

Potassium Adaptation After Reduction of Nephron Population

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Two weeks after 75 percent nephrectomy in rats fed a normal diet glomerular filtration rate was found to be reduced by 2/3 and there was no hyperkalemia. Normal K balance was maintained by a threefold increase of fractional urinary potassium excretion. When infused with 0.5 M KCl solution, both normal and 75 percent nephrectomized rats increased their fractional excretion, while normal rats kept on a very high K-diet did not further increase their fractional potassium excretion. Adaptation of fractional excretion to infused KCl was blunted in 75 percent nephrectomized rats given a low K diet.

Addition of 0.1 M KCl to the drinking water resulted in a three- to fourfold increase of potassium intake in normal rats: within 7 days, the Na-K-ATPase in the outer medulla of the kidney rose by 30 percent but no change occurred in the cortex. Further increases in dietary K load induced an increase of Na-K-ATPase activity, both in outer medulla and cortex, but not in other tissues. After 75 percent nephrectomy, specific Na-K-ATPase activity increased by 20-25 percent in the outer medulla and in the cortex.

Dietary K loading, in normal rats, also resulted in a large increase of net potassium secretion into the perfused colon and of specific Na-K-ATPase activity of the colonic mucosa. These effects of potassium loading were not abolished by adrenalectomy and were accompanied by an increase of transmural PD. It was concluded that chronic potassium loading may enhance secretion of potassium into lower nephron tubular fluid and into colonic contents by primarily stimulating the synthesis of Na-K-ATPase and the resulting increase of the number of pumping sites. 75 percent nephrectomy may induce similar changes in the remaining nephrons.

An adaptive increase in potassium secretion by renal tubular cells is characteristic of renal function in man and in animals with chronic renal insufficiency since potassium balance is well maintained, despite a reduction in nephron mass, until severe failure occurs. In previous studies in patients with chronic renal failure, it has been shown that fractional potassium excretion is inversely related to glomerular filtration rates, when normal dietary intakes are provided [1].

The characteristics of "potassium adaptation" and the cellular mechanism involved in that functional alteration were examined in our laboratory in experimental studies in which the excretory load of potassium was increased in two ways [2]. In one model, animals with intact renal function were provided with a potassium enriched diet, while in the other a normal potassium intake was administered to animals with a marked reduction in total nephron population. In the latter group chronic renal insufficiency was produced by the surgical removal of approximately five-sixths of kidney mass.

Two weeks after surgery and establishing a constant dietary intake acute clearance studies were performed to determine fractional potassium excretion under baseline, non-diuretic conditions and during the acute infusion of 0.5 M KCl, to stimulate potassium secretion. Experiments involving three groups of animals are shown in

Fig. 1, a control group, rats with 75 percent nephrectomy and a group of animals given a high potassium diet. Control animals and those with renal insufficiency were pair fed a normal diet, containing 0.13 mEq K per g, to insure a similar intake of potassium and other dietary constituents. The group given the high potassium diet received food containing 2.6 mEq K per g, 20 times the concentration of the normal diet. Surgical ablation of renal tissue reduced glomerular filtration rate to 3.8 ± 0.3 ml/min kg BW, approximately one-third the control value. The glomerular filtration rate in the group on the high potassium diet was not statistically different from control.

Fractional excretion of potassium during baseline periods is represented in Fig. 1 by clear bars. The stippled bar, labeled KCl_1 , represents the period 30–60 minutes after beginning the intravenous KCl infusion and the cross hatched bar, labeled KCl_2 , indicates the period 60–90 minutes. Two important features of “potassium adaptation” are shown by these data.

First, under baseline conditions fractional potassium excretion in 75 percent nephrectomized animals rose threefold, from seven to 20 percent, reflecting the decline in glomerular filtration rate, to one-third the control level, in the experimental group. Plasma potassium levels before acute KCl loading were normal in that group, as compared to control rats.

Second, potassium adaptation was demonstrable in both experimental groups, i.e., rats with renal insufficiency and high K animals, with increased excretory load of potassium, despite difference in oral potassium intake. Fractional potassium excretion during both experimental periods, KCl_1 and KCl_2 , was markedly increased above levels found in controls.

An important finding in this study was the observation that potassium adaptation in the nephrectomized group correlated directly with increased excretory load. When the intake of potassium was reduced by offering a diet containing 0.06 mEq K per g to animals with renal insufficiency, such that fractional excretion during baseline was not greater than control, potassium adaptation was not demonstrable.

