unopposed active potassium uptake from lumen to cell.
We propose further that it is the response of the intracellular potassium concentration to changes in luminal flow rate which plays a critical role as to whether the distal potassium transport system is flow or transfer limited. We suggest that in low-potassium rats peritubular potassium uptake must be much closer to limiting overall net secretion and that in contrast to the situation in control and high-potassium animals, peritubular potassium transport fails to maintain the intracellular potassium concentration at sufficiently high levels to assure and maintain the large increase of potassium transfer into the lumen which is necessary to sustain at a constant level the tubular concentration of potassium despite large increments of flow rate. It is virtually certain that in low-potassium animals the cellular potassium concentration falls sharply with increasing washout of potassium from tubule cells. Accordingly, the potassium flux into the lumen does not increase in proportion to tubular flow rate.

The role of sodium in generating the observed kaliuretic effects is of further interest. With the increase of fluid delivery into the distal tubule, the sodium load rises and both absolute luminal sodium concentration and absolute rate of reabsorption increase significantly (23, 38). We have shown previously that neither delivery of sodium to the distal tubule nor its rate of reabsorption is limiting to the amount of potassium secreted (31, 32). This conclusion is further supported by the present experiments in which it was shown that the rate of sodium reabsorption greatly exceeds that of potassium secretion. It has been pointed out by several investigators (3, 12-14, 24, 31), mainly on grounds of the adequacy of distal sodium supply prior to loading maneuvers, that it is difficult to conceive on the basis of a sodium-potassium exchange mechanism with a fixed exchange ratio how relatively small increments of sodium passing the site of potassium transport could effect the powerful stimulation of potassium secretion which is frequently observed. The dilemma is resolved if the following alternative mechanism is considered.

We propose that sodium delivery affects distal tubular potassium secretion by two other mechanisms. First, it is via the delivery of proportionately larger fluid loads to the distal tubule that sodium ions augment kaliuresis. Representative examples are the administration of exogenous sodium loads or inhibition of sodium reabsorption at a site prior to the distal tubule. Second, potassium secretion is further stimulated by the presence of sodium in the distal tubule and the collecting ducts where its reabsorption generates, in part, the distal luminal negativity (16, 30). By this mechanism, sodium ions play an important role in determining the magnitude of one of the driving forces favoring potassium secretion. In view of the low-anion permeability of the distal tubular epithelium (14, 30) and although not necessarily carrier mediated or proceeding at an exchange ratio of 1, potassium secretion across the luminal cell membrane represents sodium-for-potassium exchange with flow rate and the electrical potential difference providing an important link of coupling.

Of the two factors involved in the sodium effect on potassium transport, the delivery of larger than normal amounts of fluid ("flow" factor) is the more important one than the effect on the electrical potential ("electrogenic" factor). Whereas the distal tubular flow rate may vary dramatically over a range of an order of magnitude, the sodium concentration and the electrical potential difference (lumen negative) are not effected in a major way by increasing distal tubular flow rate but show only moderate variations (32). Thus, although sodium ions are necessary to maintain an electrical driving force for potassium secretion, the normal sodium concentration at this nephron site is associated with near-optimal electrical potential levels. Accordingly, the role of sodium ions with respect to its electrogenic effect is thus a minor one, whereas its role in accelerating flow rate (flow factor) is of major importance.

This interpretation of the role of sodium ions in potassium secretion also explains why the delivery of sodium-containing fluids into the distal tubule is more effective in stimulating potassium secretion than those which lower the tubular sodium concentration. A representative example is the more marked enhancement of distal tubular potassium secretion which follows the administration of isotonic or hypertonic saline loads (9) as contrasted to the less extensive kaliuresis after urea saline (see Fig. 1) or mannitol administration (9). The latter solutions contain a relatively poorly reabsorbable solute and thus limit the rise in tubular sodium concentration which uniformly occurs in the rat with the rise in distal tubular flow rate (23, 38) when sodium-containing fluid loads are administered.

The situation may be different at the level of the collecting duct where the amount of sodium available for reabsorption can be of the same magnitude as that of potassium secretion (8, 21) and where the sodium concentration may drop precipitously in states of maximal sodium conservation (8). Accordingly, the electrical potential difference (lumen negative) is affected more dramatically than at the distal tubular level. In addition, there is evidence that active sodium-potassium exchange takes place at this site (18). Accordingly, the sodium effect on potassium transport may be mediated by 1) diminished delivery of sodium affecting carrier-mediated sodium-potassium exchange and 2) diminished sodium delivery reducing intraluminal negativity and lowering the driving force for passive entry of potassium. The sum of these effects may be complete suppression of potassium secretion along the collecting duct and, indeed, the reversal of the direction of net transport. We have observed significant net reabsorption of potassium along the collecting ducts in states of low-sodium excretion (8). This latter mode of transport predominates whenever the secretory driving forces acting on potassium transfer fall below a critical level and leave unopposed the reabsorptive potassium pump.

The rather unspecific nature of coupling provided by the sodium-dependent electrical potential difference (lumen negative) at the distal tubular level is consistent with the widely varying coupling ratio between the transport rates of sodium and potassium. The exchange ratio may vary by more than an order of magnitude (compare low-potassium with high-potassium animals), depending both on the state of activity of the sodium reabsorptive and the potassium secretory system. Whereas the electrical driving force is largely dependent on sodium, the chemical driving force is set by the intracellular potassium concentration which depends on the activity of the peritubular potassium
uptake mechanism. By affecting flow rate and the magnitude of the electrical potential difference, the delivery of sodium ions provides an important control mechanism which in concert with the peritubular potassium pump determines the overall rate of distal tubular potassium secretion.

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REFERENCES


