J. Membrane Biol. 166, 205–212 (1998)

The Journal of
Membrane
Biology

Role of Apical H-K Exchange and Basolateral K Channel in the Regulation of Intracellular pH in Rat Distal Colon Crypt Cells

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Received: 31 March 1998/Revised: 8 September 1998

Abstract. An apical membrane ouabain-sensitive H-K exchange and a barium-sensitive basolateral membrane potassium channel are present in colonic crypt cells and may play a role in both K absorption and intracellular pH (pH_i) regulation. To examine the possible interrelationship between apical membrane H-K exchange and basolateral membrane K movement in rat distal colon in the regulation of pH_i, experiments were designed to assess whether changes in extracellular potassium can alter pH_i. pH_i in isolated rat crypts was determined using microspectrofluorimetric measurements of the pH-sensitive dye BCECF-AM (2′,7′-bis(carboxyethyl-5(6)-carboxyfluorescein acetoxy methylester). After loading with the dye, crypts were superfused with a Na-free solution which resulted in a rapid and reversible fall in pH_i (7.36 ± 0.02 to 6.98 ± 0.03). Following an increase in extracellular [K] to 20 mM, in the continued absence of Na, there was a further decrease in pH_i (0.20 ± 0.02, $P < 0.01$). K-induced acidification was blocked both by 2 mM bath barium, a K channel blocker, and by 0.5 mM lumen ouabain. K-induced acidification was also observed when intracellular acidification was induced by a NH_4Cl prepulse. These observations suggest that increased basolateral K movement increases intracellular [K] resulting in a decrease in pH_i that is mediated by a ouabain-sensitive apical membrane H,K-ATPase. Our results demonstrate an interrelationship between basolateral K movement and apical H-K exchange in the regulation of pH_i and apical K entry in rat distal colon.

Key words: H,K-ATPase — Intracellular K — Colon

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Introduction

Several K transport processes are present in the rat distal colon and regulate active K absorption, K secretion and intracellular K activity [3, 10]. K movement across the basolateral membrane may occur via one or more transport mechanisms, including barium-sensitive K channels, Na,K-ATPase and Na-K-2Cl cotransport. In the basal state apical membrane K movement is likely the result of a H,K-ATPase. The latter process is associated with changes in intracellular pH (pH_i) most likely as a result of K-dependent proton extrusion [14, 34].

Mammalian cells including those of the gastrointestinal tract regulate their pH_i within a narrow range which is maintained above its electrochemical equilibrium. Increases in pH_i are most often a consequence of intracellular metabolism but may also occur following activation of one or more membrane transport processes. An ubiquitous mechanism for acid extrusion and the regulation and maintenance of pH_i is Na-H exchange. Although at least five distinct Na-H exchangers have been identified, cloned and sequenced, the NHE-1 isoform present in the basolateral membrane is often referred to as the ''housekeeper'' due to its important role in the regulation of both pH_i and other cell functions (e.g., cell volume) [30, 48]. However, other proton-extrusion mechanisms present in the plasma membrane of epithelial cells including those of the colonic crypt are also likely involved in pH_i regulation which then may potentially affect ion transport.

Transport processes of the colonic crypt cells have been studied by several different approaches [12, 18, 34, 37, 45]. Although active Cl secretion has long been considered a unique property of colonic crypt cells, several other transport processes have been identified in these cells: (i) a constitutive Na-dependent fluid absorptive mechanism [37], (ii) a ouabain-sensitive H,K-ATPase [7,

34] and (iii) a Cl-dependent Na-H exchange [33]. The present studies were designed to determine whether activation of a basolateral K transport process was linked to apical membrane transport and whether these transport processes modulate pH_i resulting in further modification of intracellular K in a regulated feedback loop.

The aim of the present study was to examine the mechanism(s) involved in pH_i regulation of crypt cells of rat distal colon by both H-K exchange[1] and basolateral K uptake. These studies establish that increasing bath [K] results in an intracellular acidification that is closely linked to both basolateral K uptake and apical H,K-ATPase activity.

Materials and Methods

Materials

BCECF-AM (2′,7′-bis(carboxyethyl-5(6)-carboxy-fluorescein acetoxy methylester) was purchased from Molecular Probes (Eugene, OR). Nigericin, ouabain and DMSO were purchased from Sigma Chemical (St. Louis, MO).

