The Role of Na-K-Activated Adenosine Triphosphatase in Potassium Adaptation

STIMULATION OF ENZYMATIC ACTIVITY BY POTASSIUM LOADING

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ABSTRACT The specific activity of sodium-potassium-activated adenosine triphosphatase (Na-K-ATPase) in homogenates of rat kidneys increases when the dietary intake of potassium is chronically increased. The effect is seen first and is most prominent in the outer medulla, but large loads of potassium elicit an increase in the cortex as well. Levels of Na-K-ATPase in brain, liver, and muscle, by contrast, are unaffected by potassium loading. Although the changes in enzyme activity in the kidney resemble those reportedly produced by aldosterone, they are not induced by experimental sodium deprivation, and they can be evoked by potassium loading in the absence of the adrenal glands. The results suggest that Na-K-ATPase of renal tubular cells, presumably in the distal tubules and collecting ducts, plays an important role in the phenomenon of potassium adaptation and in the process by which potassium is excreted into the urine.

INTRODUCTION

Sodium-potassium-activated adenosine triphosphatase (Na-K-ATPase) is thought to be an essential part of the pump located in the plasma membrane of animal cells that is responsible for the active transport of sodium out of and potassium into the cell interior (1). It is present in high concentration in the kidney, especially in the distal nephron and collecting ducts (2), and has been implicated in the process of active reabsorption of sodium from the glomerular filtrate by renal tubules (3). The present experiments deal with the unexpected finding that Na-K-ATPase increases in an adaptive way when the requirement for potassium excretion by the kidneys is increased. The results suggest a major role for Na-K-ATPase in the process by which potassium is excreted into the urine and in the mechanism of "potassium adaptation."

Received for publication 24 January 1973 and in revised form 23 April 1973.

METHODS

Male Sprague-Dawley rats weighing 120–200 g were used for all experiments. Experimental animals were kept two to a cage and pair fed against control rats eating a normal diet ($Na^+ = 0.1$ meq/g of diet, $K^+ = 0.13$ meq/g) with free access to water. All diets were prepared in our laboratory.[1] Five different regimens were studied. Rats of *group I* received a normal diet but were given 0.1 M KCl as drinking water. In *group II*, the dietary content of K^+ was increased to 1.74 meq/g of diet, and in addition 0.1 M KCl was supplied as a drinking solution. In rats of *group III* sodium was removed from the diet but the normal potassium content was unchanged, and water was supplied ad lib. *Group IV* rats received no sodium in the diet but the content of potassium was high ($K^+ = 1.74$ meq/g), and 0.1 M KCl solution was supplied as drinking water. In *group V*, the animals were adrenalectomized and maintained on 50 μg of desoxycorticosterone acetate (DOCA, Upjohn Company, Kalamazoo, Mich.) given daily i.m. They were then

[1] Diet composition: (*a*) normal diet: sucrose 48.4%, casein 30%, lard 10%, corn oil 5%, vitamin diet-fortification mixture 2%, normal mineral mixture 3%, KCl 1%, NaCl 0.6%; (*b*) high potassium diet: sucrose 43%, casein 26%, lard 9%, corn oil 4%, vitamin diet-fortification mixture 1.8%, normal mineral mixture 2.7%, KCl 13%, NaCl 0.5%; (*c*) potassium diet fed to adrenalectomized rats: sucrose 45.7%, casein 28%, lard 9.5%, corn oil 4.5%, vitamin diet-fortification mixture 1.9%, normal mineral mixture 2.8%, KCl 7%, NaCl 0.6%; (*d*) no sodium diet: sucrose 49%, casein 30%, lard 10%, corn oil 5%, vitamin diet-fortification mixture 1.9%, normal mineral mixture 3%, KCl 1.1%.

fed either a normal diet plus a drinking solution containing 0.2% glucose and 0.9% saline, or a high-K diet containing $K^+ = 0.87$ meq/g plus 0.1 M KCl in solution with 0.2% glucose and 0.9% saline to drink. Except for the adrenalectomized animals which gained 10–15 g, the increase in weight both for experimental and control groups averaged 25–35 g. The animals were sacrificed at intervals of 7 and 14 days after the start of the regimen.

