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### Research Article

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# Demonstration of Active Potassium Transport in the Mammalian Colon

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**ABSTRACT** The mechanism responsible for K transport in the mammalian colon is controversial. Experiments were performed to determine whether K secretion involves active as well as passive driving forces in controls and in animals with a marked increase in K secretion. In these experiments a steady-state solution was established in proximal and distal colon of both control rats and animals fed a K-enriched diet during *in vivo* luminal perfusion, to compare the observed luminal [K] with predicted equilibrium [K] when net water and electrolyte movement approached zero. Transmural potential difference was measured simultaneously. A difference between the predicted equilibrium and observed luminal [K] under this condition indicates active transport. In controls the observed [K] of 20 mmol/liter in proximal colon markedly exceeded the predicted value of  $6.2 \pm 0.3$ , mean  $\pm$  SE, indicating active secretion. In contrast, the observed [K] in distal colon of 5 mmol/liter was less than predicted ( $10.0 \pm 1.0$ ), suggesting active absorption. In K-loaded animals active K secretion was demonstrable and increased above control in both segments of colon. In proximal colon the observed [K] rose to 40 mmol/liter, compared to a predicted value of  $7.2 \pm 0.3$ , whereas in distal colon the observed [K] was 50 mmol/liter vs. a predicted value of  $7.0 \pm 0.8$ .

These studies suggest active K secretion in proximal, but not in distal colon of control animals. Further, these data suggest that the increase in the capacity for K secretion that occurs in response to chronic K loading involves stimulation of an active mechanism in both proximal and distal colon.

## INTRODUCTION

Net K secretion is a constant phenomenon in the mammalian colon, but its mechanism is controversial. Previous studies, performed under *in vitro* conditions

in several species, in the absence of electrical gradients, have shown either no evidence of active K transport (1, 2) or small, but statistically significant net, and presumably active, K movement (3–6). There have been no *in vivo* studies performed under conditions that permit distinction between active and passive driving forces.

In the present study *in vivo* experiments were performed to determine whether an active transport process for K is present in the colon of the rat under control conditions, and whether an active transport mechanism, or a change in such a process, mediates the adaptive increases in K secretion that occurs after chronic oral K loading. This study was designed to examine the distribution of K across the colonic mucosa when net water and electrolyte movement approached zero in normal and K-loaded animals. Results indicate that in control animals active secretion of K is present in proximal colon, but suggest an active absorptive mechanism in distal colon. In K-adapted animals these data demonstrate that active K secretion was stimulated in proximal colon, and resulted in a doubling of the active transport potential above control. Under the same conditions an active secretory process was uncovered in distal colon, and resulted in an active transport potential of  $\sim 50$  mV, a value that was similar to that observed in proximal colon.

## METHODS

Male Sprague-Dawley rats, weighing 225–300 g were used in all experiments and allowed free access to food and tap water until the time of study. Control animals were fed regular Purina Chow (Ralston Purina Co., St. Louis, MO.) which contained by analysis 0.16 meq Na/g of food and 0.28 meq K/g of food. The experimental group was given the regular diet supplemented with KCl to contain 2.0 meq/g of food. Both groups were fed 20 g of their respective diets per day to insure a similar intake of calories, protein, and electrolytes, except for the dietary intake of K. After 14–21 d of dietary preparation anesthesia was induced with sodium 5-ethyl-5-(1-methyl-propyl)-2-thio-barbitursaurate (Inactin, Byk Gulden Konstanz, West Germany) in a dose of 80–120 mg/kg wt. A

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tracheostomy was performed, and a catheter (PE-20) was inserted into one carotid artery for blood sampling and into one jugular vein for fluid administration. To replace surgical losses of fluid 0.15 M NaCl was infused intravenously at the end of surgery, in a volume equal to 1% body weight. Body temperature was maintained at 37°C with a heating board or an overhead lamp, and monitored with a rectal probe.