Perfusion Solution

The standard perfusate is a Na-containing solution that contained (in mM); 128.0 NaCl; 5.0 KCl; 1.0 $CaCl_2$; 1.2 $MgSO_4$; 2.0; NaH_2PO_4; 5.0 glucose; and 32.0 HEPES/Tris. pH of all solutions was 7.40 at 37°C and osmolality was adjusted to 312 mOsm. In the Na-free solution, NaCl and NaH_2PO_4 were replaced with equivalent amounts of NMDG-Cl (N-methyl-d-glucamine-Cl) and KH_2PO_4, respectively. In the NH_4Cl solution, NaCl or NMDG-Cl was replaced with equivalent amounts of NH_4Cl. K-free solution was prepared with NMDG-Cl and H_3PO_4. Twenty mM K solutions were made by increasing KCl while decreasing the NaCl or NMDG-Cl concentration. When adding barium, an equal amount of cation was replaced.

Animals and Crypt Preparation

Non-fasting male Sprague-Dawley rats (100–150 gram body weight; Charles River Laboratories, Wilmington, MA) were sacrificed and the distal portion of the colon was removed. Crypts were isolated by incubating with a Ca^{2+}-free, EGTA solution [46]. Colonic crypts were then transferred to a temperature-controlled perfusion chamber with a bottom made of a glass coverslip that had been pre-coated with Cell-Tak™, a biological cell adhesive. The crypts in the perfusion chamber were superfused at a rate of >3 ml/min and the temperature controller ensured a temperature of 37.0 ± 0.05°C adjacent to the crypt, as monitored by a thermistor.

Microperfusion Study

Crypts were also studied in a series of microperfusion experiments using methods previously described in detail [37] that permitted perfusion of the lumen of the crypt.

pH_i Measurement

To exclude the possibility of significant differences in pH_i regulation in different portions of the crypt, all pH_i measurements presented here were performed only in cells of the middle portion of each crypt. Data obtained from several cells in a single crypt represent the single observation for each animal. To measure pH_i, 5 μM BCECF-AM was added to the control perfusate solution for ~10 min, resulting in dye uptake of the crypt cells. The perfusate was then changed to the control dye-free solution for 5 min before any data were recorded. The perfusion chamber was mounted on the stage of an inverted microscope (Nikon Diaphot, Nikon, Melville, NY) used in the epifluorescence mode with a 20× objective. BCECF was successively excited at 440 and 490 nm on a computer-controlled motorized monochrometer placed in front of a 75-watt xenon lamp. A dichroic mirror centered at 510 nm reflected the excitation light to the perfusion chamber and transmitted the emitted fluorescence, which then passed through another filter of 535 nm. Fluorescent images were obtained with an intensified CCD video camera. A set of images was taken every 2 or 3 sec. The 490/440 fluorescence intensity ratio data were converted to pH_i values by using the Nigericin calibration technique [38]. Over the pH range of 6.5~7.5, fluorescence varied in a linear fashion with extracellular pH.

Statistics

Results are reported as mean ± SEM. A P value of <0.05 was considered significant. Student's-t test was used to determine statistical significance.

Results

K-induced Acidification[2]

pH_i determined in crypt colonocytes bathed in Na-containing solution was 7.36 ± 0.03 ($n = 15$). When Na was completely removed from the bath solution and replaced by NMDG-Cl, pH_i fell by 0.39 ± 0.04 to 6.98 ± 0.08 ($P < 0.001$, $n = 7$). The addition of K to the bath solution to increase bath [K] from 5 to 20 mM during superfusion with the Na-free solution resulted in a further decrease in pH_i to 6.78 ± 0.06 ($P < 0.001$, $n = 5$) (Fig. 1 and Table 1*A*). pH_i returned to its baseline value when the [K] was reduced to 5 mM and increased to its initial value following the addition of 128 mM Na. In contrast, when bath [K] was increased to 20 mM in the

[1] Although active K absorption is generally believed a result of H-K exchange energized by an apical H,K-ATPase [38, 40], there is little direct experimental demonstration of an apical membrane H-K exchange in the mammalian intestine [2, 14]. Nevertheless, in this manuscript, we refer to the probable linkage of K uptake and proton extrusion across the apical membrane as ''H-K exchange'' activity.

