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Colonic Potassium Absorption and Secretion in Health and Disease

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Abstract

The colon has large capacities for K^+ absorption and K^+ secretion, but its role in maintaining K^+ homeostasis is often overlooked. For many years, passive diffusion and/or solvent drag were thought to be the primary mechanisms for K^+ absorption in human and animal colon. However, it is now clear that apical H^+,K^+-ATPase, in coordination with basolateral K^+-Cl^- cotransport and/or K^+ and Cl^- channels operating in parallel, mediate electroneutral K^+ absorption in animal colon. We now know that K^+ absorption in rat colon reflects ouabain-sensitive and ouabain-insensitive apical H^+,K^+-ATPase activities. Ouabain-insensitive and ouabain-sensitive H^+,K^+-ATPases are localized in surface and crypt cells, respectively. Colonic H^+,K^+-ATPase consists of α (HKC_α) and β (HKC_β) subunits which, when coexpressed, exhibit ouabain-insensitive H^+,K^+-ATPase activity in HEK293 cells, while HKC_α coexpressed with the gastric β-subunit exhibits ouabain-sensitive H^+,K^+-ATPase activity in *Xenopus* oocytes. Aldosterone enhances apical H^+,K^+-ATPase activity, HKC_α specific mRNA and protein expression, and K^+ absorption. Active K^+ secretion, on the other hand, is mediated by apical K^+ channels operating in a coordinated way with the basolateral Na^+-K^+−$2Cl^-$ cotransporter. Both Ca^{2+}-activated intermediate conductance K^+ (IK) and large conductance K^+ (BK) channels are located in the apical membrane of colonic epithelia. IK channel-mediated K^+ efflux provides the driving force for Cl^- secretion, while BK channels mediate active (e.g., cAMP-activated) K^+ secretion. BK channel expression and activity are increased in patients with end-stage renal disease and ulcerative colitis. This review summarizes the role of apical H^+,K^+-ATPase in K^+ absorption, and apical BK channel function in K^+ secretion in health and disease.

Introduction

Of the average total dietary K^+ intake in humans (~90 mEq), 90% is absorbed and only 10% is excreted in the feces (44, 133). Like the kidney, the colon has capacities for both K^+ absorption and K^+ secretion. *In vitro* flux studies performed in guinea pig, rabbit and rat colon under voltage clamp conditions (that is, in the absence of passive driving forces) have demonstrated active K^+ absorption (63, 116, 206), and a variety of physiological (127, 186), biochemical (45, 74, 101), and molecular (38, 40, 101) studies have shown that active K^+ absorption is mediated by apical H^+,K^+-ATPase in animal colon. Although there is no

physiological evidence to support active K^+ absorption in human colon, amplification of cDNA fragment suggests that H^+,K^+-ATPase is expressed in this epithelium (132, 192).

Studies in healthy human and animal colon have also demonstrated active K^+ secretion both *in vivo* and *in vitro* (8, 10, 53, 79, 114, 151), the magnitude of which is mainly dependent on the expression and activity of Ca^{2+}-activated large conductance apical K^+ (BK) channels (94, 156, 159, 176, 178, 209). Enhanced BK expression and active K^+ secretion contribute to net K^+ hypersecretion during colonic K^+ adaptation in patients with end-stage renal disease (114, 152). Increased BK expression and enhanced net K^+ secretion also occur in an animal model of colitis and in human ulcerative colitis (94, 158). This review discusses the role and regulation of H^+,K^+-ATPase-mediated colonic K^+ absorption and BK channel-regulated colonic K^+ secretion in health and disease.

Potassium Absorption

In healthy individuals, about 90% of the average dietary K^+ intake (~90 mEq/day) is absorbed, with a fecal excretion of ~9 mEq/day (44). About 10 mEq K^+/day passes from the ileum into the colon, colonic secretion accounting for an additional 5 mEq K^+/day (133). Since metabolic studies indicate fecal losses of about 10 mEq K^+/day, the human colon appears to absorb about 5 mEq K^+/day. Thus, while human small intestine has the capacity to absorb K^+, human colon has the capacity to both absorb and secrete K^+ (Figure-1). Increasing dietary K^+ intake results in only a modest change in fecal K^+ excretion, which increases by 5 mEq/day for every 50 mEq increase in dietary K^+ in healthy humans (3). In normal individuals, absorbed K^+ is mainly excreted via the kidneys (~90 mEq/day), and decreasing the dietary K^+ intake (to 9 mEq/day) reduced renal K^+ excretion from 81 mEq/day to 16.7 mEq/day (91). Thus, renal K^+ excretion mirrors dietary K^+ absorption. However, when dietary K^+ intake is restricted to zero, the obligatory renal and colonic K^+ excretion average about 6.3 mEq/day and 3.6 mEq/day, respectively (182). Since there is no evidence for facilitated K^+ absorption in human and animal small intestine, it has been suggested that K^+ absorption reflects a passive driving force (so-called solvent drag) (3). As regards to colonic K^+ absorption, some of the early studies involving *in vivo* perfusion did not measure transmucosal electrical gradients and employed a perfusing solution containing a single K^+ concentration, making interpretation of the results difficult. However, perfusion of rat colon *in vivo* using solutions of varying K^+ concentrations demonstrated that the K^+ absorptive flux was proportional to the K^+ concentration, and this flux occurred passively mainly via paracellular pathways, driven by the transmucosal electrical potential difference (PD) (13). Based on *in vivo* perfusion data from human jejunum and ileum (197) and the whole colon (49), the positive relationship between net K^+ transport and luminal K^+ concentration indicated that the rate of K^+ absorption or secretion was directly proportional to luminal K^+ concentration (3). In the colon, the regression line crossed zero at a luminal K^+ concentration of 9.5mmol/L, and using the geometric mean of the proximal and distal colonic PD (21.1mV), the predicted Nernst equilibrium K^+ concentration in colonic fluid was very similar to those obtained in human colon (18, 49). Based on these results, it was suggested that passive diffusion was the main mechanism of K^+ absorption in animal and human colon, despite the paracellular pathway having a relatively low ionic conductance (51).

Nevertheless, despite the apparent lack of physiological evidence for a mechanism for active K^+ absorption in the human colon, K^+ flux studies have demonstrated active K^+ absorption in guinea pig, rabbit and rat distal colon (52, 63, 66, 76, 116, 134, 142, 185, 206). Under voltage clamp conditions, active K^+ secretion (see below) and active K^+ absorption in animal colon occur in the proximal and distal segments, respectively (63, 183). Furthermore, both active K^+ absorption and active K^+ secretion are modulated by cAMP, dietary K^+ enhancement, dietary K^+ restriction, and dietary Na^+ restriction (the latter eliciting marked secondary hyperaldosteronism) (64–66, 77, 142). Active K^+ transport (i.e., net absorption and net secretion) are measured in sheets of colonic epithelium maintained under voltage clamp conditions in Ussing chambers. Mucosal to serosal (m-s) and serosal to mucosal (s-m) unidirectional K^+ fluxes are measured and net K^+ fluxes calculated by subtracting s-m unidirectional fluxes from the m-s unidirectional fluxes. Positive and negative net fluxes therefore represent active K^+ absorption and secretion, respectively.

Physiological evidence for active K^+ absorption in animal colon

Active K^+ absorption reflects K^+ uptake across apical membranes and K^+ exit across basolateral membranes of epithelial cells in animal colon (Figure-2). Although metabolic studies have shown the presence of K^+ absorption, a facilitated transporter has not yet been identified in human colon (3). In contrast, an ATP-driven H^+-K^+ exchange (i.e., H, $^+$-K^+-ATPase) has been shown to mediate K^+ uptake across apical membranes in animal colon (127). Either a K^+ channel that operates in parallel with a Cl^- channel (Figure-2A) or a K^+-Cl^- cotransporter (KCC) (Figure-2B) may mediate K^+ exit through the basolateral membrane in animal colon (21, 45, 76, 162). Colonic H^+,K^+-ATPase has been identified and characterized using physiological, biochemical, pharmacological and molecular techniques (1, 21, 62, 63, 74, 76, 186). *In vitro* studies based on unidirectional $^{42}K^+$ flux measurements under voltage clamp conditions showed that active K^+ absorption is electroneutral and Na^+-independent, Na^+ removal decreasing the short-circuit current (Isc) to zero. However, this electroneutral K^+ absorptive process was only partially inhibited under Cl^--free conditions, leading to the suggestion that electroneutral K^+ absorption may be mediated by apical K^+-H^+ exchange (63). Other studies also pointed to the presence of K^+-dependent proton (H^+) secretion in guinea pig distal colon (185, 186), and the demonstration of outward proton gradientdriven K^+ uptake has been interpreted as evidence for K^+-H^+ exchange in apical membrane vesicles isolated from rat ileum (19). Additional investigations revealed that electroneutral K^+ uptake is mediated by an apical ATPase (63, 76, 128, 134). Studies of unidirectional K^+ fluxes in normal and dietary Na^+ depleted (to produce secondary hyperaldosteronism) rat distal colon demonstrated that Na^+ removal from the mucosal and serosal bathing solutions resulted in increased active K^+ absorption via an apical K^+ uptake mechanism that was: 1) carrier-mediated, as increasing mucosal K^+ concentration saturated K^+ absorption; 2) competitively inhibited by mucosal Na^+; 3) inhibited by mucosal orthovanadate (VO_4, a P-type ATPase inhibitor); 4) inhibited partially by mucosal ouabain (a Na^+,K^+-ATPase inhibitor); and 5) not inhibited by mucosal omeprazole and SCH28080 (gastric H^+,K^+-ATPase inhibitors) (43). Based on these observations, Sweiry and Binder concluded that apical K^+ uptake was mediated by a H^+,K^+-ATPase that had properties which were unlike those of gastric H^+,K^+-ATPase, but similar in part to those of Na^+,K^+-ATPase (190). Further studies in rat distal colon demonstrated that mucosal ouabain completely

inhibited active K^+ absorption measured in the presence Na^+, but only partially inhibited K^+ upake in the absence of Na^+ (127). These observations suggested that two distinct H^+,K^+-ATPases mediate apical K^+ absorption – one that is ouabain-sensitive (which is also Na^+-insensitive), while the other is ouabain-insensitive (which is also Na^+-sensitive) (127). This view is consistent with the results from studies in guinea pig distal colon, which demonstrated ouabain-sensitive K^+-dependent proton (H^+) secretion measured using the pH-stat technique (185, 186). Although these animal studies provide compelling evidence that electroneutral K^+ absorption reflects a carrier-mediated processes which is most likely ATP-dependent (i.e., via H^+,K^+-ATPase), the mechanism of K^+ absorption in human colon remains unclear.