Under light ether anesthesia the animals were bled through the aorta using a heparinized syringe. Care was taken to avoid hemolysis, and grossly hemolyzed samples were discarded. The kidneys, approximately a third of the right lobe of the liver, the entire diaphragm and the brain were then removed and placed in ice-cold 0.9% saline. The excised kidneys were cleaned, stripped of their capsules and weighed. They were hemisected in the sagittal plane, and half of each kidney was used for enzyme assays and the other half for analysis of tissue electrolytes. The cortex, red medulla, and white medulla (papilla) were identified and dissected with a pair of fine scissors, discarding the tissue adjacent to the border, and placed in ice cold saline. When all kidneys were dissected, the pieces of cortex and red medulla were lightly blotted with filter paper, weighed, and then homogenized with a teflon pestle in a glass homogenizer immersed in ice in a 20/1 (vol/wt) solution containing 0.25 M sucrose, 6 mM EDTA, 20 mM imidazole, and 2.4 mM sodium deoxycholate (added just before use), pH 6.8. The homogenate was filtered through a double layer of gauze, and after 45 min assayed for enzyme activity.

Half of the portion of liver was homogenized 10/1 (vol/wt) in the same solution, and the other half was used for tissue analysis. Brain was homogenized in the same way in a 40/1 (vol/wt) solution. The diaphragm was separated into right and left halves. The right half was homogenized 10/1 (vol/wt) in the same solution using an all glass homogenizer, the rest of the procedure being the same as for the kidneys. The left half was used for determination of tissue electrolytes.

Na-K-ATPase activity was defined as the difference between the inorganic phosphate liberated in the presence and absence of potassium, corrected for spontaneous nonenzymatic breakdown of ATP. Total ATPase was determined in a 5 ml reaction mixture containing NaCl 100 mM, KCl 20 mM, imidazole buffer pH 7.8 10 mM, $MgCl_2$ 6 mM, and ATP disodium salt (Sigma Chemical Corp., St. Louis, Mo.) 6 mM, and enzyme suspension enough to bring the final protein concentration to 0.005–0.01 mg/ml. The reaction was started by the addition of ATP and $MgCl_2$ shaken in a water bath at 37°C for 15 min, and stopped by the addition of 1 ml of 35% (wt/vol) trichloroacetic acid. After centrifugation the inorganic phosphate liberated was measured by the method of Fiske and Subbarow (4), the optical density read at 660 nm in a 300 N Gilford spectrophotometer (Gilford Instrument Laboratories, Inc., Oberlin, Ohio) equipped with a quick sampling cell. The activity of the enzyme was expressed as micromoles of inorganic phosphate liberated per milligram of protein per hour (3).

5′-Nucleotidase was determined as described by Mitchell and Hawthorne (5). 0.1 ml of whole homogenate was added to 2 ml of a solution containing 100 mM KCl, 10 mM of $MgCl_2$ 10 mM of Na and K bitartrate, and 50 mM tris buffer pH 7.4. The mixture was prewarmed to 37°C and the reaction started by the addition of 0.1 ml of 100 mM 5′-adenosine monophosphate. After shaking in a Dubnoff water bath at 37°C for 45 min the reaction was stopped by the addition of 1 ml ice-cold 25% TCA. After centrifugation the supernate was assayed for inorganic phosphate as described for ATPase. The results were expressed as micromoles of inorganic phosphate liberated per milligram of protein per hour.

Determination of protein in the homogenates was carried out according to the method of Lowry, Rosebrough, Farr, and Randall (6) using crystalline bovine albumin (Sigma Chemical Corp., St. Louis, Mo.) dissolved in homogenizing solution as a standard.