[2] In this manuscript the decrease in intracellular pH_i observed following an increase in [K] in the bath solution is referred to as ''K-induced acidification.''

128 mM Na-containing solution, pH_i did not significantly change (7.34 ± 0.01 *vs.* 7.36 ± 0.01, $P > 0.05$, $n = 4$) (Table 1*A*). The rate of K-induced acidification was similar in the absence of bath Na regardless of the initial pH_i which ranged from 6.85 to 7.05.

Additional studies were performed to establish whether K-induced acidification was related to the mechanism by which the initial acidification was induced. Experiments were designed to determine whether K-induced acidification would be observed when the initial acidification was induced by an NH_4Cl prepulse [35]. Following an NH_4Cl prepulse pH_i fell to approximately 6.9. In the continued absence of bath Na, pH_i remained constant. An increase in bath [K] from 5 to 20 mM resulted in a further decrease in pH_i (6.85 ± 0.03 to 6.66 ± 0.01, $P < 0.001$, $n = 5$) (Table 2).

It is uncertain whether K-induced acidification is dependent upon the absence of Na or a relative intracellular acidification since Na was absent in both experimental conditions in which K-induced acidification was demonstrated. Therefore, experiments were performed in the presence of Na but at a reduced pH_i which was produced by initial removal of bath Na. Forty mM Na plus 10 μM EIPA, an amiloride analogue used to prevent Na-dependent alkalinization, was then added to the bath. Increasing bath [K] from 5 to 20 mM resulted in a significant decrease in pH_i from 6.96 ± 0.05 to 6.88 ± 0.06 ($P < 0.05$, $n = 6$) (*see* Table 1*B*). Parallel experiments were performed with NH_4Cl prepulse. In these experiments with 40 mM Na and 10 μM EIPA, shown in Table 2, an increase in bath [K] resulted in an acidification that was similar to that observed both in the absence of bath Na (Fig. 1) and following an NH_4Cl prepulse in the absence of bath Na (Table 2). As a result, K-induced acidification will occur either in the presence or absence of bath Na but requires an initial intracellular acidification. The mechanism by which this initial acidification is induced (i.e., removal of bath Na or NH_4Cl prepulse) does not appear to be critical.

Role of Basolateral Na-H Exchange

To determine whether basolateral Na-H exchange is responsible for a compensatory acid extrusion and thus masks K-induced acidification, experiments were performed in the presence of both bath Na (128 mM) and EIPA (10 μM). Increasing bath [K] under these conditions did not result in a significant change in pH_i (7.37 ± 0.02 to 7.33 ± 0.02, $P > 0.05$, $n = 5$) (Table 1*B*). Thus, it is likely that the failure to observe K-induced acidification at basal pH_i (i.e., 7.3~7.4) is not secondary to rapid acid extrusion by basolateral Na-H exchange.

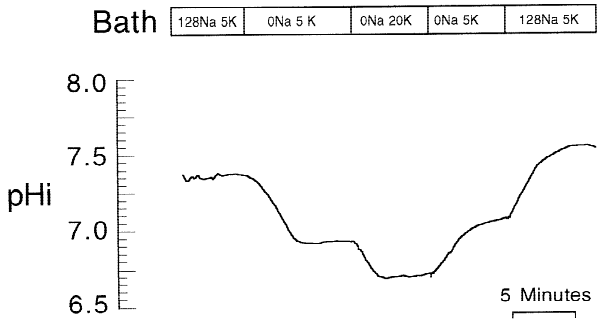

Fig. 1. K-induced acidification following initial acidification by superfusion with Na-free solution. Changing bath solution from 128 mM Na solution to Na-free (5 mM K) solution resulted in a decrease in pH_i. Addition of 20 mM K resulted in a further and reversible fall in pH_i. pH_i returned to the initial baseline when the [Na] was increased to 128 mM. Experiment is representative of 7 similar studies.