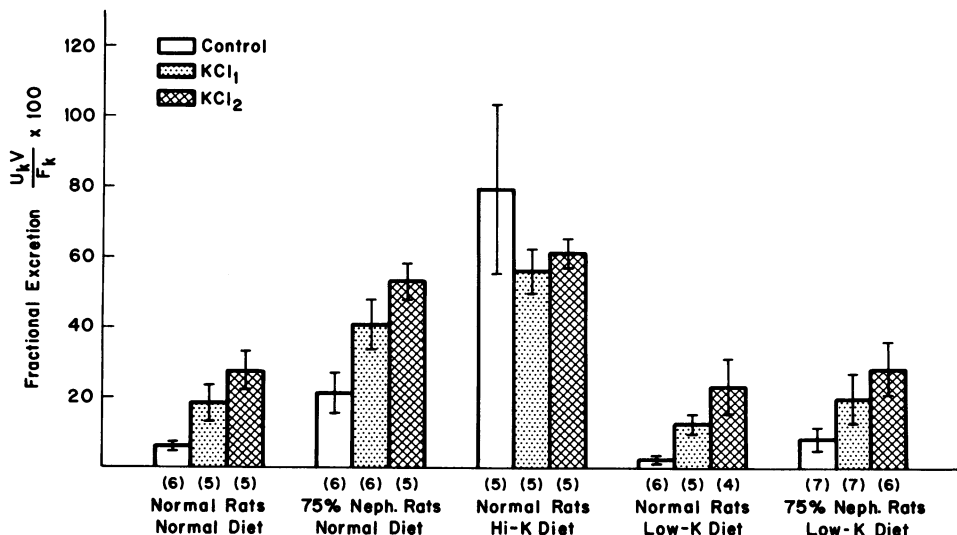


FIG. 1. Fractional excretion of potassium in normal and uremic rats on a varied potassium intake. Fractional excretion of potassium during control periods and during infusion of 0.5 M KCl in periods 30–60 minutes (KCl_1) and 60–90 minutes (KCl_2) after beginning infusion is shown. Number in parenthesis indicates number of animals studied.

Micropuncture studies have established that urinary potassium is derived predominantly from secretion in the distal tubule and collecting duct. Giebisch and coworkers [3] have provided evidence suggesting that transepithelial movement is primarily transcellular. This process involves cell uptake across the basolateral cell membrane and passive cell-lumen diffusion across the luminal membrane. It seems likely, therefore, that cell uptake of potassium would be accelerated in animals with "potassium adaptation." Since potassium uptake in exchange for sodium at that site is thought to be mediated by Na-K-ATPase it was of interest to determine whether that enzyme was linked to the mechanism of potassium adaptation.

Addition of 0.1 M KCl to drinking water increased potassium intake three to four times above the control level. After seven days the specific activity of Na-K-ATPase in the outer medulla of the kidney rose 30 percent, while no change occurred in the cortex [4]. Further increases in dietary load, by providing potassium in food and drinking water, resulted in a marked rise in enzyme activity in both outer medulla and cortex. The effect of potassium loading on enzyme activity was not apparently generalized since no change was found in other tissues examined, including brain, liver and skeletal muscle. It seemed unlikely that the increase in Na-K-ATPase activity was mediated through the action of aldosterone since chronic potassium loading induced the same changes in adrenalectomized animals. Moreover, chronic sodium deprivation, a condition known to stimulate aldosterone production, did not result in a rise in enzyme activity in animals with intact adrenals.

Since functional adaptation for rapid potassium excretion was also found in rats with 75 percent nephrectomy maintained on a normal potassium diet, Na-K-ATPase activity was determined in that group [2]. As in animals fed a high potassium diet, specific activity of Na-K-ATPase increased 20–25 percent in the outer medulla and cortex of the kidney. It was of interest that reducing potassium intake, so that the excretory load of potassium fell to normal levels in the experimental group with chronic renal failure, eliminated both functional adaptation and a rise in enzyme activity.