For determination of electrolyte content, pieces of tissue were placed in tared dry weighing vials immediately after cutting, then were weighed and dried for 24 h in an oven at 120°C and reweighed, and the tissue water content was calculated from the difference. The dry tissue was then extracted and digested as previously described (7), and Na and K measured using a IL model 143 flame photometer (Instrumentation Laboratory, Inc., Lexington, Mass.).

Statistical analysis of the data was made using Student's *t* test wherever applicable.

RESULTS

Effect of a potassium load induced by drinking 0.1 M KCl on Na-K-ATPase in the kidney (Fig. 1). Rats maintained on a normal diet but given 0.1 M KCl to drink (group I) ingested an average load of potassium equal to approximately 4.5 meq/100 g body wt per day; the potassium intake of normal rats being about 1.3 meq/100 g per day. After 7 days, the specific activity of Na-K-ATPase in homogenates of outer (red) medulla was increased by 30% over controls, from 30.2±1.6 to 39.4±1.8 μmol Pi/mg protein per h. ($P < 0.01$). A further 7 days on the same regimen, for a total of 14 days of potassium loading, did not increase the activity of the enzymes further in medullary tissue. In contrast to the increase in enzyme activity in red medulla, this degree of potassium loading did not alter Na-K-ATPase activity in renal cortex. The change in ATPase activity in the outer medulla caused by potassium administration was confined to the Na-K-stimulated moiety; Mg-ATPase was unaffected (26.7±1.8 vs. 29.2±1.9 in medulla of control and K-loaded animals, respectively).

Effect of further increasing the dietary potassium load on renal Na-K-ATPase (Figs. 2 and 3). An attempt was next made to see whether a further increase in the content of potassium of the diet would produce effects that were different or more pronounced. A diet containing 1.74 meq/g of K^+ was offered to the animals coupled with a 0.1 M KCl solution to drink (group II). Under these conditions the daily intake of potassium calculated by weighing the food jar and bottle containing the drink-solution was roughly 20.0 meq/100 g body wt per day. The average daily excretion of K^+ in the urine was 16.5±1.8 meq for the K^+-loaded animals and 1.17±1.1 for the control animals, in reasonable agreement with the calculated values for intake. The load of

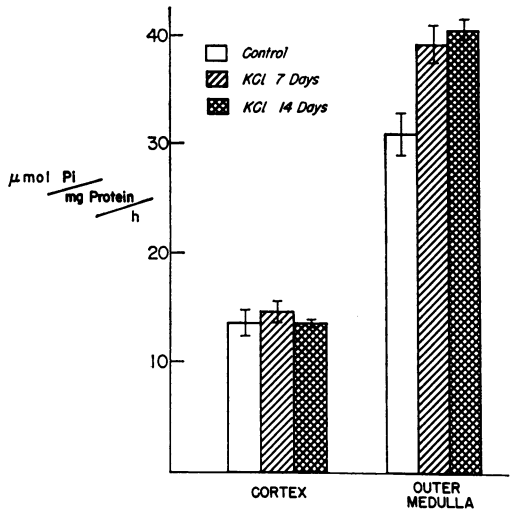

FIGURE 1 Effect of drinking 0.M KCl on renal Na-K-ATPase. The effect of a moderate increase in the daily intake of K^+ (±4.5 meq/100 g of rat per day) on renal ATPase is shown. No difference from control was found for the Na-K-ATPase in cortex after 7 or 14 days. A 30% increase ($P < 0.01$) was seen after 7 days in the outer medulla although there was no further increase after 14 days. Values are means ±SE. ($n = 6$ for control and experimental animals.)

potassium requiring excretion by the kidneys in rats of group II was therefore approximately four to five times that in group I.

Heavy potassium loading for 7 days increased the specific activity of Na-K-ATPase in kidney cortex by 27%, from 12.2±0.9 to 15.6±0.6 μmol of Pi/mg of protein per h ($P < 0.01$). Continuation of potassium loading for a total of 14 days increased cortical enzyme activity further to 58% above control (Fig. 3). Mg-ATPase was unchanged (control: 24.6±1.4 at 7 days, 27.4±1.4 at 14 days; K-loaded: 26.8±1.8 at 7 days, 24.8±1.6 at 14 days).