Mechanism of Basolateral K Uptake

It is likely that K-induced acidification is associated with an increase in intracellular [K]. However, the mechanism of K uptake across the basolateral cell membrane associated with the increase in bath [K] from 5 to 20 mM is not known. At least one of three transport processes could be responsible for K uptake across the basolateral cell membrane: K channel, Na,K-ATPase and Na-K-2Cl cotransport. An additional series of experiments was performed to establish the mechanism of basolateral K uptake in K-induced acidification. To assess whether K-induced acidification is associated with K uptake across the basolateral cell membrane, experiments were performed in the presence of bath barium, a K-channel blocker. The presence of 2 mM barium in the bath solution prevented K-induced acidification in experiments performed in the absence of bath Na (Fig. 2 and Table 1*A*). Thus, in the presence of 2 mM barium, pH_i remained constant when [K] was increased from 5 to 20 mM (6.88 ± 0.05 to 6.92 ± 0.01, $P > 0.05$, $n = 4$). In contrast, in the same series of experiments, barium did not affect pH_i recovery observed following the subsequent addition of Na to the bath solution prior to the conclusion of the experiment (0.22 ± 0.02 *vs.* 0.24 ± 0.02, $P > 0.05$, $n = 4$).

The experiment with barium is consistent with K movement from bath to cell. This K uptake may occur either via a basolateral K channel, and/or via Na,K-ATPase as it is known that barium ions inhibit Na pump activity by blocking K efflux via a basolateral K channel. One mM bath ouabain failed to modify the K-induced acidification (Table 3); this latter observation does not exclude K uptake via Na pump as the rat Na,K-ATPases are relatively insensitive to ouabain. The demonstration of K-induced acidification in the absence of bath Na

Table 1. K-induced acidification

Condition[1]	pH_i prior to K addition	ΔpH_i after K addition[2,3]	$\Delta pH_i/\Delta dt$ 3		
			P[4]	(10^{-3} pH/min)	N[5]
A. −EIPA in bath solution					
a) Na-free	6.98 ± 0.03	0.20 ± 0.01	<0.001	81 ± 10	7
b) 128 mM Na	7.34 ± 0.01	−0.02 ± 0.01	N.S.	2.4 ± 2.1	4
c) Na-free+barium	6.88 ± 0.05	−0.04 ± 0.01	N.S.	−23 ± 4.8	4
B. +10 μM EIPA in bath solution					
d) 128 mM Na+EIPA	7.37 ± 0.02	0.04 ± 0.01	N.S.	7.4 ± 0.5	4
e) 40 mM Na+EIPA	6.96 ± 0.05	0.08 ± 0.02	<0.05	38 ± 13	6

Data represent mean ± SEM.
[1] The experiment was designated by the composition of the solution at the time [K] was increased from 5 to 20 mM. (a) initial acidification was induced by the removal of bath Na; (b) no change in initial 128 mM Na solution was made; (c) 2 mM barium was added to Na-free bath solution; (d) 128 mM Na solution plus 10 μM EIPA; (e) following initial acidification induced by the removal of bath Na, 40 mM Na with 10 μM EIPA was added to bath solution.
[2] pH_i changes represent the change in pH_i observed immediately following an increase in bath [K] from 5 to 20 mM.
[3] Positive numbers indicate a decrease pH_i while negative ones indicate an increase in pH_i.
[4] Represents the statistical assessment of the comparison of pH_i prior to and following the addition of 20 mM K to the bath solution.
[5] The *N* indicates the number of animals studied in each group.

Table 2. K-induced acidification after NH_4Cl prepulse

Condition[1]	pH_i prior to K addition	ΔpH_i after K addition[2,3]	P[4]	$\Delta pH_i/\Delta dt$[3] (10^{-3} pH/min)	N[5]
Na free	6.85 ± 0.03	0.19 ± 0.01	<0.001	68 ± 11	5
40 mM Na+EIPA	7.02 ± 0.02	0.14 ± 0.01	<0.01	64 ± 9	4

Data represent mean ± SEM.
[1] The experiment was designated by the composition of the solution at the time [K] was increased from 5 to 20 mM. Initial acidification was induced by NH_4Cl prepulse followed by either Na-free solution or 40 mM Na solution plus 10 μM EIPA.
[2] pH_i changes represent the change in pH_i observed immediately following an increase in bath [K] from 5 to 20.
[3] Positive numbers indicate a decrease pH_i.
[4] Represents the statistical assessment of the comparison of pH_i prior to and following the addition of 20 mM K to the bath solution.
[5] The *N* indicates the number of animals studied in each group.

provides further evidence that Na-K-2Cl cotransport is not involved in the K uptake associated with K-induced acidification.