Biochemical evidence for colonic H^+,K^+-ATPase in animal colon

Physiological studies have provided evidence that VO_4-sensitive P-type ATPase mediates electroneutral K^+ absorption across the mucosal membranes of rat colon (190). Other work demonstrated ATPase activities in epithelial cells which are distinct from Na^+,K^+-ATPase in animal distal colon (1, 45, 74, 96, 186). Gustin and Goodman identified ouabain-insensitive K^+-activated ATPase in apical membranes , while Abrahamse *et al* demonstrated ouabain-insensitive and SCH28080-sensitive K^+-activated ATPases in rabbit distal colon (1, 74). Rabbit distal colon also exhibits two pharmacologically distinct H^+-activated ATPase activities – one which is N-ethylmaleimide (NEM)-sensitive and VO_4-insensitive, and a second which is NEM-insensitive and VO_4-sensitive (96). However, the membrane localization of these two H^+-activated ATPases has not been established (96). Suzuki and Kaneko demonstrated ouabain-sensitive ^{86}Rb (K^+ surrogate) absorption and mucosal K^+-dependent H^+ secretion in guinea pig distal colon, consistent with apical membrane H^+,K^+-ATPase-mediated K^+ absorption (185, 186). Del Castillo *et al* showed that K^+-activated ATPase (i.e., H^+,K^+-ATPase) activities were present in apical, but not in basolateral membranes isolated from rat distal colon (45). In keeping with oubain-sensitive and ouabain-insensitive K^+ absorption (127), apical membranes enriched 10-fold with respect to H^+,K^+-ATPase activity exhibited both ouabain-sensitive (~65%) and ouabain-insensitive (~35%) components (45). Both oubain-sensitive and ouabain-insensitive H^+,K^+-ATPase activities were inhibited by VO_4, but not by omeprazole and SCH2808 (both gastric H^+,K^+-ATPase inhibitors). Furthermore, isolated apical membranes were enriched 4-fold with respect to Na^+,K^+-ATPase activity, which was completely inhibited by ouabain. Based on these findings, it was concluded that ouabain-sensitive Na^+,K^+-ATPase in isolated apical membranes might reflect cross-contamination from basolateral membranes. However, Rajendran *et al* demonstrated that apical H^+,K^+-ATPase, in the presence of Na^+ and K^+ functioned as Na^+,K^+-ATPase (139). In addition, M1-antibody [a polyclonal antibody raised against a fusion peptide designed from the putative colonic H^+,K^+-ATPase α-subunit (40, 101)] inhibited H^+,K^+-ATPase activity, and also inhibited apical but not basolateral Na^+,K^+-ATPase activity (139), which suggested that apical Na^+,K^+-ATPase activity was an alternative mode of H^+,K^+-ATPase activity (139). Based on these observations, it was speculated that colonic apical H^+,K^+-ATPase, which characteristically differs from basolateral Na^+,K^+-ATPase and gastric H^+,K^+-ATPase, may represent a unique and distinct type of ATPase that mediates active K^+ absorption in animal colon, and that this novel H^+,K^+-ATPase has both ouabain-sensitive and ouabain-insensitive components.

Molecular identification of colonic H^+,K^+-ATPase

Active K^+ absorption, mediated by apical H^+,K^+-ATPase, is a unique function of animal distal colon (45, 63, 76, 128, 139, 186). Since it is inhibited by VO_4, colonic H^+,K^+-ATPase is also a P-type ATPases, and a member of the gene family that includes gastric H^+,K^+-ATPase and Na^+,K^+-ATPase (172, 173). P-type ATPases are in general heterodimers, which consist of α- and β-subunits. The α-subunit catalyzes ATP and transports cations (Na^+, K^+, NH_4^+ and H^+), while the β-subunit regulates structural and functional aspects of the P-type ATPases (69, 72, 90, 117, 188). Molecular studies have cloned the colon-specific H^+,K^+-ATPase α (HKC_α) and β (HKC_β) subunits from rat distal colon (35, 40, 163). Coexpression of these putative HKC_α and HKC_β subunit cDNAs in HEK293 cells results in ouabain-insensitive H^+,K^+-ATPase activity (165). These results indicate that the cloned HKC_α and HKC_β subunits encode ouabain-insensitive H^+,K^+-ATPase present in the apical membranes of the surface cells in rat distal colon.

Molecular cloning of the HKC_α subunit—Based on the prediction that colonic H^+,K^+-ATPase is a P-type ATPase (45, 190), Crowson and Shull used a cDNA probe designed from the human gastric H^+,K^+-ATPase α-subunit (HKG_α; known as ATP4A) gene to screen for and isolate the putative HKC_α cDNA which encodes a 1036 deduced amino acid protein. Using the putative HKC_α cDNA to probe northern blots, HKC_α-specific mRNA was shown to be expressed mainly in surface cells of distal but not proximal colon (40). The HKC_α is also known as nongastric K^+ transporting ATPase α_2 ($HK_{\alpha 2}$), ATP1AL1 and Atp12A (131, 187). HKC_α orthologs have also been cloned from guinea pig colon (9), rabbit kidney (57), toad bladder (89), and the human genome (73). These HKC_α orthologs exhibited 75 – 85% amino acid identity with each other, and shared 63.3% and 62.9 − 63.6% amino acid identities with the gastric HKG_α and Na^+,K^+-ATPase α-subunit ($NaK_{\alpha 1}$), respectively (40). When expressed *in vitro*, HKC_α exhibited both ouabain-sensitive and/or ouabain-insensitive function (37, 38, 101). In addition to K^+ and H^+, the *in vitro* expressed HKC_α also showed affinity for Na^+ and NH_4^+ (Table-1) (72, 189). The observation that HKC_α was expressed in surface (i.e., absorptive) cells of distal but not proximal colon, suggested that HKC_α might mediate electroneutral K^+ absorption in animal distal colon.

In contrast to animal colon, facilitated K^+ absorption and H^+,K^+-ATPase activities have yet to be indentified in human colon. However, amplification of the ATP1AL1 gene-specific cDNA fragment suggests the presence of an H^+,K^+-ATPase-like transporter in human colon (132, 192). It is possible that human colonic H^+,K^+-ATPase has different characteristics, as H^+,K^+-ATPase-mediated intracellular pH (pHi) recovery was inhibited by the gastric H^+,K^+-ATPase inhibitor SCH28080 in CaCo2 cells (a human colorectal adenocarcinoma cell line). Colonic H^+,K^+-ATPase inhibition may therefore contribute to the diarrhea which occurs in some patients treated with proton pump inhibitors (2, 171). However, to establish the presence of facilitated K^+ absorption in human colon, additional molecular and functional studies of the human HKC_α ortholog and native H^+,K^+-ATPase are required.

Molecular cloning of the HKC_β subunit—Although P-type ATPases comprise α- and β-subunits, the putative HKC_α expressed alone in the baculovirus-*Sf9* (*Spodoptera frugiperda*) cell expression system exhibited H^+,K^+-ATPase activity (101). However, the

β-subunit appears a prerequisite for full HKC_α function, as HKC_α expressed alone in *Xenopus* oocytes did not exhibit H^+,K^+-ATPase activity when assessed by ^{86}Rb uptake (37, 38). By contrast, there was ^{86}Rb uptake by oocytes coinjected with cRNA transcribed from HKC_α and either toad bladder β (TB_β), gastric H^+,K^+-ATPase β (HKG_β), or Na^+,K^+-ATPase β1 ($NaK_{\beta1}$) subunits (37, 38). Similarly, guinea pig HKC_α expressed in HEK293 cells exhibited H^+,K^+-ATPase activity in the presence of either HKG_β or NaK_β, but not in the absence of a β subunit (9). Thus, the β-subunit is critical for HKC_α function and Codina *et al* showed by co-immunoprecipitation that HKC_α coassembles with the $NaK_{\beta1}$-subunit in rat distal colon (36). This is surprising, given that $NaK_{\beta1}$ co-assembles with $NaK_{\alpha1}$ in epithelial cell basolateral membranes (11, 23). Sangan et al probed a rat colon cDNA library using astrocytoma β-subunit cDNA, which strongly hybridized with rat colonic mRNA, and isolated a putative cDNA (HKC_β) that encoded a 279 deduced amino acid protein (163). The cloned HKC_β had 80% amino acid homology with human $NaK_{\beta3}$, which is expressed in colon (112, 163). Polyclonal antibody raised against HKC_β that localized proteins in the apical membranes co-immunoprecipitated HKC_α, while M1 antibody co-immunoprecipitated the HKC_β protein from epithelial cell homogenate of rat distal colon (163, 165). These observations clearly establish that a β-subunit is critical for the functional expression of HKC_α, and that the putative HKC_β might compliment HKC_α in the rat distal colon.