On the basis of these data it was suggested that Na-K-ATPase played a critical role in renal potassium adaptation. Having determined this relationship the question remained as to how changes in the activity of this enzyme enhanced the capacity of epithelial cells for potassium secretion. To explore the characteristics of this process further the effect of chronic potassium loading on colonic function was studied [5]. Previous reports had indicated a striking similarity in function between the distal nephron and colon in the mammal. Both epithelia are normally poised towards potassium secretion, exhibit low electrical conductance and are responsive to the action of mineralocorticoids [6,7]. In both tissues sodium is absorbed against a steep electrochemical gradient while net potassium movement appears to be passive.

In these experiments net movement of electrolytes and water was determined during continuous luminal perfusion, *in vivo*, of small intestine and colon and transepithelial electrical potential difference was measured simultaneously with agar bridges placed in the intestinal lumen and peritoneal cavity. Standard notation indicates a + sign for net absorption and a - sign for net secretion.

As shown in Fig. 2 chronic dietary loading with potassium resulted in a strikingly increased rate of net potassium secretion, which rose from a control value of 0.8 to 3.9 $\mu\text{Eq/hr g dry weight}$. Under the same conditions transmural PD rose twofold from a mean control value of 26 to 54 mV (lumen negative), and there was a marked increase in Na-K-ATPase activity. After seven days of a high potassium diet enzyme activity was $11.4 \pm 1.0 \mu\text{M P}_i/\text{mg protein/hr}$, compared to 5.0 ± 0.5 in controls ($p < 0.001$). The increase in net potassium movement in the colon of rats on a high

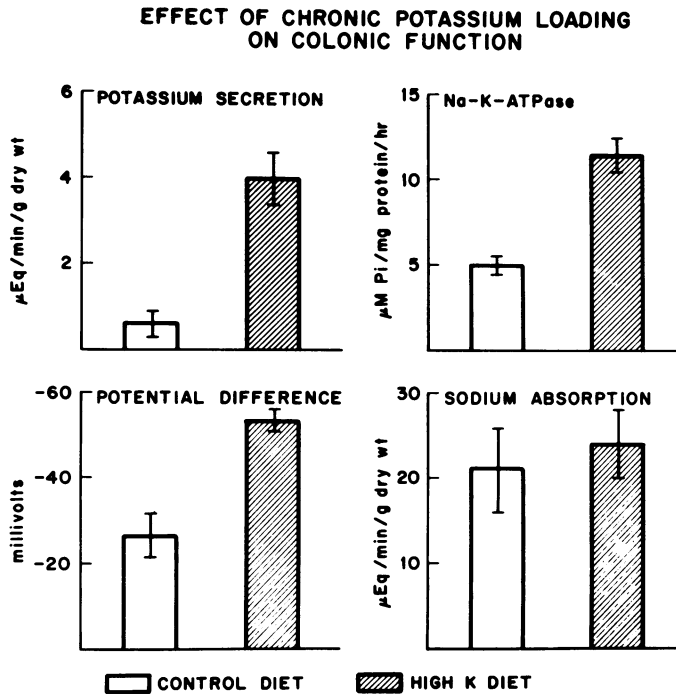


FIG. 2. Mean \pm SE values for net potassium secretion, Na-K-ATPase activity, transepithelial PD and net sodium absorption are shown for animals on a control diet and a high potassium diet.

potassium diet was not associated with changes in absorption of either water, sodium or chloride. Further experiments demonstrated that the functional and enzymatic alterations which occurred in colonic mucosa cells as the result of potassium loading were not mediated by aldosterone. Although adrenalectomy reduced baseline values of net potassium secretion, transmural PD and Na-K-ATPase activity, compared to levels in normal rats with intact adrenal tissue, chronic potassium loading induced an increase in each of these parameters in adrenalectomized rats. Moreover, chronic potassium loading did not influence transport function or enzyme activity in the small intestine. Net potassium absorption, transmural PD and Na-K-ATPase levels were similar in control and experimental groups.

An increase in enzyme activity may have resulted from an alteration in chemical properties or an increase in the number of pump sites. Changes in specific activity of Na-K-ATPase, in light microsomes, were therefore, determined as potassium concentration was varied. Although the apparent K_m of Na-K-ATPase was not statistically different between control and experimental groups V_{max} rose strikingly above control as potassium concentration was increased in tissue from potassium adapted animals. It seemed likely, therefore, that increased activity reflected a larger number of Na-K-ATPase pump sites.