Role of Apical H,K-ATPase

Recent studies indicate that ouabain-sensitive H,K-ATPase in the apical membrane of crypt cells of rat colon is associated with a K-dependent intracellular alkalinization [34]. Thus, it is possible that an increase in basolateral K uptake is linked to a change in the activity of the apical H,K-ATPase. Experiments were therefore performed in which 0.5 mM ouabain was perfused through the crypt lumen prior to the increase in bath [K] from 5 to 20 mM. Figure 3 and Table 3 demonstrate that luminal

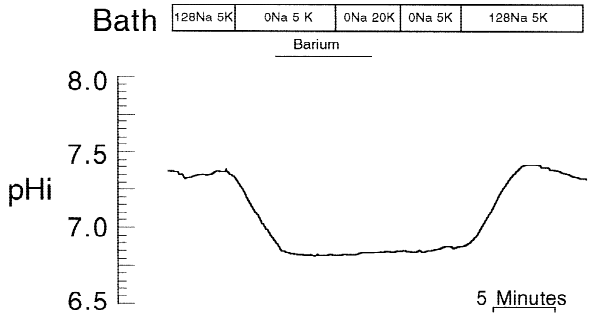

Fig. 2. Effect of bath barium on K-induced acidification. pH_i decreased during superfusion with Na-free solution with 2 mM barium. When [K] was increased from 5 to 20 mM, no further acidification was noted. Experiment is representative of 4 similar experiments.

Table 3. Effect of ouabain on K-induced acidification.

Condition[1]	pH_i prior to K addition	ΔpH_i after K addition[2,3]	$\Delta pH_i/\Delta dt$[3]		
			P[4]	(10^{-3} pH/min)	N[5]
A: Increase in bath [K] from 5 to 20 mM					
Control	6.98 ± 0.03	0.20 ± 0.01	<0.001	81 ± 10	7
Lumen ouabain	6.67 ± 0.05	0.03 ± 0.04	N.S.	6.1 ± 3.0	5
Bath ouabain	7.01 ± 0.02	0.14 ± 0.02	<0.01	70 ± 6	4
B: Increase in bath [K] from 0 to 20 mM					
Control	6.97 ± 0.01	0.22 ± 0.02	<0.001	71 ± 11	8
Lumen ouabain	6.73 ± 0.06	−0.03 ± 0.03	N.S.	4.1 ± 2.4	5

Data represent mean ± SEM.
[1] The experiment was designated by the composition of the solution at the time [K] was increased either (A) from 5 to 20 mM or (B) from 0 to 20 mM. Initial acidification was induced by the removal of Na from bath and lumen solutions. Either 1 mM bath ouabain or 0.5 mM lumen ouabain was present, as indicated.
[2] pH_i changes represent the change in pH_i observed immediately following an increase in bath [K].
[3] Positive numbers indicate a decrease pH_i while negative ones indicate an increase in pH_i.
[4] Represents the statistical assessment of the comparison of pH_i prior to and following the addition of 20 mM K to the bath solution.
[5] The *N* indicates the number of animals studied in each group.

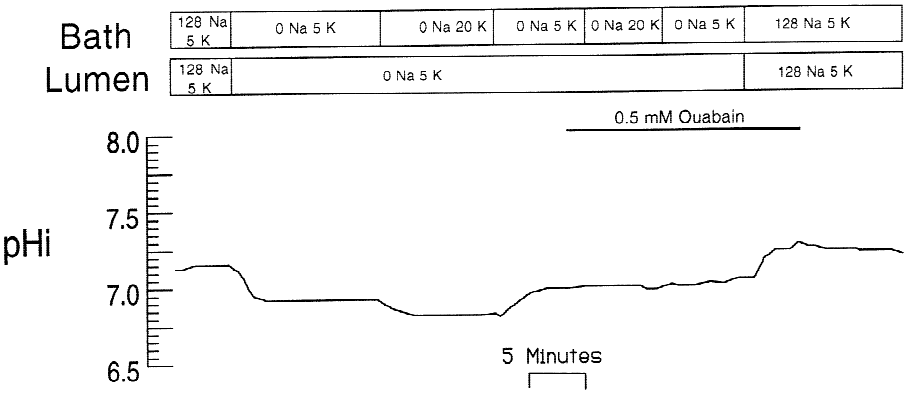

Fig. 3. Effect of luminal ouabain on the K-induced acidification. Crypt lumen and bath were separately perfused. pH_i decreased during superfusion with Na-free solution; when bath [K] increased from 5 to 20 mM, a reversible decrease in pH_i was observed. Perfusion of the lumen with 0.5 mM ouabain prevented K-induced acidification. pH_i recovery to the initial baseline pH_i was observed when 128 mM Na was added to the bath. Experiment is representative of 5 similar experiments.