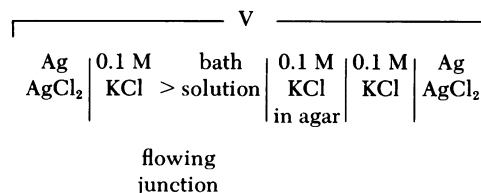
After induction of anesthesia and rinsing of lumen with warmed test solution to clear the intestinal contents, the proximal and distal colon were identified, and the proximal and distal ends of each segment were cannulated with PE-250 polyethylene tubing. The proximal colon was regarded as extending from the ileocecal value to the midpoint of the colon, and the distal colon as extending from the midpoint to the anus. Each segment was perfused at a constant rate of 0.20 ml/min by an infusion pump (model 975, Harvard Apparatus Co., Inc., So. Natick, Mass.). The solution labeled Ringer's solution contained (mmol/liter) 140 Na, 5 K, 120 Cl, and 25 HCO<sub>3</sub>. The perfusion solution contained both unlabeled and [<sup>14</sup>C]polyethylene glycol, as a nonabsorbable marker to permit measurement of net water movement. Experimental solutions contained different amounts of NaCl, KCl, KHCO<sub>3</sub>, as required by the experimental design, and mannitol in a concentration sufficient to provide a final osmolality of 290 mosmol/kg H<sub>2</sub>O. After a 45-min equilibration period samples of effluent from three periods of 20 min each were obtained to determine net fluid and electrolyte movement. An arterial sample was obtained at the midpoint of each clearance period for measurement of the plasma concentration of Na<sup>+</sup>, Cl<sup>-</sup>, and K. At the completion of the study each intestinal segment was dried to a constant weight to determine dry weight.

Standard equations were used to estimate net water and electrolyte movement (7). Mean values were obtained for each animal by averaging the results from three individual 20-min collection periods. A positive value (+) denotes net absorption and a negative value (−) indicates net secretion.

The transmural electrical potential difference (PD)<sup>1</sup> was measured simultaneously with the determination of net water and electrolyte movement during perfusion studies. Polyethylene tubing (PE-205) containing 4% agar in 0.1 M KCl was placed in the lumen through the distal end of each intestinal segment and in the peritoneal cavity. Agar bridges were connected to balanced calomel half cells (Beckman Instruments Inc., Fullerton, Calif.). The transmural PD between intestinal lumen and the peritoneal cavity was measured by a direct current potentiometer (610c solid state electrometer; Keithly Instruments Inc., Cleveland, Ohio). The tips of the exploring electrodes were placed at the site of the maximal PD in distal colon, as determined experimentally (8). Because the PD remained constant throughout the length of proximal colon, the electrode tip was placed in the middle of the segment. During perfusion studies, the PD was determined at 10-min intervals.

Since perfusion solutions of varying ionic strength and composition were used in this experiment, it was necessary to correct for different diffusion potentials created between those solutions and the tip of the exploring electrode. The values of the diffusion potentials were determined in vitro by comparing the difference in electrical asymmetry between Ringer's solution and each of the experimental test solutions. The in vitro set-up is shown below, and each electrolyte solution was placed in the compartment labeled "bath". The flowing junction had a diffusion potential of approximately zero. Appropriate corrections of the observed in vivo values were made based upon the in vitro determinations.

Diffusion potentials between Ringer's solution and experimental solutions varied between 3–4 mV.



The Student's *t* test was used for statistical comparison and values are given as mean ± SEM.

The predicted equilibrium concentration of K in luminal fluid was calculated from the Nernst equation, where PD = 26.7 mV ln [K] lumen/[K] plasma, using the observed PD and [K] plasma values. The active transport potential ( $E_i^{\text{act}}$ ) for K and Na across colonic epithelium was defined as;  $E_i^{\text{act}} = \text{PD} + 26.7 \text{ mV} \ln [i] \text{ lumen}/[i] \text{ plasma}$ , where *i* is either Na or K and PD, [i] lumen, and [i] plasma are the experimentally observed values. Under the condition of zero net solvent movement the value  $E_i^{\text{act}} \neq 0$  indicates that the distribution of the ion (*i*) cannot be accounted for on basis of the physicochemical properties of the two phases separated by the membrane.