The experimental observations made in this series of experiments permit some further insight into the mechanism of "potassium adaptation." Cellular modification to increase the capacity for potassium secretion occurs in both epithelia that are normally poised for potassium secretion. It is of interest that both the distal nephron and colon exhibit low electrical conductance and a high luminal negativity under normal conditions. Renal potassium adaptation occurs when the excretory load of

this ion is chronically increased. While previous studies have suggested that the distal tubule is the major nephron site responsible for increased potassium secretion after feeding a high potassium diet [8], the medullary collecting duct appears to play a predominant role in chronic renal failure [9,10,11]. The present studies indicate for the first time potassium adaptation in colonic mucosal cells during chronic potassium loading.

In both epithelia the capacity for enhanced rates of potassium secretion is associated with two characteristics—an increased activity of Na-K-ATPase and a marked rise in luminal negativity. The change in electrical properties of the distal tubule have been demonstrated by micropuncture techniques in the distal tubule [8] and in the colon by the present studies. How do these characteristics contribute to the process of net potassium secretion?

A hypothesis concerning cell modification for “potassium adaptation” depends on whether the observed increase in transepithelial electrical potential is due to depolarization of the luminal membrane and/or hyperpolarization of the basolateral cell membrane as shown in Fig. 3. In the event that depolarization of the luminal membrane occurred, perhaps as a result of increased lumen to cell movement of sodium, the rise in Na-K-ATPase could reflect a secondary phenomenon due to a rise in cell sodium and an increase in extrusion of sodium across the basolateral cell

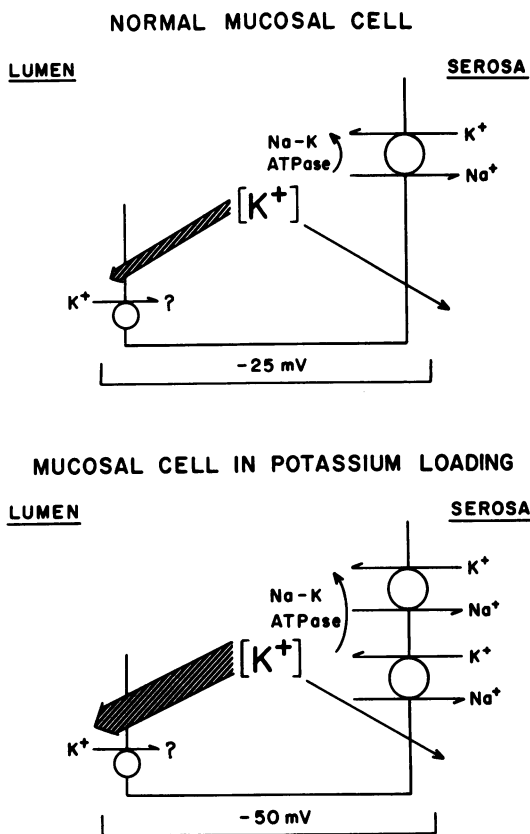


FIG. 3. Illustration showing changes in transepithelial PD, Na-K-ATPase and net potassium secretion. These parameters are shown in the normal cell in the upper portion of the figure and in the adapted cell in the lower portion.

membrane. Since luminal membrane PD is an electrical force that opposes leakage of potassium from the cell, a decrease in that factor would lead to a rise in the rate of passive entry of potassium into the lumen. In the steady state a corresponding increase in cell uptake of potassium would be required to maintain cell potassium at normal or slightly lower levels. Although a dissociation between net sodium absorption and potassium secretion rates has been demonstrated in the distal tubule of the rat [8] and in the colon, by the present study, unidirectional sodium fluxes have not been measured.

An alternative hypothesis can be characterized by a primary effect to cause hyperpolarization of the cell membrane separating interstitial fluid and cell. An increase in intracellular potassium concentration due to an enhanced neutral transport process in the basolateral membrane could increase cell negativity by the change in transmembrane difference of potassium concentration. Hyperpolarization could also result from an increased electrogenic transport process in that portion of the cell surface in association with levels of cell potassium concentration reflecting the more favorable gradient at the basolateral membrane. In either case the rise in cellular potassium would increase the driving force between cellular and luminal compartments favoring an increase in the rate of passive entry of potassium into luminal fluid. Future experiments involving measurement of unidirectional fluxes of sodium and potassium across the individual cell membranes, cell ion concentrations and corresponding electrical potential changes will help to define these relationships.

In respect to the close association between Na-K-ATPase and transepithelial PD it is tempting to speculate that the activity of this enzyme has an important influence on electrical properties of potassium secreting epithelia.

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