Functional expression of HKC_α and HKC_β subunits—Depending upon the co-expressed β-subunit (i.e., HKC_β, HKG_β or $NaK_{\beta1}$), the putative HKC_α exhibits either ouabain-sensitive and/or ouabain-insenstive function (Table-1). The functionality of HKC_α in *in vitro* expression systems (i.e., Xenopus oocytes, *Sf9* and HEK293 cells) has been evaluated by measuring ^{86}Rb uptake or H^+,K^+-ATPase activity (9, 37, 38, 101, 165). HKC_α co-expressed with TB_β also exhibited ouabain-sensitive ^{86}Rb uptake (38), but exhibited only partial ouabain-sensitive ^{86}Rb uptake when co-expressed with either HKG_β or $NaK_{\beta1}$ in *Xenopus* oocytes (37). Lee *et al* showed that when HKC_α was expressed alone in the *Sf9* expression system, it exhibited ouabain-insensitive H^+,K^+-ATPase activity (101). They also used a polyclonal antibody (M1) raised against a HKC_α fushion protein to localize a protein to the plasma membranes of HKC_α-transfected but not untransfected *Sf9* cells (101). The M1-antibody also localized proteins in surface but not crypt cells, and detected a 100 kD protein in mucosal membranes of rat distal but not proximal colon (101). Furthermore, the M1-antibody inhibited expressed (i.e., *Sf9*) and native (i,e., apical membrane) H^+,K^+-ATPase activities, but not basolateral Na^+,K^+-ATPase activity in rat distal colon (101, 139). Thus, these results established that HKC_α protein with H^+,K^+-ATPase activity could be expressed in the plasma membrane of *Sf9* cells. By contrast, Asano *et al* showed that transfection with guinea pig HKC_α alone failed to express HKC_α protein in the plasma membrane of HEK293 cells, but co-expression with either rabbit HKG_β or Torpedo NaK_β subunit resulted in the expression of plasma membrane HKC_α protein with ouabain-sensitive H^+,K^+-ATPase activity (9). Similarly, Sangan *et al* showed that when expressed individually, neither HKC_α nor HCK_β protein was delivered to the plasma membranes, while both proteins were incorporated into membranes when HKC_α and HKC_β were co-expressed in HEK293 cells (165). Although guinea pig HKC_α co-expressed with either rabbit HKG_β or Torpedo NaK_β (9) leads to the expression of HKC_α protein with ouabain-

sensitive H^+,K^+-ATPase activity, rat HKC_α/HKC_β expressed in HEK293 cells exhibited ouabain-*insensitive* H^+,K^+-ATPase activity (165). Thus, while HKC_β is the complementary β-subunit for HKC_α, HKC_α could co-assemble with different β-subunits (e.g., $NaK_{\beta1}$ and HKG_β) to form H^+,K^+-ATPase proteins with different ouabain sensitivities.

Distribution of ouabain-sensitive and ouabain-insensitive H^+,K^+-ATPase along surface-crypt cell axis in rat distal colon

Physiological and biochemical studies have shown that both ouabain-sensitive and ouabain-insensitive H^+,K^+-ATPases are present in the apical membranes that mediate ouabain-sensitive and ouabain-insensitive electroneutral K^+ absorption in rat distal colon, respectively (45, 63, 127, 190). However, molecular studies have cloned only HKC_α that exhibit either ouabain-insensitive and/or ouabain-sensitive function in different *in vitro* expresssion systems (9, 37, 40, 165). As previously discussed, the rat HKC_α expressed alone in *Sf9* cells, or coexpressed with colonic HKC_β-subunt in HEK-293 cells, exhibited ouabain-insensitive H^+,K^+-ATPase activity (101, 165), while HKC_α coexpressed with either $NaK_{\beta1}$ or HKG_β exhibited ouabain-insensitive and partially ouabain-sensitive ^{86}Rb uptake in *Xenopus* oocytes (9, 37, 38). Further studies of H^+,K^+-ATPase activity in apical membranes showed that ouabain-sensitive H^+,K^+-ATPase is present in crypt cells, while other studies evaluating extracellular K^+-dependent intracellular pH (pHi) recovery from an acid load established that ouabain-insensitive and ouabain-sensitive H^+,K^+-ATPase are localized in the apical surface cells and crypt cells of rat distal colon, respectively (Figure-3) (140). In addition, aldosterone upregulated HKC_α-specific mRNA abundance and protein expression, and ouabain-insensitive K^+ absorption and H^+,K^+-ATPase activity in rat distal colon (164, 190). The surface cell specific localization of ouabain-insensitive H^+,K^+-ATPase is in agreement with physiological observations demonstrating increased ouabain-insensitive K^+ absorption in aldosterone-treated rat distal colon (127, 190). Thus, although both ouabain-sensitive and ouabain-insensitive H^+,K^+-ATPases and K^+ absorption are present, only HKC_α that encodes ouabain-insensitive H^+,K^+-ATPase has been cloned, while the molecular identity of the ouabain-sensitive H^+,K^+-ATPase isoform has yet to be identified. Despite H^+,K^+-ATPase having been established as the mechanism for active K^+ absorption in animals, the mechanism for K^+ absorption in human colon in unknown, and warrants further study.

Mechanism of K^+ exit across the basolateral membrane

Active K^+ absorption requires coordinated regulation of K^+ uptake and K^+ exit across apical and basolateral membranes of epithelial cells, respectively. As discussed, H^+,K^+-ATPase mediates K^+ uptake across apical membranes. Potassium (K^+) channels have been suggested as the route for K^+ exit across basolateral membranes, as Ba^{2+} (nonspecific K^+ channel blocker) inhibited mucosal to serosal electroneutral K^+ fluxes in turtle and rabbit colon (75, 76). Since K^+ absorption is electroneutral, the negative membrane potential generated by basolateral K^+ exit should be compensated by the exit of an anion (e.g., Cl^-) and/or the influx of a cation (e.g., Na^+, H^+). Ca^{2+}-activated and cAMP-activated K^+ channels have been identified in the basolateral membranes of rat and human colon (118, 169). However, Sweiry and Binder suggested that basolateral K^+ channels are not involved in electroneutral K^+ absorption in rat distal colon, as the serosal addition of K^+ channel blockers (TEA,

Ba^{2+}, and Cs^{+}) did not inhibit electroneutral K^{+} absorption in hyperaldosterone-treated rat distal colon (190). In a subsequent study by Sangan *et al*, northern and western blot analyses identified KCC1-specific mRNA and protein expression in rat distal colon, and KCC1-specific mRNA abundance and protein expression were increased in dietary-K^{+}, but not dietary-Na^{+} depleted rat distal colon, which suggested that the KCl cotransporter-1 (KCC1) might mediate electroneutral K^{+} exit across the basolateral membrane in rat distal colon (162). However, despite the evidence that KCC1 mediates basolateral K^{+} exit during active K^{+} absorption in rat distal colon, further studies are required to investigate possible species differences in the relative roles of KCC1 and K^{+} channels.

Role of colonic H^{+},K^{+}-ATPase

Although ouabain-sensitive and ouabain-insensitive H^{+},K^{+}-ATPases have been characterized, only HKC_{α} has been cloned, which exhibits both ouabain-sensitive and ouabain-insensitive H^{+},K^{+}-ATPase function, depending upon different β-subunits (HKC_{β}, HKG_{β} or NaK_{β}) that are coexpressed *in vitro* (9, 21, 37, 38). Mice lacking HKC_{α} ($HKC_{\alpha}^{-/-}$) fed a regular (i.e., K^{+}-containing) diet were shown to have fecal K^{+} losses twice those of normal mice, but nevertheless maintained normal body K^{+} homostasis (121). However, $HKC_{\alpha}^{-/-}$ mice fed a K^{+}-deprived diet had low intracellular and plasma K^{+} levels, and lost twice their body weight compared with normal animals (121). Hyperaldosteronism induced by dietary Na^{+} depletion also increased fecal K^{+} losses in $HKC_{\alpha}^{-/-}$ mice. In addition, K^{+} recycled through colonic H^{+},K^{+}-ATPase has been shown to play critical role in epithelial Na^{+} channel (ENaC)-mediated Na^{+} absorption, which is significantly reduced in $HKC_{\alpha}^{-/-}$ mouse colon (181). Thus, it is likely that colonic H^{+},K^{+}-ATPase may be important for both K^{+} conservation and ENaC-mediated Na^{+} absorpion.