## RESULTS

To determine whether K transport in the colon is driven by an active process, the ratio of K concentrations predicted at equilibrium from the observed electrical potential difference, under the condition where net water and electrolyte movement approached zero, was compared with the observed ratio of K concentration that existed experimentally across the intestinal epithelium, under the same conditions, in both control and experimental animals.

In preliminary studies we used the technique of evaluating the steady-state electrochemical gradients of electrolytes across epithelium between extracellular fluid and a stationary column of luminal fluid containing a poorly absorbable solute; a method that has been employed in vivo micropuncture experiments on renal tubules (9). Because net water, Na and Cl secretion occurred over a wide range of Na and Cl concentrations in luminal fluid, including the Ringer's solution, it was not possible to achieve a steady-state condition (or to observe fluid movement at a rate close to zero). Although the mechanism of secretion under this experimental condition was not elucidated, it was assumed to reflect the effect of limited distension of the colon, which in small intestine is associated with net fluid, Na, and Cl secretion (10).

To determine the electrochemical gradient for K when net movement of water and all major electrolytes had been reduced to near zero, a method of continuous luminal perfusion was devised. In these experiments the proximal and distal segments of colon were perfused with solutions containing varying concentrations of Na, Cl, HCO<sub>3</sub>, and K to ascertain their steady-state

<sup>1</sup> Abbreviation used in this paper: PD, potential difference.

levels. In these experiments the individual concentrations of Na, Cl, and  $\text{HCO}_3$  in the perfusate did not differ by more than 10 mmol from the levels in the steady-state solutions characterized by zero movement of K. Isotonicity was maintained by the addition of mannitol. In addition, the transmural electrical potential difference, corrected for diffusion potential, was simultaneously measured.

Net water and electrolyte movement during perfusion of proximal and distal colon of control and K-loaded animals with the experimentally derived steady-state solutions are shown in Figs. 1 and 2 as a percentage of levels observed during perfusion with Ringer's solution. The composition of the steady-state solution in control and experimental animals, and the respective PD measurements, obtained under the same conditions, are shown in Table I. These data show that net transport of water and solutes were

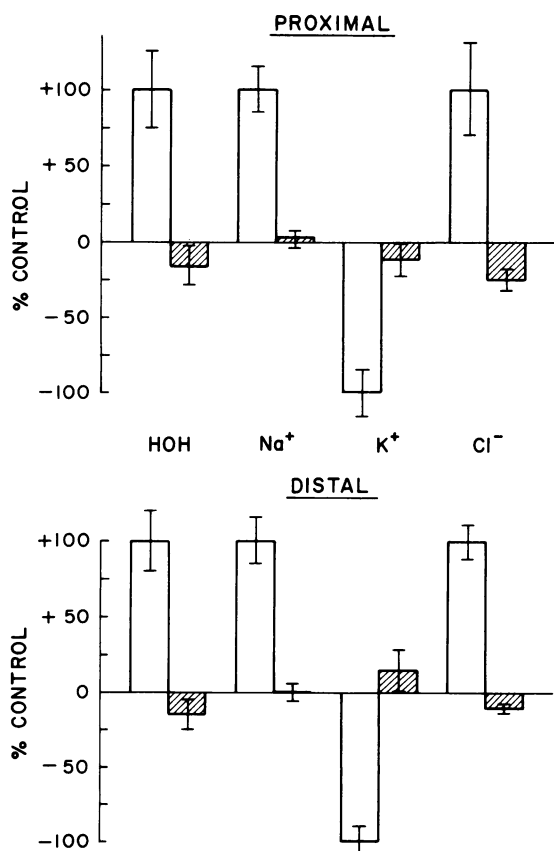


FIGURE 1 Net movement of HOH and electrolytes during perfusion of controls with the steady-state solution, used to determine the K concentration when net HOH and electrolyte transport approached zero, is shown by the hatched bars as a percentage of net transport during perfusion with Ringer's solution (open bars). The bars and brackets represent mean  $\pm$  SE. Only the rate of movement of Cl in the proximal segment was significantly different from zero ( $P < 0.05$ ).