As in rats with a smaller potassium load, the activity of Na-K-ATPase in red medulla was also increased after 7 and 14 days of potassium administration. Again, no increase in Mg-ATPase was seen (control: 26.6±2.1 at 7 days, 31.1±1.7 at 14 days; K-loaded: 26.2±2.3 at 7 days, 26.8±2.6 at 14 days).

While potassium loading increased renal Na-K-ATPase, potassium deprivation did not do the reverse. Rats maintained on a potassium-free diet long enough to deplete muscle potassium stores and reduce serum potassium concentrations, had levels of Na-K-ATPase in kidney cortex and medulla that were indistinguishable from normal, confirming previous studies (3).

Effect of potassium loading on plasma and tissue electrolytes (Table I). After 1 wk of potassium loading at approximately 20 meq/100 g per day (group II)

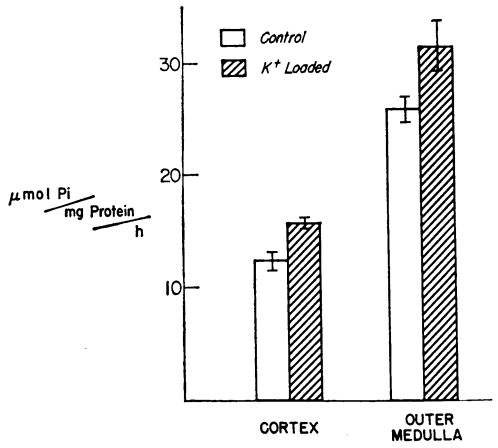

FIGURE 2 Effect of heavy K^+ loading for 7 days on renal Na-K-ATPase. Increasing the daily load of K^+ to approximately 20 meq/100 g of body wt per day stimulated the activity of Na-K-ATPase not only in the renal outer medulla but also in the renal cortex, increasing by 27% ($P < 0.01$) in the latter. Values are means ±SE. ($n = 14$ for controls and 18 for K-loaded rats.)

plasma potassium levels were not significantly higher in the potassium-loaded animals than in their controls, (4.7±0.3 vs. 4.1±0.1 meq/liter, $P < 0.05$). The animals had therefore adapted adequately to the large increase in potassium intake, presumably by increasing renal potassium excretion. Previous reports have shown that the plasma potassium levels of potassium loaded animals are significantly lower than those of their controls (8–

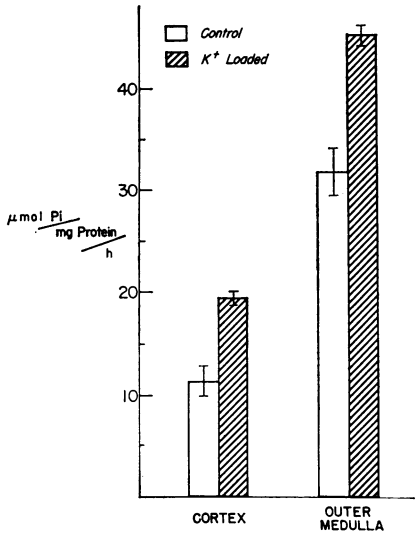

FIGURE 3 Effect of heavy K^+ loading for 14 days on renal Na-K-ATPase. After 14 days of high K^+ loading the activity of the renal Na-K-ATPase rose further both in cortex and outer medulla, by 58% ($P < 0.01$) and 44% ($P < 0.01$), respectively. Values are means ±SE. ($n = 6$ for controls, 8 for K-loaded animals.

