Review

Apical potassium (BK) channels and enhanced potassium secretion in human colon

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Summary

The human colon has the capacity to secrete potassium (K⁺) ions and enhanced K⁺ secretion is a feature of a variety of diarrhoeal diseases. Recent work points to K⁺ secretion in human colon being mediated by high conductance (BK) K⁺ channels located in the apical membrane of colonic epithelial cells. The aim of this review is to highlight the importance of these channels in maintaining K⁺ homoeostasis in health and disease.

Introduction

Potassium (K⁺) is the most abundant ion in the body. The gradient between intracellular K⁺ concentration (∼75 mmol/l) and plasma/interstitial fluid K⁺ concentration (3.5–5.0 mmol/l) is essential for normal cell function and is, therefore, tightly controlled. Although it is widely accepted that the kidneys have a critical role in maintaining K⁺ homoeostasis, it is not generally recognized that the human colon, with its large surface area (∼2000 cm²), is not only capable of K⁺ secretion in health¹,² but also increases its K⁺ secretory capacity in patients with end-stage renal disease (ESRD).³,⁴ In addition, it seems likely that colonic K⁺ hypersecretion leads to excessive faecal K⁺ losses and hypokalaemia in patients with severe ulcerative colitis (UC),⁵ secretory-type rectal villous adenomas⁶ and those abusing certain laxatives.⁷

Our understanding of colonic K⁺ transport has developed over the past 30 years. Initial studies in normal rat colon identified clear-cut segmental differences in K⁺ transport, with net K⁺ absorption and net K⁺ secretion occurring in the distal and proximal segments, respectively.⁸,⁹ Following the observation in animals with experimentally induced renal insufficiency that surviving nephrons adapted by increasing their capacity for K⁺ secretion,¹⁰,¹¹ ‘colonic K⁺ adaptation’ involving stimulation of an active K⁺ secretory process was demonstrated during chronic dietary K⁺ enrichment in renal-intact animals.⁸,⁹ Enhanced colonic K⁺ secretion reflected the additive effects of secondary hyperaldosteronism and the elevated dietary K⁺ load per se, resulting in an increase in proximal net K⁺ secretion and an even greater change in the distal segment, with the reversal of net K⁺ absorption to net K⁺ secretion.⁸,⁹,¹² While it is generally accepted that K⁺ transport proteins and K⁺ channels are present in the apical and basolateral cell membranes of mammalian colon,¹³ it is only relatively recently that functionally important K⁺ channels have been identified in these domains in human colon,⁵,¹⁴,¹⁵ which has led to renewed interest in colonic K⁺ handling in health and disease.
K⁺ secretion in normal human colon

Early perfusion studies in human colon demonstrated net K⁺ secretion into the lumen that could be explained, at least in part, by passive K⁺ movement secondary to the relatively high (20–35 mV) lumen-negative transmucosal electrical potential difference (PD). Subsequent studies demonstrated small but significant net K⁺ secretory fluxes across isolated sheets of human colon even when the transmucosal PD was clamped to zero, indicating the presence of an active (that is, independent of the concentration and potential gradients) K⁺ secretory process. While it is now established that K⁺ movement from interstitial fluid into colonic epithelial cells is mediated by basolateral membrane Na⁺,K⁺-ATPase pumps and Na⁺-K⁺-2Cl⁻ cotransporters, the nature of the apical K⁺ exit step remained unclear until intracellular microelectrode and current fluctuation ('noise') analysis studies provided evidence of an apical K⁺ conductance in parallel with amiloride-sensitive apical Na⁺ channels (ENaC) in human distal colon. A combined approach using ion channel recording, immunostaining and RT-PCR has recently shown that the apical K⁺ conductance reflects high conductance (~220 pS) K⁺ channels (KCNMA1, commonly known as BK channels) located in surface cells and cells in the upper 20% of the crypts in normal human colon (Figure 1). To date, no other type of apical K⁺ channel has been identified in human colonic cells. Moreover, in BK-knockout mice, colonic K⁺ secretion is absent, which suggests that apical BK channels are the sole exit pathway for K⁺ ions into the lumen. This review highlights the likely role of apical BK channels in mediating increased colonic K⁺ losses in a variety of diseases.