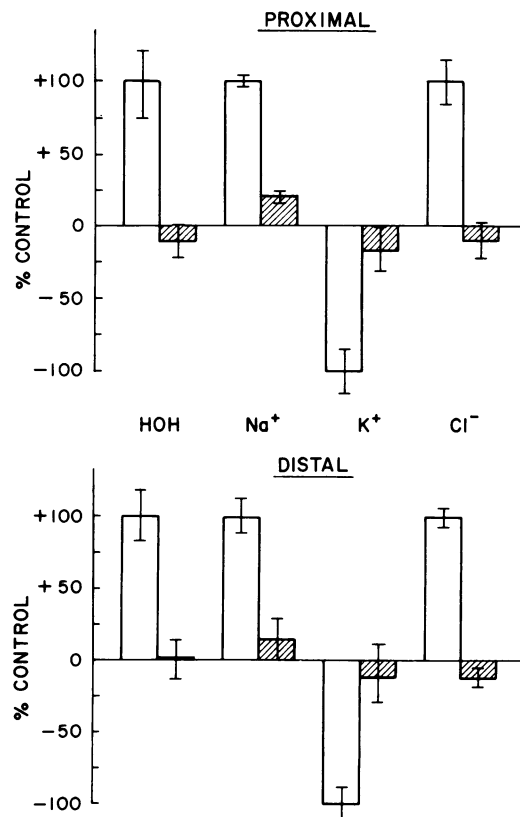


FIGURE 2 Net movement of HOH and electrolytes during perfusion of experimental animals with the steady-state solution, used to determine the K concentration when net HOH and electrolyte transport approached zero, is shown by the hatched bars as a percentage of net transport during perfusion with Ringer's solution (open bars). The bars and brackets represent mean  $\pm$  SE. Only the rate of movement of Na in the proximal segment was significantly different from zero ( $P < 0.05$ ).

markedly reduced compared with levels observed during perfusion with Ringer's solution, and net water and potassium movement were not statistically different from zero during perfusion with the steady-state solution in each segment of colon.

In proximal colon of control animals zero net movement of K, in the absence net water movement, occurred during perfusion with a K concentration of 20 mmol/liter. Additional experiments were performed to study the effect of increases or reductions in K concentration, relative to the steady-state value. In these studies the concentrations of the other ionic constituents were varied by changes of 5–10 mmol/liter about their respective steady-state values shown in Table I. Although net water movement continued to approach zero, K secretion, shown in Fig. 3, was observed during perfusion with solutions with K concentrations of 5 and 15 mmol/liter and net absorption with K concentrations

TABLE I  
*Composition of Perfusate and Transmural Potential Difference during Perfusion with the Steady-State Solution When Net Movement of Water and Electrolytes Approached Zero*

	K	Na	Cl	HCO <sub>3</sub>	PD*	Plasma K concentration
	mmol/liter				mV	mmol/liter
Control animals						
Proximal colon	20	15	25	10	6.8±1.3	4.7±0.3
Distal colon	5	35	10	27	18.4±2.2	
Potassium adapted						
Proximal colon	40	25	40	25	12.9±0.9	4.3±0.2
Distal colon	50	20	30	40	11.4±2.7	

\* Values of PD are mean±SE observed during perfusion with steady-state solution, corrected for diffusion potentials.

of 25 and 30 mmol/liter. In contrast, in the distal colon of control animals zero net movement of K occurred during perfusion with a K concentration of 5 mmol/liter. Using a technique similar to that employed in proximal colon, variations in K concentration resulted in net K secretion at concentrations of 0 and 2 mmol/liter and net absorption when the concentration was raised to 10 mmol/liter.