Regulation of colonic K^{+} absorption and H^{+},K^{+}-ATPase

Hyperaldosteronism secondary to dietary Na^{+} depletion or dietary K^{+} loading regulates both active K^{+} absorption and H^{+},K^{+}-ATPase activity in rat distal colon (63, 66, 88, 164, 190). Enhanced K^{+} absorption in response to dietary Na^{+} depletion is mediated by aldosterone, since aldosterone infused via osmotic mini-pumps and dietary Na^{+} depletion had similar effects on K^{+} absorption. Furthermore, both dietary Na^{+} depletion and aldosterone infusion induce active K^{+} secretion (191). However, inhibition of the active K^{+} secretion by serosal bumetanide [Na^{+}-K^{+}−$2Cl^{-}$ cotransport (NKCC) inhibitor] unmasked aldosterone-enhanced active K^{+} absorption in rat distal colon (190, 191). Thus, aldosterone stimulates both active K^{+} absorption and active K^{+} secretion (Figure-4) (64, 127, 190). Bearing in mind that active K^{+} absorption has both ouabain-sensitive and ouabain-insensitive components (190), it is interesting that aldosterone upregulated ouabain-insensitive K^{+} absorption, and HKC_{α}-specific mRNA abundance and protein expression, as well as ouabain-insensitive H^{+},K^{+}-ATPase activity, in rat distal colon (164, 190), although aldosterone had no effect on HKC_{β}-specific mRNA abundance or protein expression in this epithelium (163). By contrast, aldosterone did not alter ouabain-sensitive K^{+} absorption and H^{+},K^{+}-ATPase activity (127, 164, 190). Although active K^{+} absorption is not present in normal rat proximal colon, aldosterone upregulated HKC_{α}-specific mRNA abundance and protein expression (164). Further studies are necessary to identify whether the enhanced HKC_{α} mRNA and

protein expression are also associated with increased active K^+ absorption in aldosterone-treated rat proximal colon.

Dietary K^+ modulation and aldosterone regulate active K^+ absorption and H^+,K^+-ATPAse by different mechanisms (64, 66, 163, 164). The model of dietary K^+ depletion has provided evidence that active K^+ absorption is mediated by two different transport processes – one Cl^--dependent, the other Cl^--independent (66). Removal of mucosal Cl^- demonstrated that dietary K^+ depletion stimulated Cl^--dependent, but not Cl^--independent active K^+ absorption, since substitution of Cl^- completely inhibited active K^+ absorption stimulated by K^+ depletion, but did not affect Cl^--independent K^+ absorption (66). The effect of Cl^- substitution on active K^+ absorption stimulated by aldosterone, and on the effect of ouabain on dietary K^+ depletion-stimulated active K^+ absorption, have yet to be determined. Thus, it is difficult to be certain whether dietary K^+ depletion-stimulated active K^+ absorption is mediated by ouabain-sensitive or ouabain-insensitive H^+,K^+-ATPase. Similarly, it is also unclear whether aldosterone-stimulated ouabain-insensitive active K^+ absorption is mediated by a Cl^--dependent or Cl^--independent process. However, whereas aldosterone has been shown to stimulate active K^+ absorption by enhancing HKC_α-specific mRNA abundance and protein expression, dietary K^+ depletion stimulated active K^+ absorption by enhancing HKC_β-specific mRNA abundance and protein expression, but had no effect on HKC_α-specific mRNA abundance and protein expression (163, 164). Thus, aldosterone and dietary K^+ depletion stimulate active K^+ absorption by enhancing the expression of HKC_α and HKC_β, respectively.

Potassium Secretion

Active K^+ secretion requires K^+ uptake and exit across the basolateral and apical membranes of epithelial cells, respectively (Figure-5). Basolateral K^+ uptake is mediated by both Na^+,K^+-ATPase and NKCC, while K^+ exit across the apical membrane is K^+ channel-mediated (151, 156, 157). Na^+ and Cl^- entering cells via NKCC exit across the basolateral membrane through Na^+,K^+-ATPase and Cl^- channels, respectively. In addition to facilitating K^+ exit, basolateral K^+ channels also help to regulate several important physiological functions (58, 86). Under basal conditions, intracellular K^+ recycles via basolateral K^+ channels to be delivered to Na^+,K^+-ATPase (i.e., Na^+-pump), a critical active transporter which catalyzes the cellular egress of 3 Na^+ ions in exchange for 2 K^+ ions entering the cells. By maintaining Na^+,K^+-ATPase activity, the basolateral K^+ channels help maintain low intracellular Na^+ and high intracellular K^+ concentrations, resulting in an electrochemical gradient that generates a negative (~ −50 mV) membrane potential. This electrochemical gradient provides the driving force for secondary active transporters, such as electroneutral (i.e., Na^+-H^+ exchange) and electrogenic (i.e., epithelial Na^+ channel, ENaC-mediated) Na^+ absorptive processes present in the apical membranes of colonic epithelial cells (Figure-6A) (33). In addition to maintaining membrane potential, basolateral K^+ channels also help maintain basolateral Na^+-K^+−2Cl^- cotransporter (Cl^- loader) activity, which mediates Cl^- uptake into cells during active Cl^- secretion (e.g., Cl^--driven secretory diarrhea), Cl^- exiting from cells via apical CFTR Cl^- channels in the colon (Figure-6B) (20, 32, 58). It should be noted that although apical H^+-K^+-ATPase and apical K^+ channels are present in animal colon, channel-mediated K^+ secretion does not appear to be linked to

H^+,K^+-ATPase-mediated K^+ absorption, but when upregulated makes a major contribution to K^+ homeostasis (86, 99).

Molecular identities of K^+ channels

The colonic K^+ channels include both Ca^{2+}-activated K^+ (K_{Ca}) channels and cAMP-activated K^+ channels. Molecular studies have identified five different K_{Ca} channels. These K_{Ca} channels include three small conductance K^+ channels (SK1–3), an intermediate conductance K^+ channel (IK; also known as SK4, $K_{Ca3.1}$ and Kcnn4), and a large conductance K^+ channels (BK, also known as hSlo, $K_{Ca1.1}$ and KCNMA1). In the case of colonic epithelial cells, only BK and IK channels are expressed in the apical and/or basolateral membranes and we will discuss their molecular identities and functional roles. The BK channels have conductances ranging between of 150 *pS* and 230 *pS*, while IK channels have conductances between 12 *pS* and 39 *pS* (Table-2). cAMP-activated K^+ channels with conductance of 1 − 3 *pS* have also been characterized on both apical and basolateral membranes of intestinal epithelial cells (Table-2).

Ca^{2+}-activated K^+ (K_{Ca}) channels of colon:

K_{Ca} channels are present in both the apical and basolateral membranes of colonic epithelial cells. Ion flux studies indicate that K^+ channels mediate K^+ secretion across apical membranes, while basolateral membrane K^+ channels provide the driving force for active Cl^- secretion (21, 32, 48, 50, 113). Patch clamp studies have characterized K^+ channels with conductances of approximately 39 pS and 200 p*S* that are designated intermediate IK and BK channels, respectively (29, 109, 157, 158). BK channels are activated by Ca^{2+} and cAMP, and inhibited by Ba^{2+}, tetraethyl ammonium (TEA) and quinidine (29, 130). IK channels are activated by Ca^{2+} and cAMP, and inhibited by Ba^{2+}, diphenylamine-2-carboxylic acid (DPC) and quinidine, but not by TEA (157). Patch clamp studies have also characterized BK and IK channels on the basolateral membranes of rat and guinea pig small intestine (119, 122, 170, 202), and rat, guinea pig, and rabbit colon (27, 29, 145, 157, 198). Immunological studies have also identified IK and BK channel-like proteins in both the apical and basolateral membrane of intestinal epithelial cells (12, 60, 81, 114, 166, 175, 179, 209).

Large conductance K^+ (BK) channels: BK channels are composed of pore-forming α ($BK_α$) and Ca^{2+}/voltage sensing β ($BK_β$) subunits. Two $BK_α$ splice variants (STREX and ZERO) transcribed from a single gene (28), and four $BK_β$-subunits ($β_{1–4}$, known as $KCNMB_{1–4}$) that display tissue-specific distribution, have been cloned (106, 135). Expression of $BK_α$ alone results in functional large conductance (~150 − 200 *pS*) K^+ channels, while coexpression with different β-subunits results in large conductance K^+ channel activity with different sensitivities to Ca^{2+} and voltage. The $BK_α$ splice variants STREX and ZERO have distinct sensitivities to cAMP, as STREX is inhibited, while ZERO is activated, by cAMP. Exon-18 present in STREX is deleted in ZERO (194). Only ZERO transcripts appear to be expressed in guinea pig and human colon (158, 209). However, both STREX and ZERO transcripts are expressed in mouse colon (179). In addition, $BK_α$ (ZERO) has also been shown to exhibit three splice variants of the COOH-terminal in

human brain and guinea pig colon (195, 209). The BK_α with exon-27 termination resulted in an amino acid sequence ending of QEERL, whereas the termination in exon-28 resulted in an amino acid sequence of EMVYR (61). Splicing of exon-28 resulted in two variants that differed by an omission of three base pairs at the beginning of exon-28 (61). BK_α variants ending with amino acid sequences QEERL and EMVYR are known as BK_α^{RL} and BK_α^{YR}, respectively. Both BK_α^{RL} and BK_α^{YR} are expressed in guinea pig colon (23). The COOH-terminal variants of BK_α^{RL} and BK_α^{YR} contribute to the membrane-specific delivery (apical *vs* basolateral membrane) of BK channels (34, 100, 111). In guinea pig colon, a BK_α^{YR} variant that localizes to both the apical and basolateral membrane of immature cells at the crypt base is expressed only at the apical membrane of matured surface cells (209). Although the molecular identities of BK_α splice variants of rat and human colon have yet to be established, the demonstration that cAMP activates BK channel activity, and forskolin (FSK; which activates adenylate cyclase and increases intracellular cAMP) activates K^+ secretion, suggest that BK channels encoded by ZERO transcripts mediate K^+ secretion in rat and human colonic epithelial cells (Figure-7) (130, 159). Hyperaldosteronism induced by both dietary Na^+ depletion and chronic dietary K^+ loading enhance BK_α-specific mRNA abundance and protein expression, and stimulate iberiotoxin (IbTX, BK channel blocker)-inhibitable K^+ secretion in rat distal colon (159). Aldosterone appears to stimulate K^+ secretion through the ZERO isoform, since FSK (i.e., cAMP) did not inhibit aldosterone-enhanced K^+ secretion in rat distal colon (130, 176).