TABLE I

*Tissue Sodium and Potassium Content in K^+ Loaded Rats**

	Sodium		Potassium	
	Control	K^+ loaded	Control	K^+ loaded
Papilla	182.5±15.6 (10)	175.8±12.7 (10)	54.4±3.0 (10)	58.5±3.8 (10)
Outer medulla	99.9±8.1 (10)	102.9±7.0 (10)	90.5±3.0 (10)	87.6±3.1 (10)
Cortex	105.7±8.0 (10)	105.1±6.9 (9)	84.1±2.9 (10)	85.7±3.9 (10)
Liver	55.6±5.5 (8)	48.8±2.8 (10)	136.6±6.4 (10)	139.2±4.6 (10)
Diaphragm	62.1±3.4 (9)	62.1±3.7 (10)	117.2±4.0 (9)	123.3±5.4 (10)
Plasma	136.0±1.0 (6)	137.3±1.5 (6)	4.1±0.1 (6)	4.7±0.3 (6)

* Values are mean±SE (*n*). All tissue values expressed as milliequivalents per kilogram of tissue water; plasma values are milliequivalents per titer of plasma. Animals were fed approximately 20 mEq of K^+/100 g per day for 7 days.

10); however, in those experiments the animals were fasted for a prolonged period before blood was taken, whereas in our experiments rats were allowed free access to food until just prior to sacrifice. It seems likely that this difference in protocol explains the difference in results (11).

No difference from control was found in the electrolyte composition of muscle (diaphragm), liver or kidney, or in electrolyte distribution throughout the kidney.

Effect of potassium loading on 5′-nucleotidase. Ample experimental evidence supports the fact that Na-K-ATPase is located in the plasma membrane of cells (1). We therefore measured the activity of another membrane-bound enzyme, 5′-nucleotidase, (12) to see if the increase in Na-K-ATPase brought about by potassium loading might be a general effect on enzymes associated with the plasma membrane. No difference in 5′-nucleotidase was detected in the cortex (3.9±0.1 control vs. 3.7±0.1 experimental). A small but significant decrease was apparent in the outer medulla (1.1±0.1 in control vs. 0.7±0.1 in potassium-loaded rats). A similar decline in the activity of 5′-nucleotidase in outer medulla has been reported in animals treated with methyl-prednisolone, although its biological significance is not clear (13).

Effect of K-loading on extrarenal ATPase (Table II). It was important to determine if potassium adaptation involved an increase in the Na-K-ATPase activity in other organs than the kidney, especially since it has been suggested that the underlying mechanism of potassium adaptation may be an extrarenal one (8). The activity of Na-K-ATPase in brain (whole homogenates) liver (whole homogenate and microsomes) and diaphragm (whole homogenate and microsomes) was unchanged by potassium loading. The effect on Na-K-ATPase appeared, therefore, not to be a general one, but to be localized to kidney tissue.

Possible role of aldosterone: the effect of salt deprivation on renal Na-K-ATPase (Figs. 4 and 5). Potassium loading stimulates the secretion of aldosterone (10, 14), and aldosterone increases the activity of renal Na-K-ATPase (15). It was therefore important to decide if the increase in Na-K-ATPase activity induced by potassium loading was mediated by an increase in aldosterone secretion.

Sodium deprivation and potassium loading each increase the secretion of aldosterone in rats to about the same degree (10). Accordingly, the effect of removing sodium from the diet for 7 days on renal Na-K-ATPase was measured (group III rats). In agreement with ear-

TABLE II

*Extrarenal ATPase in Potassium-Loaded Animals**

	Na-K-ATPase		Mg-ATPase	
	Control	K-loaded	Control	K-loaded
Brain (whole homogenate)	59.0±2.8 (8)	61.0±2.4 (8)	42.3±1.7 (8)	44.0±1.9 (8)
Liver (whole homogenate)	1.3±0.4 (6)	1.3±0.3 (6)	15.2±1.9 (6)	13.4±1.4 (6)
Liver (microsomes)	0.6±0.5 (6)	0.3±0.1 (6)	5.1±0.5 (6)	4.8±0.2 (6)
Muscle (whole homogenate)	4.1±0.9 (6)	2.8±0.6 (6)	36.6±3.5 (6)	36.0±1.8 (6)
Muscle (microsomes)	1.3±0.3 (6)	1.4±0.3 (6)	25.5±1.0 (6)	27.8±1.1 (6)

* Values are means±SE (*n*). Units are micromoles Pi per milligram protein per hour. Animals were fed a high potassium diet (±20 meq/100 g per day) for 7 days (group II).