Using the average plasma K concentration of 4.7 mmol/liter and transmural electrical potential difference, the equilibrium luminal concentration of K which would satisfy the electrochemical equilibrium across the entire epithelium was calculated using the Nernst equation. The predicted value of K was then compared with the value experimentally observed during zero net K movement. The results are shown in Fig. 4. In proximal colon the observed steady-state value of K concentration of 20 mmol/liter was approximately threefold higher than the predicted equilibrium  $6.2 \pm 0.3$  mmol/liter and indicates the presence of active K secretion. In contrast, the observed K concentration in luminal fluid in distal colon of 5.0 mmol/liter was less than the predicted value of  $10.1 \pm 1.0$  mmol/liter and is consistent with the concept that, under these experimental conditions, active K absorption was present. Because the observed steady-state value of K was determined as the concentration at which net transport was not statistically different from zero, in the absence of net water movement, a value for variance cannot be provided.

Using these data it was also possible to calculate the active transport potential for K, which was defined as the difference between the electrical and chemical driving forces acting on K distribution across the membrane. In proximal colon secretion occurred against a force of  $+31.9 \pm 1.3$  mV, whereas in distal colon absorption occurred against a gradient of  $-16.7 \pm 2.2$  mV.

The administration of a K enriched diet for 2–3 wk

has been shown to result in a marked increase in net K secretion in vivo during perfusion of the entire colon with Ringer's solution (8). In the present study an increase in K secretion was found to occur in both proximal and distal portions of colon. During perfusion with Ringer's solution K secretion in the K-loaded animals was  $1.60 \pm 0.25$   $\mu$ eq/min per g dry tissue weight (compared with  $0.86 \pm 0.13$   $\mu$ eq/min per g dry tissue weight in controls,  $P < 0.01$ ) and  $3.96 \pm 0.77$   $\mu$ eq/min per g dry tissue weight (compared with  $2.00 \pm 0.37$   $\mu$ eq/min per g dry tissue weight,  $P < 0.01$ ) in the proximal and distal colon, respectively.

To determine whether an active transport process plays a role in the adaptive change in secretion in experimental animals, the steady-state concentration of K was estimated during perfusion with steady-state solutions (composition is indicated in Table I). In the proximal colon of control animals, as already noted, perfusion with a solution containing 20 mmol/liter of K resulted in zero K movement. In contrast, in K-loaded animals, zero net movement during perfusion with the steady-state solution occurred with a K concentration of 40 mmol/liter, as shown in Table I and Fig. 4. Variations in K concentration, using the method employed in control experiments, resulted in net secretion at K concentrations of 20, 25, and 30 mmol/liter as shown in Fig. 5.

In distal colon of K-loaded animals similar results were obtained. In contrast to control animals, in which a steady-state value of 5 mmol/liter was observed, perfusion of distal colon in experimental animals with solutions containing K at 20, 30, and 40 mmol/liter, and near steady-state levels of Na, Cl, and HOH, resulted in net secretion. Zero net K movement, in the absence of HOH transport, was achieved when the K concentration of perfusate was increased to 50 mmol/liter, as shown in Table I and Fig. 4.