The BK_α-subunit links with auxiliary β-subunits, which have the ability to modify the activation kinetics (i.e., Ca^{2+} and voltage sensitivities) and inhibitor sensitivity of the BK channel complex (17, 39, 54, 106, 135). Four isoforms of BK_β subunits have been identified, each of which may associate with the BK_α-subunit to modulate BK channel activities in unique ways (54, 201). Earlier studies identified the expression of all four β-subunits (60, 138), while a recent study identified only β2 subunit expression in mouse colon (179). Similarly, although different studies have shown expression of all four β subunits, β1 and β3 subunits were found to be the dominant β subunits in human colon (16, 26, 158). β1 and β4 were the only β subunits detected in guinea pig colon (209). Thus, BK_α splice variants (BK_α^{RL} and BK_α^{YR}) may co-express with different β-subunits in mouse, guinea pig, rat and human colon. Further studies are required to establish whether BK_α^{RL} and BK_α^{YR} splice variants co-express with the same or different β-subunits, and whether BK_α^{RL} and BK_α^{YR} expression differs between cell types (i.e., villus vs crypt cells) and different membrane domains (i.e., apical vs basolateral) in colonic epithelial cells.

Intermediate conductance K^+ (IK) channels: The IK channel gene that encodes 427 amino acids was originally cloned from human placenta (93). Human and rat colonic IK orthologues that encode 424 amino acids have been cloned from T84 cells and a rat colonic cDNA library, respectively (92, 204). When expressed *in vitro*, rat colonic IK channels exhibited Ca^{2+}-activated K^+ currents with a single channel conductance of 36 *pS*, which were inhibited by clotrimazole (CLT, an antifungal inhibitor) (92). Immunofluorescence studies have localized IK channel-like proteins to the apical and basolateral membranes of epithelial cells in rat distal colon, while immunogold labeling studies have localized IK-like proteins to the apical and basolateral membranes of rat and human colon (Figure-8) (12, 68).

Extensive cloning studies have isolated two additional IK splice variants that encode 425 and 395 amino acid proteins from a rat colon cDNA library (12). The IK channel isoform mRNAs encoding 425, 424 and 395 amino acid proteins were designated IK_a ($Kcnn_{4a}$), IK_b ($Kcnn4_b$) and IK_c ($Kcnn_{4c}$), respectively. Since IK_a (i.e., 425 amino acid protein) had 100% homology with the mouse IK channel (mIK1) orthologue that was cloned from smooth muscle (125), it was concluded that IK_a encodes smooth muscle IK channels, while IK_b and IK_c encode basolateral (40 kD) and apical (37 kD) IK channels in epithelial cells, respectively (12).

The IK_c isoform lacks 29 amino acids, which constitutes the entire second membrane spanning domain (MSD), plus 5 exofacial and 2 endofacial amino acids in the IK_c isoform. Thus, the membrane topology of IK_c, with five predicted MSDs, differs from IK_a and IK_b, which have six MSDs. Although even MSDs are common for transport proteins, several transport proteins, including K^+ channels with odd MSDs, have been shown to express functional proteins (25, 120, 143). However, although IK protein was readily expressed on the surface membrane of *Xenopus* oocyte injected with IK_b cRNA, IK protein was identified in cytoplasm of oocytes that were injected with IK_c cRNA. By contrast, when IK_c cRNA was coinjected with β-subunit cRNA transcribed from KCNMB1 (i.e., $BK_{β1}$-subunit), IK protein was readily localized on the plasma membranes of oocytes (Figure-9). The IK_c and $BK_{β1}$ cRNA coinjected oocytes also exhibited TRAM-34 (IK channel specific inhibitor)-sensitive K^+ uptake, indicating IK channel functionality (12). These observations indicated that although a specific β-subunit has not yet been identified, IK_c requires a β-subunit (i.e., chaperone protein) for its membrane expression. It is not known whether IK_c lacking a MSD utilizes $BK_{β1}$, or a complementary ‘chaperone’ protein for its membrane expression in colon.

cAMP activated K^+ channels:

cAMP-activated K^+ channels are located in the basolateral membranes of rat and human colon (102, 118, 205). Inhibition by chromanol-293B, a slow delayed rectifier K^+ current blocker is the unique feature of these cAMP-activated K^+ channels (205). This cAMP-activated K^+ channel is encoded by voltage-gated K_vLQT1 channel gene (98). K_vLQT1 consists of α- (known as KCNQ1) and β- (known as KCNE) subunits. Five different β-subunits (KCNE1–5) have been isolated (123). KCNQ1 complexed with different KCNE isoforms expressed in different cells and membrane domains exhibit different cell functions (123). KCNQ1 complexed with KCNE1 is found in the basolateral membranes of colon (70, 203). KCNQ1/KCNE3 complexes have been identified in the basolateral membranes of mouse epithelial cells (4, 43, 46, 137). Chromanol 293-sensitive KCNQ1-mediated K^+ channels play a critical role in cAMP-stimulated Cl^- secretion in mouse colon (43), and they appear to be essential for cAMP-stimulated Cl^- secretion in guinea pig colon (104). However, since both cAMP- and Ca^{2+}-mediated agonists have been shown to activate IK channels, it is likely that basolateral IK channel-mediated K^+ exit maintains the intracellular negative membrane potential which provides the driving force for both cAMP (e.g., cholera toxin) and Ca^{2+} (e.g., bile acid) agonist-activated secretory diarrhea (118, 149, 157, 160).

Apical membrane K^+ channels

Role of apical membrane BK channels in colonic K^+ secretion: Apical membrane K^+ channels play a critical role during active K^+ secretion (Figure-5), Slow marker perfusion studies have shown that the human colon, but not the small intestine, secretes 4.7 mEq K^+ per day (133). Both passive K^+ permeation and active K^+ secretion contribute to luminal and stool K^+ concentration. In the colon, paracellular (passive) K^+ permeation is driven by the lumen-negative transepithelial (~20–30 mV) electrical potential difference (18, 141), although the potential difference in the small intestine is much lower. By contrast, transcellular (active) electrogenic K^+ secretion is a feature restricted to the salivary gland, gastric mucosa and colon (85, 102, 146). Active K^+ secretion contributes significantly to stool K^+ losses in diarrheal diseases. For example, whereas normal individuals excrete ~10 mEq K^+/day in their stools, cholera patients with severe diarrhea excrete 119 mEq K^+/day (3, 200). Active K^+ secretion involves K^+ uptake across the basolateral membrane and K^+ exit across the apical membrane (Figure-5). In addition, electrogenic K^+ secretion requires exit mechanisms for Na^+ and Cl^- across the basolateral membrane. K^+ uptake across the basolateral membrane is mediated by Na^+,K^+-ATPase and Na^+-K^+−$2Cl^-$ cotransport, while K^+ exit across the apical membrane is mediated by K^+ channels. Basolateral uptake of Na^+ reflects Na^+-K^+−$2Cl^-$ cotransport, and Na^+ is pumped out by Na^+,K^+-ATPase. Basolateral Cl^- uptake also reflects Na^+-K^+−$2Cl^-$ cotransport, and Cl^- exits via Cl^- channel-2 (CLC2), which has been identified in the basolateral membrane of mouse and guinea pig colon (30, 31, 208). The use of ouabain to inhibit Na^+,K^+-ATPase-mediated K^+ uptake and bumetanide to inhibit NKCC-mediated K^+ uptake across basolateral membranes has established that both Na^+,K^+-ATPase and NKCC have pivotal roles in the regulation of active K^+ secretion (134, 177, 179, 191). Na^+,K^+-ATPase regulates active K^+ secretion under basal conditions, whereas NKCC is the predominant regulator of stimulated active K^+ secretion (179, 191). It should be emphasized that K^+ uptake across the basolateral membrane far exceeds its transepithelial movement, which points to K^+ recycling across the basolateral membrane. Consistent with this view, the addition of Ba^{2+} (a nonspecific K^+ channel blocker) increased net K^+ secretion in turtle and rabbit colon (134, 191). However, since the addition of K^+ channel blockers to the serosal bath did not alter K^+ absorption, it was suggested that K^+-Cl^- co-transport might be responsible for K^+ recycling across the basolateral membranes in rat distal colon (191). However, since active K^+ secretion was enhanced in IK channel knockout mice, it seemed likely that IK channels might regulate K^+ recycling across basolateral membranes of colon (12, 92, 179, 209). Colonic K^+ secretion is activated by cellular second messengers (e.g., cAMP and Ca^{2+}), and stimulated during dietary K^+ loading, dietary Na^+ depletion (aldosterone), and in an animal model of dextran sulfate sodium (DSS)-induced ulcerative (64, 66, 94, 118, 159, 176, 191). Diarrhea is a major symptom in ulcerative colitis, and while enhanced active Cl^- secretion usually underlies diarrhea originating from the colon, defective ENaC-mediated Na^+ absorption appears to be the main pathophysiologic mechanism of diarrhea in patients with ulcerative colitis (7, 41). Absence of FSK (cAMP)-activated and CCH (Ca^{2+})-activated Cl^- secretion also suggest that active Cl^- secretion is not responsible for diarrhea in DDS-induced ulcerative colitis (Figure-13). Moreover, K^+ (but not Na^+) enriched diarrhea has been reported in patients with colonic pseudo-obstruction (175, 200), and we therefore predicted that in addition to defective ENaC-mediated Na^+ absorption, enhanced K^+ secretion might also contribute to diarrhea in

ulcerative colitis. Additional studies are therefore required to determine whether K^+ channel inhibition decreases K^+-driven water secretion in ulcerative colitis, which might ameliorate diarrhea in patients with this disease.