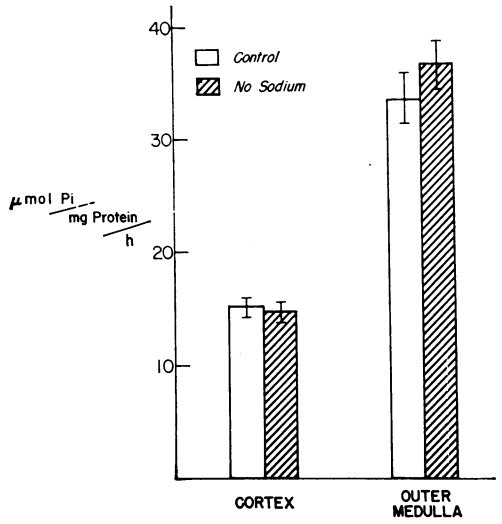

FIGURE 4 Effect of sodium deprivation on renal Na-K-ATPase. Feeding animals a no sodium diet for 7 days did not change the activity of Na-K-ATPase either in the cortex or the outer medulla. ($n = 6$ for normal and salt-deprived animals.

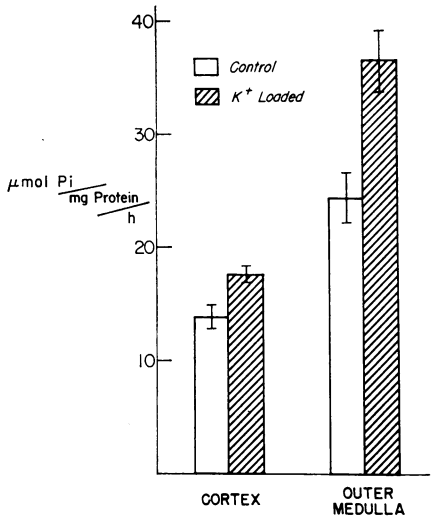

FIGURE 6 Effect of potassium loading on renal Na-K-ATPase in adrenalectomized rats. Both the adrenalectomized control and experimental animals were maintained on 0.2% glucose in 0.9% saline, and 50 μg of desoxycorticosterone acetate. Experimental group were given a potassium load of ±10 meq/100 g of rat per day. A 30% ($P < 0.01$) and 50% ($P < 0.01$) increase was observed after 7 days in both the cortex and outer medulla. Values are means ±SE. ($n = 6$ for both groups.)

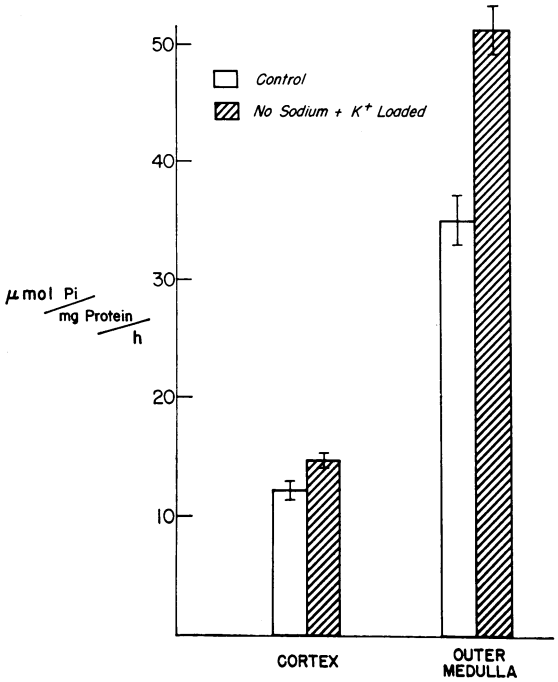

FIGURE 5 Effect of sodium deprivation and potassium loading on renal Na-K-ATPase. The activity of Na-K-ATPase increased 20% ($P < 0.05$) and 40% ($P < 0.01$) in the cortex and outer medulla, respectively, when a high load of K^+ (±20 meq/100 g of rat per day) was fed concurrently with a no sodium diet. Values are mean ±SE. ($n = 6$ for both groups.)