perfusion of colonic crypts with 0.5 mM ouabain prevented K-induced acidification thus establishing that a ouabain-sensitive, apical membrane H,K-ATPase mediates, at least in part, K-induced acidification.

To clarify the possible effect by bath K concentration on membrane potential and its effect on pH_i, a parallel series of experiments was performed in which bath [K] was increased from 0 to 20 mM. As shown in Table 3, no significant difference was detected in experiments in which [K] was increased from 0 to 20 mM compared to an increase from 5 to 20 mM. These present observations suggest that the possible effect of potential difference on K-induced acidification is minimal.

Discussion

The role of the apical membrane H,K-ATPase(s) in mediating K absorption and proton secretion in the distal colon has been studied under several different experimental conditions [9, 28, 39, 41, 47]. First, active K absorption has been demonstrated both in vitro and in vivo in the distal colon of rat, rabbit and guinea pig [15, 19, 24, 27, 32, 40, 41, 47] as electroneutral, Na-independent, partially Cl-independent K absorption and is consistent with a H-K exchange. Second, K-dependent proton secretion has been characterized as partially ouabain-sensitive in guinea pig distal colon [39]. Third,

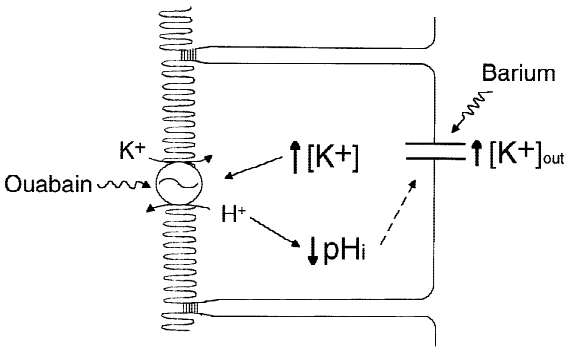

Fig. 4. Model of K-induced acidification. See text for discussion of relationship between pH_i and [K].

ouabain-sensitive, K-dependent intracellular alkalinization was recently reported in microperfusion studies of rat distal colonic crypts [34]. Fourth, the present studies suggest that an increase in bath K modulates crypt cell pH_i via apical H,K-ATPase. These experiments show the interaction between intracellular K and pH_i; however, it is uncertain if the change in pH_i causes a change in the movement of intracellular K or if the change in K concentration regulates apical membrane H,K-ATPase.

The present experiments were designed to assess the interrelationship between basolateral and apical membrane K transport processes in the regulation of pH_i, and the role of pH_i in determining the net movement of K. This K-dependent acidification is inhibited both by bath barium and by luminal ouabain. The regulation of K-dependent acidification by both agents allows speculation that increasing bath K can lead to an increase in K entry, which in turn results in either reduced apical membrane H,K-ATPase activity, or in fact may cause a reversal in H,K-ATPase activity similar to that shown for Na,K-ATPase activity in red cells [17]. By eliminating the basolateral Na-H exchanger by EIPA, the cell relies on the H,K-ATPase to regulate pH_i, thereby allowing us to unmask the role of intracellular [K] in regulating proton efflux. The luminal ouabain microperfusion experiments allow us to confirm that the apical H,K-ATPase(s) have a ouabain sensitivity (*data not shown*), with minimal resting H,K-ATPase activity. Addition of ouabain to the apical perfusate, or varying apical [K] (0~5 mM) does not lead to a change in pH_i (*unpublished observation*). However, as we have demonstrated in the present studies varying basolateral [K] (5–20 mM) results in a rapid and reversible intracellular acidification in the perfused crypt that is inhibited by pretreatment with luminal ouabain.