Ion flux studies performed under voltage clamp condition have shown that the specific BK channel inhibitors iberiotoxin and paxilline block apical membrane K^+ channels mediating both basal and stimulated K^+ secretion in animal colon (159, 166, 176, 179, 180, 209), while patch clamp studies have characterized K^+ channels in rat and human colon (29, 129, 130, 150, 156). The absence of K^+ secretion in BK_α knockout mice established that BK channels mediate both basal and activated K^+ secretion in murine colon (166). It is currently accepted that absorptive and secretory transport processes are distributed differentially along the surface-crypt axis, surface cells being the site of absorption (e.g., ENaC-mediated Na^+ absorption) and crypt cells being the site of secretion (e.g., CFTR-mediated Cl^- secretion). By contrast, there are conflicting views about BK_α protein localization in normal guinea pig, mouse and human colon (114, 158, 166, 175, 179, 209). In normal human colon, BK_α-like protein appears to be restricted to the apical membrane of surface cells and cells in the upper third of crypts, while in mouse colon it is seen only in crypt cells. Absence of BK_α proteins in BK channel knockout mice supported the presence of BK channels in crypt cells of normal murine colon (166, 179), while BK channel expression in surface cells of normal human colon has been established by patch clamp and immunostaining (114, 158, 175). Unlike mouse and human colon, BK_α proteins have been identified in both surface and crypt cells in guinea pig distal colon (209). Despite the species differences in cell localization of BK_α protein, it is well established that apical BK channels mediate both basal and active K^+ secretion in colon.

Role of apical IK channels in K^+ secretion: Patch clamp studies have characterized IK channels only in the basolateral membranes of crypts from rat and human colon (24, 109, 157, 204). However, immunofluorescence studies have localized IK channel-like proteins to the apical membranes of rat and human colon (6, 12, 68, 92). The apical IK channel is encoded by a IK_c transcript in rat distal colon (12), and the role of apical IK channels is starting to emerge (92, 124). The observations that mucosal clotrimazole inhibits carbachol-stimulated K^+ secretion (92), and that the IK channel blocker TRAM-34 inhibits K^+ secretion induced by the mucosal application of DC-EBIO (IK channel opener), provide strong support for the presence of functional mucosal IK channels in rat colon (Figure-10) (124). In addition, the complete absence of DC-EBIO-induced K^+ secretion suggests that down-regulation of apical IK channels may play critical role in K^+ conservation in rat distal colon during dietary K^+ depletion (171). Although agonist (e.g. cAMP) stimulated K^+ secretion is mediated by apical BK channels, apical IK channels may mediate basal K^+ secretion, a possibility that could be explored using an appropriate animal knockout model.

Role of basolateral membrane K^+ channels—By recycling K^+ across the basolateral membrane, K^+ channels regulate both Na^+,K^+-ATPase and the Na^+-K^+−$2Cl^-$ cotransporter. In the basal state, constitutively open basolateral K^+ channels maintain a negative membrane potential, which is the driving force for Na^+-dependent nutrient absorption and Na^+/H^+-exchanger-mediated electroneutral Na^+ absorption in the small intestine. Basolateral K^+

exit is counterbalanced by Na^+,K^+-ATPase-mediated K^+ uptake, which maintains the high intracellular K^+ concentration. In animal and human distal colon, the electrochemical gradient also provides the driving force for electrogenic Na^+ absorption mediated by epithelial Na^+ channel (ENaC). By contrast, under stimulated conditions, the Na^+-K^+−2Cl^- cotransporter mediates basolateral Cl^- uptake, Cl^- exiting through apical cystic fibrosis transmembrane regulator (CFTR) Cl^- channels, resulting in membrane depolarization. K^+ exits through agonist-activated (e.g., Ca^{2+} and cAMP) basolateral K^+ channels, thereby repolarizing the basolateral membrane to maintain the driving force required for sustained electrogenic Cl^- secretion (Figure-6B). Patch clamp studies have identified and characterized different types of basolateral K^+ channels in colonic crypt cells in a variety of species (32, 109, 119, 184, 199), and these K^+ channels can be divided into three categories: 1) small (< 6 pS), 2) intermediate (~25 pS) and 3) large (~130 pS) conductance K^+ channels. Molecular studies have identified that the small, intermediate and large conductance K^+ channels correspond to KCNQ1/KCNE3, IK and BK channels, respectively (12, 137, 156, 159). In addition, 27–30 pS nonselective cation channels have also been identified in turtle and rat colon (27, 144), but their molecular identities are not known. Small conductance basolateral (KCNQ1/KCNE3) K^+ channels are activated by cAMP, while both Ca^{2+} and cAMP activate basolateral IK channels. The physiological role of basolateral BK channels is yet to be identified (27, 47, 109, 119, 209). Since KCNQ1/KCNE3 channels make only a small contribution to basolateral K^+ conductance in human colonic crypt cells (4), it is likely that the highly abundant basolateral IK channel plays a critical role in regulating Cl^--driven fluid secretion (5, 32).

Regulation of K^+ channels and K^+ secretion—Corticosteroids (both the glucocorticoids cortisol and corticosterone, and the mineralocorticoid aldosterone) secreted by the adrenal glands are required for basal intestinal electrolyte transport function (103, 148). Although both natural and synthetic glucocorticoids and mineralocorticoids regulate electrolyte transport, aldosterone is the main regulator of electrolyte transport in the colon (148). Glucocorticoids and mineralocorticoids exert different effects on electrolyte transport through specific receptors present in the epithelial cells of the small intestine and colon, respectively (136, 196). Although K^+ channels are present throughout the entire intestinal tract (32, 68, 156), only colonic K^+ channels are regulated by corticosteroids (20, 148). The distal colon is a major target for mineralocorticoids (15), since mineralocorticoid receptor expression is greater in this colonic segment (67). *In vitro* studies based on unidirectional ion flux measurement under voltage clamp conditions, and intracellular microelectrodes, demonstrated that hyperaldosteronism produced qualitatively different changes in electrolyte transport by enhancing electroneutral (i.e., Na^+-H^+ exchange mediated) and inducing electrogenic (i.e., ENaC mediated) Na^+ absorption in the proximal and distal segments of rat colon, respectively (63, 87, 153). These segmental variations may reflect different types of corticosteroid receptors in the mucosa (14, 22). Receptor binding studies showed both glucocorticoid and mineralocorticoid receptors to be present throughout the entire colon, but glucocorticoid receptors outnumbered mineralocorticoid receptors in the proximal colon (14, 168). Initial studies regarding the effect corticosteroids on electrolyte transport showed that both glucocorticoids (i.e., dexamethasone) and mineralocorticoids stimulated electrogenic colonic K^+ secretion (20, 148). However, additional studies showed that

aldosterone, but not RU-28362 (a specific glucocorticoid agonist), stimulated electrogenic K^+ secretion in rat proximal and distal colon (108, 196). RU-28362 binds more avidly to glucocorticoid receptors than dexamethasone or corticosterone, and does not compete for radio-labeled aldosterone binding to the mineralocorticoid receptor (193). It seems likely that dexamethasone-stimulated electrogenic K^+ secretion reflected crossover binding to mineralocorticoid receptors. Thus, stimulation of electrogenic K^+ secretion in animal colon reflects the activation of specific mineralocorticoid receptors, but not specific glucocorticoid receptors.

Ion flux studies have shown that hyperaldosteronism, secondary to exogenous aldosterone administration or chronic dietary Na^+ depletion stimulates electrogenic K^+ secretion in mouse and rat distal colon (55, 56, 63, 84, 176, 179). Studies with site-directed intracellular microelectrodes showed that aldosterone enhanced the apical K^+ conductance of surface epithelial cells in rat distal colon (107, 108). Aldosterone reversed the basal active K^+ absorption normally present to active K^+ secretion in rat distal colon (Figure-11) (176). Flux measurements under voltage clamp condition have shown that both IK and BK channels contributed to the aldosterone-enhanced K^+ secretion, and that the BK made a larger contribution than that of IK channels (64% versus 29%, respectively) (176). Quantitative-PCR and western blot analyses are consistent with aldosterone enhancement of both IK_c and BK_α specific mRNA abundance and protein expression, respectively. *In vitro* aldosterone exposure also enhanced IK_c and BK_α specific mRNA abundance, which was prevented by actinomycin D (DNA-dependent RNA polymerase inhibitor) in normal rat distal colon (Figure-12). These observations strongly suggest that aldosterone induced active K^+ secretion by regulating both IK_c and KCNMA1α expression at the transcriptional level (176).