The equilibrium values and experimentally observed

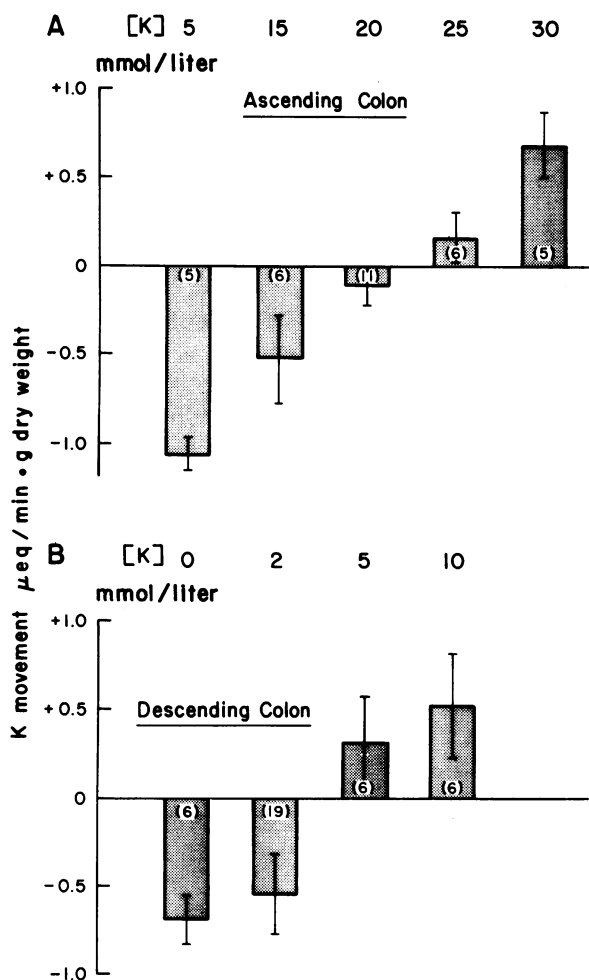


FIGURE 3 Net movement of K in proximal (A) and distal (B) colon of control animals during perfusion of lumen with reductions or increases in K concentration relative to the steady-state value. In these studies the concentration of other ionic constituents were varied by 5–10 mmol/liter about their respective steady-state values. The number in parenthesis represents the number of animals studied.

values of K in perfusate of experimental animals are shown in Fig. 4. In this group of experiments the average plasma K concentration was 4.3 mmol/liter. The observed values of K concentration are approximately four- to sixfold higher than those predicted from the electrochemical driving force at equilibrium. The calculated active transport potential was  $+46.7 \pm 0.9$  and  $+54.1 \pm 2.7$  mV in proximal and distal segments, respectively. These data suggest that an active transport process for K movement is stimulated by chronic K loading in both portions of colon.

The composition of the steady-state solutions also provided information on the characteristics of Na transport in colon. In the control group the active transport

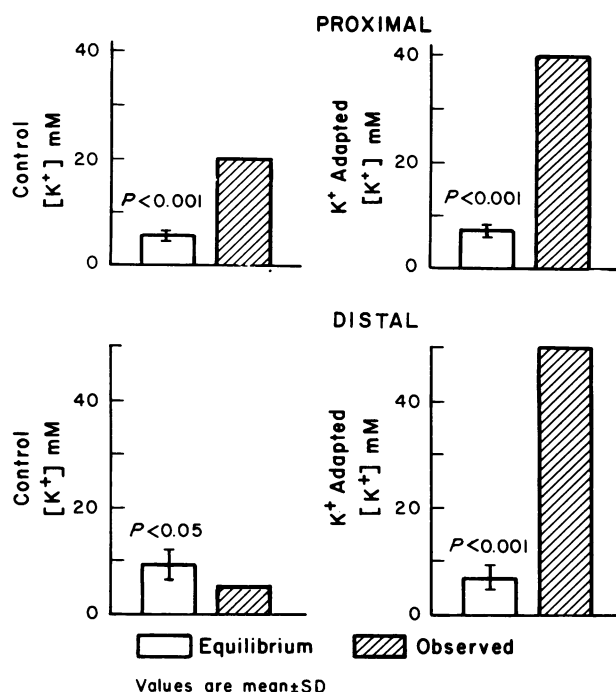


FIGURE 4 Comparison of predicted equilibrium (open bar) and observed (hatched) concentration of K luminal fluid of control and experimental animals during perfusion with the steady-state solutions. The heights of the bars and brackets represent mean  $\pm$  SD. Since the observed value was the perfusate concentration when net K movement did not occur, a statistical variance is not included. Statistical comparison was determined using Student's *t* test.

potential of  $+75.0 \pm 2.3$  mV in proximal colon and  $+56.8 \pm 2.6$  mV in distal colon are similar to values previously reported by our laboratory (11), and are consistent with active Na absorption. In K-loaded animals the active transport potentials were  $+58.8 \pm 0.9$  mV and  $+63.4 \pm 2.7$  mV in proximal and distal segments of colon, respectively. Although experimental values were statistically different from control, the small differences between mean values suggest that potassium adaptation is not associated with major stimulation of the active force involved in Na absorption.