lier reports (13), no change in enzyme specific activity was detected (Fig. 4). On the other hand, when additional potassium was given to animals on a low-sodium diet, Na-K-ATPase activity increased in both medulla and cortex (Fig. 5). The response was similar to that seen in rats on a diet containing normal amounts of sodium. Sodium restriction did not therefore, block the capacity of the kidney to increase its Na-K-ATPase activity in response to potassium loads.

Possible role of aldosterone: potassium loading in adrenalectomized rats (Fig. 6). Adrenalectomized rats (group V) and their adrenalectomized controls were maintained on 50 μg of desoxycorticosterone acetate intramuscularly daily and given 0.2% glucose in 0.9% NaCl as drinking water. Because massive potassium loads are lethal in adrenalectomized rats, the daily intake of potassium was set at approximately 10 meq/100 g per day for 7 days, about half of that given to normal rats to induce potassium adaptation in the experiment previously described.

Potassium loading increased the specific activity of Na-K-ATPase in the kidney in adrenalectomized rats (Fig. 6). Na-K-ATPase in the outer medulla was augmented by 50%, from 24.3±2.4 to 36.5±2.6 μM Pi/μg protein per h. The activity in the cortex rose as well, though not as strikingly, from 13.7±1.0 to 17.5±2.0, an increase of 27%. No change in Mg-ATPase was seen

(control cortex 38.8±1.2; K-loaded cortex 41.1±1.3; control medulla 42.8±0.6; K-loaded medulla 45.1±1.1).

DISCUSSION

When animals are chronically loaded with potassium they rapidly develop the ability to avoid hyperkalemia by excreting large amounts of potassium into the urine (16). The mechanism by which this protective adaptation is accomplished involves the secretion of potassium into the urine by cells of the distal convoluted tubule and collecting duct (9). Giebisch, Boulpaep, and Whittembury have shown that the secretory movement of potassium into the lumen of the distal convoluted tubule proceeds down an electrochemical gradient (17). Peritubular uptake of potassium is thought to control the magnitude of the intracellular potassium pool and thus the driving force acting on potassium as it moves across the luminal cell membrane. If this is the case, even small elevations in intracellular potassium concentration might be expected to enhance greatly the rate at which potassium is secreted into the distal tubule and excreted into the urine.

The present experiments suggest that an important mechanism of chronic adaptation to potassium loads involves a selective increase in Na-K-ATPase in renal tubular cells. An increase in dietary potassium amounting to roughly three to four times the normal intake regularly produced an increase in renal Na-K-ATPase which was apparent in the outer medulla, where thick ascending limbs of Henle abound, but not in the cortex, where proximal convoluted tubules predominate (18). A further massive increase in the requirement for potassium excretion resulted in substantially increased activity of the enzyme in renal cortex as well as medulla. The increase in enzyme activity in the kidney was selective in that it was not seen in liver, brain, or muscle, and it was not accompanied by any change in the activity of Mg-ATPase or of 5′-nucleotidase, another enzyme thought to be bound to the plasma membrane. Since the Na-K-ATPase of renal tubular cells is largely localized to the basal portion of the cell (19), it seems reasonable to assume that an increase in the activity of this enzyme in renal cells would result in an increased capacity to accumulate potassium from the blood and extracellular fluid, and that the intracellular concentration of potassium might therefore be raised, thus accelerating the excretion of potassium into the urine. Though we could not demonstrate an increase in tissue potassium in the kidney in the present potassium-loading experiments, this may have been because cellular potassium was increased only in a minority of cells—those lining the distal tubules. It is clear that the activity of Na-K-ATPase, per unit dry weight is six to eight times as great in the distal nephron as in the proximal convoluted tubule of the rat kidney (2). Adaptation to potassium loads increased the potential difference across the perfused collecting duct of the rabbit kidney (20) and across the distal tubule in the rat (9). The explanation suggested by our present findings is that this is due to enhancement of the Na-K-ATPase pump in the basal borders of tubular cells by potassium loading.