The ability of aldosterone to increase IK_c expression suggests that the IK gene is regulated by aldosterone acting on its cognate receptor (i.e., mineralocorticoid receptor; MR). Chromatin immunoprecipitation (ChIP) assay studies identified the MR response elements (MREs) in regions that spanned 20 kb upstream and 10 kb downstream of the presumed transcription start site in chromatin of colonic epithelial cells from normal and aldosterone-treated rats (126). MREs were immunoprecipitated in a ~5 kb region spanning the first and second introns in aldosterone-treated rats. When co-expressed with MR, these clones exhibited aldosterone-activated enhancer activity in HEK293T and CaCo2 cells. Bioinformatics analyses have identified two MRE regions. These clones lost enhancer activity after mutation of the presumptive MREs, thus establishing the functionality of MREs in the IK gene (126). Although transcriptional regulation IK channel by aldosterone is established, it is not yet known whether MREs are also present in BK_α gene.

Pathophysiology of colonic K^+ channels

Role of apical and basolateral K^+ channels in ulcerative colitis: Healthy human colon absorbs 1.5 − 2 liters of water a day, which is driven by the net absorption of large amounts of Na^+ and Cl^-. These net absorptive fluxes of Na^+ and Cl^- reflect several different transport mechanisms operating in different segments of the colon, which have been described in detail elsewhere (147). Human colon is also capable of water secretion, but in healthy

individuals fluid absorption far outweighs fluid secretion. However, in patients with active ulcerative colitis (UC), where the mucosa of the rectum and (to a variable extent) the colon is inflamed, diarrhea is the main and most debilitating symptom. Based on the results of a variety of studies, it is now clear that impaired Na^+ and Cl^- absorption (rather than increased Cl^- secretion) leads to decreased colonic water retention, and this is the main cause of diarrhea in this disease (7, 71, 80, 155).

Basolateral IK channels in ulcerative colitis: Studies comparing differences in electrolyte transport between healthy individuals and patients with active UC have been done mainly in the distal colon and rectum, where electrogenic Na^+ absorption is normally the dominant Na^+ absorptive process. This generates a substantial lumen-negative trans-mucosal electrical potential difference (PD) in healthy distal colon (161). By contrast, a marked decrease (depolarization) or loss of this PD is the bioelectric hallmark of active UC, which reflects defective apical Na^+ channel function with the virtual disappearance of electrogenic Na^+ absorption (7, 71), as well as basolateral membrane depolarization (155). During Na^+ absorption across healthy human distal colon and rectum, the basolateral membrane (and thus the cell interior) is maintained in a hyperpolarized state by K^+ ions recycling across the membrane via K^+ channels. Indeed, the negative intracellular potential is a prerequisite for apical Na^+ entry. Several studies in healthy human colon identified intermediate conductance (~25 pS) Ca^{2+}-activated K^+ channels encoded by the Kcnn4 gene (referred to as IK channels), as the dominant basolateral K^+ channel in colonic crypt cells (24, 105, 157). Immunolabeling revealed basolateral IK channels are distributed uniformly along the surface-crypt axis in healthy individuals, with greatly decreased channel expression in active UC colon (5). Patch clamp analysis showed cell conductance to be dominated by basolateral IK channels in healthy individual, but channel abundance and overall activity were decreased by 53% and 61% respectively in active UC, equating to a 75% decrease in basolateral membrane K^+ conductance in this disease (5). Thus, in addition to defective apical Na^+ channel function, substantial decreases in basolateral IK channel expression and activity occur in active UC. This loss of IK channel functions most likely accounts for the epithelial cell depolarization that occurs in active UC, resulting in a decreased electrical driving force for electrogenic Na^+ absorption across the inflamed mucosa. Interestingly, IK channel expression and activity reverted to normal in UC patients in clinical remission (5), which fits well with results from *in vivo* rectal dialysis studies, where UC patients in clinical remission had lumen-negative transmucosal PDs and net Na^+, Cl^-, and water absorptive fluxes identical to those in healthy individuals (154).

Basolateral KCNQ1/KCNE3 channels in ulcerative colitis: While IK channels dominate basolateral K^+ conductance in human colon, basolateral membranes of mouse colonic crypt cells also contain small conductance K^+ (KCNQ1/KCNE3) channels. The KCNQ1/KCNE3 complex functions as a constitutively open basolateral K^+ channel and, as described earlier, has a critical role in cAMP-stimulated electrogenic Cl^- secretion. KCNQ1/KCNE3 (or SK) channels maintain the Cl^- secretory response by recycling K^+ entering the cell via the basolateral Na^+-K^+−2Cl^- cotransporter, thus hyperpolarizing the cell while Cl^- entering basolaterally exits the cell via apical CFTR channels. Although the inflamed mucosa in active UC contains high levels of a number of inflammatory cytokines that increase

intracellular cAMP, the low/absent transmucosal PD seen in active UC is inconsistent with electrogenic Cl^- secretion (154), and Cl^- secretion is not a feature of this disease (80, 154), raising the possibility that the expression/activity of putative SK channels in the inflamed colon might be decreased. In a recent study, however, despite similar levels of KCNQ1 and KCNE3 mRNA expression in colonic crypts from healthy and active UC patients, single cAMP-activated 6.8 pS channels were seen in 36% of basolateral patches in healthy individuals and in 74% of patches in active UC patients, with two or more channels per patch. Furthermore, overall channel activity was 10-fold greater in active UC, with a 20-fold greater contribution to basolateral conductance than in normals. Thus, SK channels appear to make a relatively small contribution to basolateral K^+ conductance in normal colonic epithelial cells, and even though enhanced, SK channel activity in active UC is insufficient to prevent cell depolarization. This provides additional evidence that defective Na^+ absorption rather than enhanced Cl^- secretion is the main pathophysiological mechanism of diarrhea in UC.

Apical BK channels in ulcerative colitis: Apical BK channels have been studied extensively in mouse colon, where they are present along the entire surface cell-crypt cell axis (166, 179). By contrast, in rat colon, apical BK channels localize to surface cells and cells in the upper 20% of crypts, with relatively low levels of channel abundance (as judged by patch clamp recording) in both the proximal and distal segments, although BK channel expression and abundance are greatly enhanced in the distal colon during chronic dietary K^+ loading (129). The distribution of apical BK channels (214 pS) along the crypt axis in normal human colon is similar to that in normal rat colon, without any obvious proximal-distal variation in channel expression (158). However, in patients with UC, the pattern of BK channel distribution is altered, so that BK channel protein is expressed uniformly along the entire surface cell-crypt cell axis, a change that is present irrespective of whether the disease is active or quiescent (158). It is presently unclear whether the wider distribution of BK channel protein along the entire crypt in UC patients results in an increase in luminal (apical) K^+ permeability, but if that is indeed the case, it may explain the increased colonic K^+ secretion that occurs in some patients with active UC (8, 78, 80), leading to excessive fecal K^+ losses and hypokalemia. The fact that the wider cryptal distribution of BK channel expression persists in quiescent UC (where colonic K^+ secretion is likely to be normal), suggests that fecal K^+ losses in UC are also dependent upon overall BK channel activity, which is likely to be stimulated in active UC by cAMP and/or Ca^{2+}-mediated inflammatory cytokines.

Recent studies using an experimental model of dextran sulfate sodium (DSS)-induced distal colitis in rats, have shown changes in apical BK channel expression and upregulation of active K^+ secretion, as well as histological changes, that are remarkably similar to those seen in human active UC (94). Whereas there was zero net K^+ transport in control animals, there was active K^+ secretion in DSS-treated animals, which was inhibited by 98, 76, and 22% by Ba^{2+} (a nonspecific K^+ channel blocker), iberiotoxin (IbTX; a specific BK channel blocker), and TRAM-34 (a specific IK channel blocker), respectively. Compared to controls, apical BK channel α-subunit mRNA abundance and protein expression were enhanced 6- and 3-fold respectively. Thus, in DSS-induced colitis, active K^+ secretion involved upregulation

of apical BK channel expression (94). Since similar changes in K^+ transport occur in patients with UC, diarrhea in this disease may reflect water secretion driven by increased colonic K^+ secretion, in addition to defective Na^+ and Cl^- absorption. It is worth noting that both Ca^{2+}- and cAMP-stimulated Cl^- secretion are defective in DSS-colitis rat distal colon (Figure-13). This experimental model of chronic colitis is likely to be extremely useful for future studies into the intracellular mechanisms that determine the ion transport defects underlying diarrhea in human UC.