BK channel expression in ESRD

The first hint that the colon might adapt to become an important accessory organ of K⁺ secretion in patients with ESRD came from extensive studies >40 years ago. Subsequent work using the rectal dialysis technique indicated that net K⁺ secretion in the proximal rectum was greatly enhanced in normokalaemic ESRD patients undergoing continuous ambulatory peritoneal dialysis and also in patients maintained on haemodialysis (even when hypokalaemic after haemodialysis). The fact that the increase in rectal (and presumably pan-colonic) K⁺ secretion in ESRD patients occurred independently of plasma K⁺ concentration, transmucosal PD and aldosterone status suggested that augmented colonic K⁺ secretion reflected an active K⁺ secretory process. Recent rectal dialysis studies have shown that intraluminal barium ions (which block all types of K⁺ channel) decreased the higher basal levels of K⁺ secretion in ESRD patients by 45% but had no effect on K⁺ transport in patients with normal renal function. Immunostaining revealed greater levels of BK channel protein expression in colonic surface and crypt cells in ESRD patients than in patients with normal renal function, in whom low levels of expression were mainly restricted to surface cells. Taken together, these results provide strong evidence that colonic K⁺ hypersecretion in ESRD reflects an increase in apical K⁺ permeability secondary to up-regulated apical BK channel expression. The mechanism for this is currently unknown, but it may involve a relative increase in the dietary K⁺ load circulating to the colonic epithelium in these patients, since acute oral K⁺ loading caused sustained and significantly greater increases in the plasma K⁺ concentration in ESRD patients compared with control subjects. Furthermore,
colonic apical BK channel activity is stimulated by cAMP-dependent protein kinase A (PKA),\textsuperscript{21} which may benefit ESRD patients, as treatment with bisacodyl (a cAMP-mediated laxative) significantly decreased the interdialytic plasma K\textsuperscript+ concentration in haemodialysis patients but had no effect in control subjects.\textsuperscript{22} It remains to be seen whether patients with ESRD also exhibit up-regulation of the expression/activity of basolateral Na\textsuperscript{+},K\textsuperscript{+}-ATPase pumps and/or Na\textsuperscript{+}-K\textsuperscript{+}-2Cl\textsuperscript{−}/Cl\textsuperscript{−} cotransporters, the other components of the active K\textsuperscript{+} secretory process.\textsuperscript{13}

**BK expression in UC**

In some cases of severe UC, colonic K\textsuperscript{+} losses may be so great as to cause hypokalaemia, although the mechanism of increased colonic K\textsuperscript{+} secretion has been unclear. However, recent studies have demonstrated that, whereas BK channels are immunolocalized to surface cells and upper crypt cells in normal colon, BK channels are expressed in surface cells and along the entire crypt axis, irrespective of whether the disease is active or quiescent.\textsuperscript{5} Thus, it is feasible that increased faecal K\textsuperscript{+} losses in active UC reflect the combined effects of an increase in the overall apical K\textsuperscript{+} permeability of the colonic epithelium secondary to the wider distribution of BK channels throughout the crypts, and a general enhancement of BK channel activity stimulated by the high intramucosal levels of cAMP-mediated prostaglandin E\textsubscript{2}.\textsuperscript{24} The sensitivity of BK channels to PKA may reflect the proportionate expression of splice variants of the channel \(\alpha\)-subunit, since PKA activates the ZERO splice variant but inhibits the STREX splice variant.\textsuperscript{25} The fact that faecal K\textsuperscript{+} excretion is not increased in patients with quiescent UC,\textsuperscript{2} despite the persistence of BK channels along the crypt axis, presumably reflects relatively low levels of channel activity in the presence of basal intramucosal prostaglandin E\textsubscript{2} concentrations.\textsuperscript{24} Apical BK channel expression in Crohn’s colitis has yet to be studied.