The increase in Na-K-ATPase induced in the kidney by potassium loading is similar to that produced by aldosterone in that both appear most prominently in the outer medulla of the kidney (15). The fact that potassium stimulates aldosterone secretion makes it attractive to speculate that potassium loads exert their entire effect on renal Na-K-ATPase via aldosterone. Nevertheless several facts stand in the way of this interpretation. Sodium depletion, a powerful stimulus to aldosterone production, is not associated with enhanced Na-K-ATPase activity in the kidney. The possibility that there might be something peculiar about sodium deprivation that blocked an increase in enzymatic activity is rendered unlikely by the observation that when potassium loads are superimposed on sodium depletion, rats show the expected increase in renal Na-K-ATPase. Finally, the demonstration that potassium administration increases renal Na-K-ATPase in adrenalectomized animals eliminates the possibility that the effect of potassium depends on an increase in the secretion of aldosterone or other adrenal hormones. The possibility that mineralocorticoids exert a permissive action is not eliminated, since the adrenalectomized rats in this study were maintained on desoxycorticosterone.

Physiological adaptation by the kidney to potassium loading must involve several components, some rapid and some slow. A simple increase in serum potassium probably results directly in increased cellular uptake of potassium by renal cells and increased potassium secretion into the urine. Aldosterone secretion is increased by potassium administration, and aldosterone in turn accelerates sodium reabsorption from distal tubular urine in exchange for potassium (21). This effect is apparent within hours. The increase in Na-K-ATPase activity is a slower process, occurring within days. A similar increase can be produced by injections of aldosterone, and it is therefore possible that aldosterone contributes to the enzymatic effects of potassium loading in normal animals. But it is also apparent from the present experiments that potassium loading has an effect of its own upon enzyme adaptation in the kidney, even in the absence of aldosterone. The mechanisms by which this is accomplished is not clear; it may involve a special sensitivity of certain renal tubular cells to levels of potassium in serum or urine, or the participation of other hormonal factors not yet identified. It is conceivable that chronic potassium loading might somehow diminish reabsorption

of sodium in the proximal tubule, thus presenting distal tubules with an increased reabsorptive load and thereby stimulating the activity of Na-K-ATPase. This seems unlikely from the experiments of Wright, Streider, Fowler, and Giebisch (9) who showed that the absolute rate of delivery of sodium to the distal tubule of potassium-loaded rats was the same as in rats on a normal diet.

Much attention has heretofore been focused on the role of Na-K-ATPase in maintaining the electrolyte composition of intracellular fluid, in controlling cell volume, and in influencing the transepithelial transport of sodium by many organs including the kidney. The present experiments emphasize its importance in a different physiological role: that of mediating the secretion of potassium into the urine. The fact that Na-K-ATPase changes in an adaptive way when the requirements for potassium excretion increase suggests that it plays a central part in that process, and this invites speculation about its role in pathological states. Secretion of potassium into the urine is accelerated by remaining nephrons in renal insufficiency, as well as by normal kidneys during potassium loading. It seems likely that a key function of the increased specific activity of Na-K-ATPase that characterizes compensatory hypertrophy of the kidneys (3) is to enhance their ability to excrete potassium.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Mrs. Nadia Myketey, Mrs. Deborah F. Perlman, Mrs. Adele Powell, and Mrs. Trudy Klein-Robenhaar for valuable technical assistance.

This work was supported by U. S. Public Health Service grants HL-00834, HL-15571, and AM-1634, and by the American Heart Association.

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