From these results we can conclude that the apical membrane of the crypt possesses at least one form of the H,K-ATPase, and that addition of K to the basolateral membrane results in either a decrease in proton efflux from the cell due to an increase in intracellular [K] (*see* Fig. 4). A second alternative is that the direction of K and proton movement across the apical membrane reverses resulting in efflux K to the apical surface and proton uptake. A final alternative is that there are two H,K-ATPases present in the apical membrane; one that acts to add K to the cell and a second that is capable of extruding K in exchange for protons. These K-dependent pH_i regulatory mechanisms are observed only when the basolateral Na-H exchanger is inhibited, as the latter transporter is the primary acid extruder mechanism.

Functional studies that include differences in both spatial distribution and ouabain-sensitivity of H,K-ATPase activity in surface and crypt cells strongly suggest the presence of at least two distinct H,K-ATPases [1, 31, 34]. One, the α-subunit of the colonic H,K-ATPase (HK$c\alpha$1), has been identified, cloned and sequenced [8, 22]. HK$c\alpha$1, which has significant homology to the α-subunits of Na,K-ATPase and gastric H,K-ATPase [21], is located primarily in surface cells of rat distal colon, based on the distribution of its message and protein by in situ hybridization and immunocytochemistry, respectively [22, 26]. More recent studies of colonic crypts have identified both ouabain-sensitive H,K-ATPase activity in the apical membrane and luminal K-induced intracellular alkalinization that is also ouabain-sensitive and speculate that the H,K-ATPase in crypt cells represents the other colonic H,K-ATPase isoform [34].

Several factors are required for the induction of intracellular acidification following an increase in bath K and include; (i) basolateral K uptake through a barium-sensitive K channel, (ii) a ouabain-sensitive apical membrane H,K-ATPase and (iii) an initial acid load. The experiments presented in Table 1*A* and Table 2 demonstrate that the mechanism by which pH_i is reduced (i.e., Na-removal or NH_4Cl prepulse) is not critical for K-induced acidification. As K-induced acidification was not observed in the presence of bath Na at basal pH_i, K-induced acidification might represent a compensatory mechanism that is operative only in the absence of other proton extrusion mechanisms (i.e., when basolateral Na-H exchange is inhibited). Since bath EIPA in the presence of Na at basal pH_i did not unmask K-induced acidification, it is likely that other mechanisms must account for the failure to observe K-induced acidification in the presence of bath Na at pH_is of approximately 7.3.

The data in Table 1*B* and Table 2 also reveal that K-induced acidification occurs in the presence of Na, provided Na-induced pH_i recovery is prevented by bath EIPA. Thus, a reduced pH_i, not the absence of Na, is required for K-induced acidification.

Although there is little available information regarding the relationship between pH_i and K channel activity in colonic crypt cells [4, 11, 23], studies in other epithelia indicate that K channel activity may be modified by pH_i

[20, 42, 44]. If a decrease in pH_i reduces the activity of colonic basolateral membrane barium-sensitive K channels, these present observations permit the speculation that the interrelationship between basolateral K movement and pH_i via the apical H,K-ATPase could provide a mechanism to regulate K uptake across the basolateral membrane.

The role of and the factors that regulate the apical membrane H,K-ATPase in the colonic crypt have not been established. Prior studies in renal epithelia indicate that changes in acid-base status, lumen [K], and dietary K intake modify H-K exchange activity [6, 13, 43]. Evidence exists that dietary K depletion upregulates H-K exchange activity in the distal colon of both rat and mice [16, 29], and changes in acid-base balance affect renal H-K exchange activity [6, 36]. Although Na-H exchange in both the distal tubule and distal colon is enhanced by metabolic acidosis [5, 25], the effect of such changes in acid-base balance on colonic K transport has not, as yet, been reported.

In conclusion, the present observations establish a close relationship between K movement and pH_i. It is likely that pH_i modifies K movement via an effect on both K channel activity and H,K-ATPase activity, and that changes in intracellular K activity alter pH_i. The interrelationship between K transport processes at apical and basolateral membranes demonstrates important regulatory loops for controlling colonocyte pH_i and $[K]_i$.

This study was supported by USPHS research grants DK14669 (HJB, JG), DK 17433(JG), DK 18777 (HJB) and DK 50230(JG) from the National Institute of Diabetes, Digestive and Kidney Diseases.

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