**BK channels and colonic K\textsuperscript{+} losses in secretory diarrhoea**

There is increasing evidence that BK channels have a role in colonic K\textsuperscript{+} losses in various types of secretory diarrhoea.

**Enteric infections**

A variety of enteric pathogens are capable of eliciting severe watery diarrhoea resulting in excessive stool K\textsuperscript{+} losses, which seem likely to reflect stimulation of apical BK channel activity. For example, in acute cholera, activation of cAMP-dependent apical BK channels probably underlies the enhanced colonic K\textsuperscript{+} secretion that accompanies the marked small intestinal secretion of Cl\textsuperscript{−} and water.\textsuperscript{26} A similar mechanism may trigger increased colonic K\textsuperscript{+} secretion in other enteric infections, including Clostridium difficile colitis.\textsuperscript{27–29}

**Colonic pseudo-obstruction**

Severe K\textsuperscript{+} secretory diarrhoea, apparently driven by an active K\textsuperscript{+} secretory process, has been described in colonic pseudo-obstruction associated with profound hypokalaemia.\textsuperscript{30} In a similar case with a very high faecal K\textsuperscript{+} output, immunostaining revealed massive over-expression of apical BK channels throughout the surface-crypt axis, a change consistent with enhanced pan-colonic active K\textsuperscript{+} secretion.\textsuperscript{31}

**Villous adenoma**

Hypokalaemia is the commonest electrolyte disturbance in patients with villous adenomas of the rectum presenting with watery diarrhoea. Villous adenomas may be either non-secretory or secretory in type, with only the latter exhibiting an excess of goblet cells.\textsuperscript{6} Bile salts stimulate the parallel secretion of mucus and K\textsuperscript{+} in guinea pig colon,\textsuperscript{32} which raises the interesting possibility that the watery diarrhoea seen in patients with secretory villous adenomas of the rectum may reflect a substantial increase in K\textsuperscript{+} secretion with an obligatory loss of water, rather than the increase in mucus secretion per se. This idea is supported by our preliminary studies, showing gross over-expression of apical BK channel protein in secretory villous adenomas (Figure 2).

**Laxative abuse**

Patients who abuse laxatives are frequently chronically depleted of sodium and water, resulting in increased renin secretion and secondary hyperaldosteronism.\textsuperscript{7} Such patients commonly develop hypokalaemia, which reflects not only the renal effects of secondary hyperaldosteronism but also excessive K\textsuperscript{+} losses in their stools. Hypokalaemia more often occurs in those abusing diphenoic laxatives (e.g. phenolphthalein and bisacodyl) and anthroquinones (e.g. senna glycosides and danthron), all of which increase intramucosal levels of cAMP.\textsuperscript{7} Given that cAMP stimulates colonic apical BK channels,\textsuperscript{23} excessive stool K\textsuperscript{+} losses in patients chronically abusing these particular laxatives are likely to reflect the dual stimulatory effects of elevated levels of cAMP and aldosterone on the colonic epithelium.
Apical BK channels are emerging as important determinants of faecal K+ losses in a variety of diseases, not all of which are primarily colonic in origin. However, this is likely to be only part of an increasingly complex picture, as other types of K+ channels [e.g. Ca2+-sensitive, intermediate conductance K+ channels (KCNN4) and cAMP-sensitive, low conductance K+ channels (KCNQ1/KCNE3)] are located in the basolateral membranes of human colonic cells,14,15,33 which are likely to play key roles in the pathophysiology of secretory diarrhoea of widely differing aetiologies. We are currently some way from being able to influence colonic apical BK channels and thus intestinal K+ losses in patients with diarrhoeal diseases. However, somatostatin has recently been shown to inhibit these channels through a mechanism involving phosphoprotein tyrosine phosphatase-mediated dephosphorylation,23 which could be developed as a new strategy to limit intestinal K+ losses in secretory diarrhoea.

Conflict of interest: None declared.

References