## DISCUSSION

The question of whether K secretion in mammalian colon is mediated, in part, by an active mechanism or solely by passive driving forces has been controversial due to conflicting results of previous studies. Efforts to define an active mechanism must account for the strong passive force acting on K distribution across the colonic epithelium that is established by the high negative luminal potential. In vitro studies of K transport across isolated colonic mucosa have yield

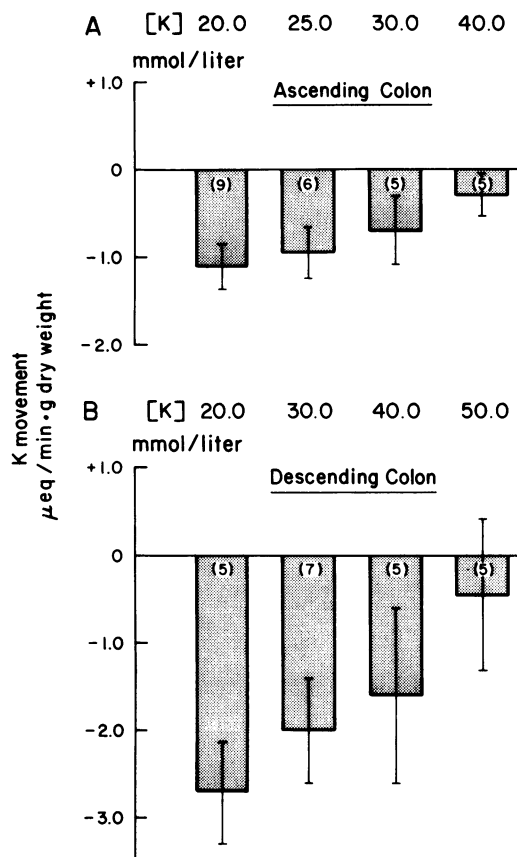


FIGURE 5 Net movement of K in proximal (A) and distal (B) colon of  $K^+$  adapted animals during perfusion of lumen with K concentrations less than the steady-state value. The numbers in parentheses represent the number of animals studied.

opposing conclusions from different laboratories. Separate studies using colonic mucosa of man, rabbit, and pig, in which unidirectional fluxes of K were measured under short-circuited conditions have reported small, statistically significant, net secretion, compared to zero; a result that is consistent with active K secretion (3–6). In addition, in studies with human tissue net K secretion was abolished in a Na-free media suggesting a possible link between Na and K transport (6). In contrast, Frizzell and co-workers (1, 2) studied K transport under short-circuited conditions across descending colonic mucosa of the rabbit, and failed to demonstrate evidence for active K transport. In their experiments, serosal-to-mucosal K movement was ascribed to ionic diffusion alone. Additional studies indicated that, at least in the rabbit descending colon, transmural Na movement was independent of serosal K transport. On the basis of these results Frizzell et al. (1) suggested that K movement was restricted to paracellular pathways.

Edmonds and Godfrey (12) performed studies in normal human subjects under in vivo conditions in which K transport was measured simultaneously with recordings of the PD. Luminal K concentrations were determined in the rectum by means of the dialysis bag method. In these studies the luminal concentration of K was greater than that predicted by the Nernst equation from the observed PD. Although these results were considered as evidence for an active K secretory process in the rectum, their data cannot be used to determine the mechanism of K secretion. Since net water and electrolyte movement was not reduced to zero, the possible influence of solvent drag and other passive mechanisms were not excluded. In addition, luminal K concentration may have been artifactually elevated from K derived from colonic mucus or unmonitored water absorption.

Edmonds also studied K secretion in vivo in the rat large intestine during continuous luminal perfusion with a 150-mM NaCl solution containing varying amounts of K (13). Studies were performed in the proximal and distal colon of both normal and Na-depleted animals, and included the concurrent measurement of the luminal PD. Since the luminal concentration of K exceeded the value predicted by the electrical gradients, Edmonds postulated active K secretion in rat colon. Unfortunately, that conclusion cannot be derived from the experimental observations since steady-state conditions were not present in the study. Other studies designed to study the mechanism of K secretion in vivo included similar technical limitations (14, 15).

The present work was designed to compare the steady-state observed luminal K concentration with the theoretical concentration that would satisfy electrochemical equilibrium across the entire epithelium. A discrepancy between these concentrations implies that some force, presumably an active process, acts on K distribution in addition to the electrochemical diffusion. The Nernst equation is the only valid equation for defining the predicted equilibrium potential for potassium and for calculating the “active transport potential”, which expresses the electrochemical potential disequilibrium in electrical units. It is recognized that a secondary active process as well as a primary active mechanism could account for a difference between an observed and theoretical equilibrium concentration of K.

Since these studies were performed in both control and K-loaded animals, an experimental condition associated with an increase in net K secretion, an evaluation of the mechanism of K movement in at least two conditions characterized by marked differences in net K movement was possible. Experiments performed in both proximal and distal colon after pre-

liminary data suggest that K loading produces a significant increase in K secretion in both segments, despite a difference in cell morphology (16).

Measurement of the electrochemical gradient for K in the proximal colon of control animals demonstrated that the observed concentration in luminal fluid was approximately threefold greater than predicted equilibrium value, indicating an active transport process. It seems unlikely that our result was significantly influenced by small variations in water or electrolyte flux (net flux was not absolutely zero) because the calculated active transport potential of 32 mV was quite large. In distal colon the concentration of K was less than the predicted value, and was consistent with an active absorptive process capable of overcoming an estimated gradient of 17 mV. Although net K absorption has not previously been demonstrated in colon, even in K-deficient animals during luminal perfusion with Ringer's solution (11), potassium secretion, at least in the human colon, is in part, linked to Na absorption. It is possible therefore, that under the experimental condition of zero net Na movement, net K absorption was unmasked in the distal colon of normal animals.

After chronic dietary loading with K, a marked increase in the rate of net K secretion occurred in both proximal and distal portions of large intestine during perfusion with Ringer's solution. The present study suggests that active transport was stimulated in proximal colon, since the active transport potential rose from 32 to 47 mV. Although these data demonstrate that potassium loading increases the electrochemical gradient against which K is secreted in colon, they do not distinguish between a more efficient K pump in basolateral membrane and a decrease in back-leak of K from luminal to serosal surfaces.

In contrast to the proximal colon active secretion of K in distal colon was demonstrated only in experimental animals. The active transport potential of 54 mV in descending colon was quantitatively similar with the level found in the proximal segment, suggesting that a chronic K load has a similar action on both portions of rat colon. Furthermore, these data suggest that in the adapted state K secretion in distal colon is not dependent upon the presence of net Na absorption. Indeed, the results of this study indicate that alterations in active transport in K-loaded animals are independent of changes in the properties of the Na pump. These data are in agreement with the absence of a change in net Na absorption on K-loaded animals observed in this study (results not shown) and in an earlier report (8) during perfusion with Ringer's solution. In contrast, net Na absorption, as well as K secretion, increased markedly in Na-deprived animals, apparently owing to the action of aldosterone (13).

Recent studies by our laboratory have elucidated a

complex array of changes that occur in colonic epithelium after chronic K loading. The capacity for increased rates of K secretion correlated with an increase in activity of Na-K-ATPase (8) and increase on surface area of the basolateral cell membrane (16). These data have suggested that K adaptation is linked to an increase in the number of K pumps per cell, which augment the cellular capacity for absolute transcellular K flux from serosal to mucosal sides of the membrane. The present study extends those observations by demonstrating an alteration in the active transport potential for K, as well.

In summary, these studies provide compelling evidence that an active K secretory process is present in at least a portion of the colon of the rat under control conditions. The failure to observe active K secretion in the distal colon of control animals may explain the varying results of prior investigations (1, 2). The present results demonstrate that the mechanism of the increase in net K secretion in K-loaded animals is, at least in part, secondary to active K secretion, and support the enzymatic and morphologic studies that suggest that the mechanism of chronic K adaptation is due to change in transcellular movement of K. These data do not indicate the relative contribution of active and passive driving forces to overall net K secretion in either control or experimental animals maintained on a K-enriched diet.

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