Role of apical BK channels in end-stage renal disease: An important feature of the natural progression of end-stage renal disease (ESRD) is that patients tend to remain normokalemic for long periods in the face of steadily deteriorating renal excretory function. Adaptive changes occur within the remaining functional renal tubules, namely enhanced K^+ uptake across the basolateral (peritubular) membrane, which is mediated by increased cortical and outer medullary Na^+, K^+-ATPase activity (83, 167). However, this response alone cannot entirely explain the maintenance of K^+ homeostasis in the pre-dialysis phase (during which there is usually no or only a relatively small restriction of dietary K^+ intake), because urinary K^+ losses are generally substantially lower than in healthy individuals. This raises the question of how the body continues to excrete K^+ when renal K^+ excretory capacity is so impaired. A possible clue came from metabolic studies performed nearly 50 years ago, which showed enhanced fecal K^+ losses in patients with ESRD, with a strong correlation between dietary K^+ intake and fecal K^+ output, raising the possibility that some part of the intestinal tract developed an accessory K^+ excretory role during progressively deteriorating renal function (82, 207). Indeed, such an adaptive response may account for sustained normokalemia in many patients, before they eventually require additional intervention in the form of continuous ambulatory peritoneal dialysis (CAPD), hemodialysis, and ultimately, renal transplantation. Subsequent studies into intestinal K^+ transport in rats with normal renal function fed a high K^+ diet for 10–14 days indicated that the colon, but not the small intestine, was capable of increasing its capacity for K^+ secretion in response to dietary K^+ enrichment (59). Chronic dietary K^+ loading stimulated a pan-colonic active K^+ secretory process (64, 65, 97), which involved increased Na^+,K^+- ATPase-mediated K^+ uptake across an amplified basolateral membrane, a rise in intracellular K^+ concentration, and an increase in apical membrane K^+ conductance (95, 150). Furthermore, *in vivo* dialysis studies in healthy individuals and patients with ESRD indicated that rectal K^+ secretion was substantially greater than normal in normokalemic patients with ESRD who were not yet established on dialysis, normokalemic patients maintained on CAPD, and patients undergoing hemodialysis (151, 152). Enhanced rectal K^+ secretion in these groups was independent of the transmucosal electrical potential difference, as well as the rate of Na^+ absorption and the circulating level of plasma aldosterone, which suggested that altered K^+ transport reflected the stimulation of an active K^+ secretory process (151).

A critical component of the upregulated active K^+ secretory process in rat colon elicited by chronic dietary K^+ loading is the induction and/or activation of high-conductance (BK; 220 pS) apical K^+ channels in surface colonic epithelial cells (29, 129). Similar if not identical apical BK channels occur in surface cells around the luminal openings of human colonic crypts (114, 158). In a recent study, the apical K^+ permeabilities of the proximal rectum

in ESRD patients and patients with normal renal function were compared using the rectal dialysis technique, and the expression of BK channels in the distal colon of these two groups of patients evaluated using a specific BK channel antibody (114). Rectal K^+ secretion was almost threefold greater in ESRD patients than in patients with normal renal function, and intraluminal Ba^{2+} (a general inhibitor of K^+ channels) decreased K^+ secretion in the ESRD patients by 45%, but had no effect on K^+ transport in normal patients. Immunostaining with a specific antibody to the BK channel α-subunit demonstrated significantly greater levels of BK channel protein expression in surface colonocytes and crypt cells in ESRD patients than in patients with normal renal function, in whom low levels of expression were mainly restricted to surface colonocytes. Taken together, these results suggest that upregulated colonic K^+ secretion in ESRD reflects enhancement of the apical K^+ permeability of the large intestinal epithelium, most likely the result of increased expression of apical BK channels (114). What drives this adaptive change in apical BK channel expression in ESRD is unclear, but one possibility is post-prandial increases in plasma K^+ concentration. This hypothesis was tested by measuring plasma K^+ concentrations in the fasting state, and for 180 minutes after the oral administration of 30 mmol of K^+ to control subjects and normokalemic patients with ESRD who were ‘pre-dialysis’ or undergoing CAPD. Plasma K^+ concentrations were also monitored in fasting controls and ESRD patients who were not given the oral K^+ load. Oral K^+ loading caused plasma K^+ concentration to rise within the normal range in control subjects, while significantly higher concentrations were achieved in ‘predialysis’ patients and sustained hyperkalemia developed in CAPD patients (115). Thus, by raising the “K^+ load” presented to the colonic epithelium, postprandial increases in plasma K^+ concentration may be an important signal in maintaining the colon in a state of K^+ hypersecretion.

Despite the rise in colonic K^+ secretory capacity in ESRD, interdialytic hyperkalemia remains a potentially life-threatening problem in hemodialysis patients. cAMP elicits a greater proximal colonic net K^+ secretory response in dietary K^+ loaded rats than in normal animals (65). This raises the possibility that interdialytic hyperkalemia might be attenuated by further enhancing colonic K^+ secretion using a cAMP-mediated laxative, thus limiting postprandial increases in plasma K^+ concentration in hemodialysis patients. This was evaluated by measuring plasma K^+ concentrations in control subjects and hemodialysis patients before and during two weeks treatment with bisacodyl (a cAMP-mediated laxative), and in hemodialysis patients before and during two weeks treatment with lactulose (an osmotic laxative) (115). Bisacodyl treatment had no effect on plasma K^+ concentrations in control subjects, but significantly decreased the mean interdialytic plasma K^+ concentration in hemodialysis patients, whereas there was no change during lactulose treatment (115). Since cAMP stimulates both colonic apical BK channel expression and net colonic K^+ secretion (65, 130), these findings suggest that cAMP-mediated laxatives may be a novel approach to the reduction of severe interdialytic hyperkalemia in hemodialysis patients.

Conclusion

The colon plays critical role in K^+ homeostasis, as it has enormous adaptive capacities to absorb and secrete K^+ in physiological and pathophysiological conditions. This review summarizes the evidence that apical H^+,K^+-ATPase, composed of catalytic α-

(HKC_α) and regulatory β- (HKC_β) subunits, and operating in parallel with basolateral K^+ and Cl^- channels, mediates active K^+ absorption in animal colon. Furthermore, dietary Na^+ (hyperaldosteronism) and dietary K^+ deprivation upregulate H^+,K^+-ATPase-mediated K^+ absorption by regulating HKC_α and HKC_β expression, respectively. Although we now have a detailed understanding of how changes in dietary K^+ intake regulate colonic H^+,K^+-ATPase activity and K^+ absorption, the effect of disease (e.g., UC and malignant transformation) on H^+,K^+-ATPase-mediated colonic K^+ absorption remains to be established.

Active K^+ secretion is mediated by the coordinated regulation of apical K^+ channels and basolateral Na^+-K^+−$2Cl^-$ cotransporter in both animal and human colon. To a lesser degree, basolateral Na^+,K^+-ATPase also participates in active K^+ secretion. Although both IK and BK channels are localized to colonic apical membranes, BK channels play a critical role in secretory agonist (i.e., cAMP and Ca^{2+})- and aldosterone-stimulated colonic K^+ secretion. Both BK channel expression and BK channel-mediated K^+ secretion are enhanced in patients with ESRD and UC, and in experimental UC in animals. BK channels are composed of α- and β-subunits, there being two BKα ($BK_\alpha{}^{RL}$ and $BK_\alpha{}^{YR}$) and four BK_β ($BK_{\beta 1–4}$) splice variants. $BK_{\beta 1}$ and $BK_{\beta 3}$ are expressed in human colon. It is not known whether $BK_\alpha{}^{RL}$ and/or $BK_\alpha{}^{YR}$ encode the BK channels that mediate active K^+ secretion during physiological and pathophysiological conditions in animal and human colon. It is also unclear whether $BK_\alpha{}^{RL}$ and $BK_\alpha{}^{YR}$ are expressed in same and/or different cell types in animal and human colon. Cellular K^+ exit through apical and basolateral IK channels contributes, at least in part, to maintaining membrane hyperpolarization, a prerequisite for sustained agonist-stimulated active Cl^- secretion.

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Didactic Synopsis

Major Teaching Points:

The gastrointestinal (GI) tract has enormous capacity to absorb and secrete K^+ to maintain K^+ homeostasis.

1. K^+ absorption:
   - **a.** *In vivo* perfusion studies to evaluate unidirectional K^+ fluxes showed passive K^+ absorption is mediated by solvent drag in both animal and human colon.
   - **b.** *In vitro* ion fluxes measured under voltage clamp condition, and biochemical and molecular studies of enzyme activities, identified apical H^+,K^+-ATPase as the mediator of active K^+ absorption in animal colon..
   - **c.** Aldosterone-stimulated active K^+ absorption in animal colon reflects enhanced apical H^+,K^+-ATPase mRNA expression and protein activity.
   - **d.** Although apical H^+,K^+-ATPase mediates active K^+ absorption in animal colon, the molecular basis for K^+ absorption in human colon has yet to be idenitified.
2. K^+ secretion:
   - **a.** Active K^+ secretion occurs in both animal and human colon.
   - **b.** Apical K^+ channels and basolateral Na^+-K^+−$2Cl^-$ cotransport coordinate active K^+ secretion.
   - **c.** Ca^{2+}-activated large conductance K^+ (BK) channels constitute the main apical K^+ conductance for K^+ exit into the lumen.
3. Role and regulation of active K^+ secretion:
   - **a.** Aldosterone and high-K^+ diet stimulate apical BK channel expression and active K^+ secretion.
   - **b.** Upregulated BK channel expression is the adaptive mechanism for K^+ secretion in patients with end-stage renal disease.
   - **c.** Increased BK channel expression and K^+ secretion likely contribute to diarrhea in patients with ulcerative colitis.
   - **d.** Potassium channels could be a potential therapeutic target to control diarrhea in ulcerative colitis.

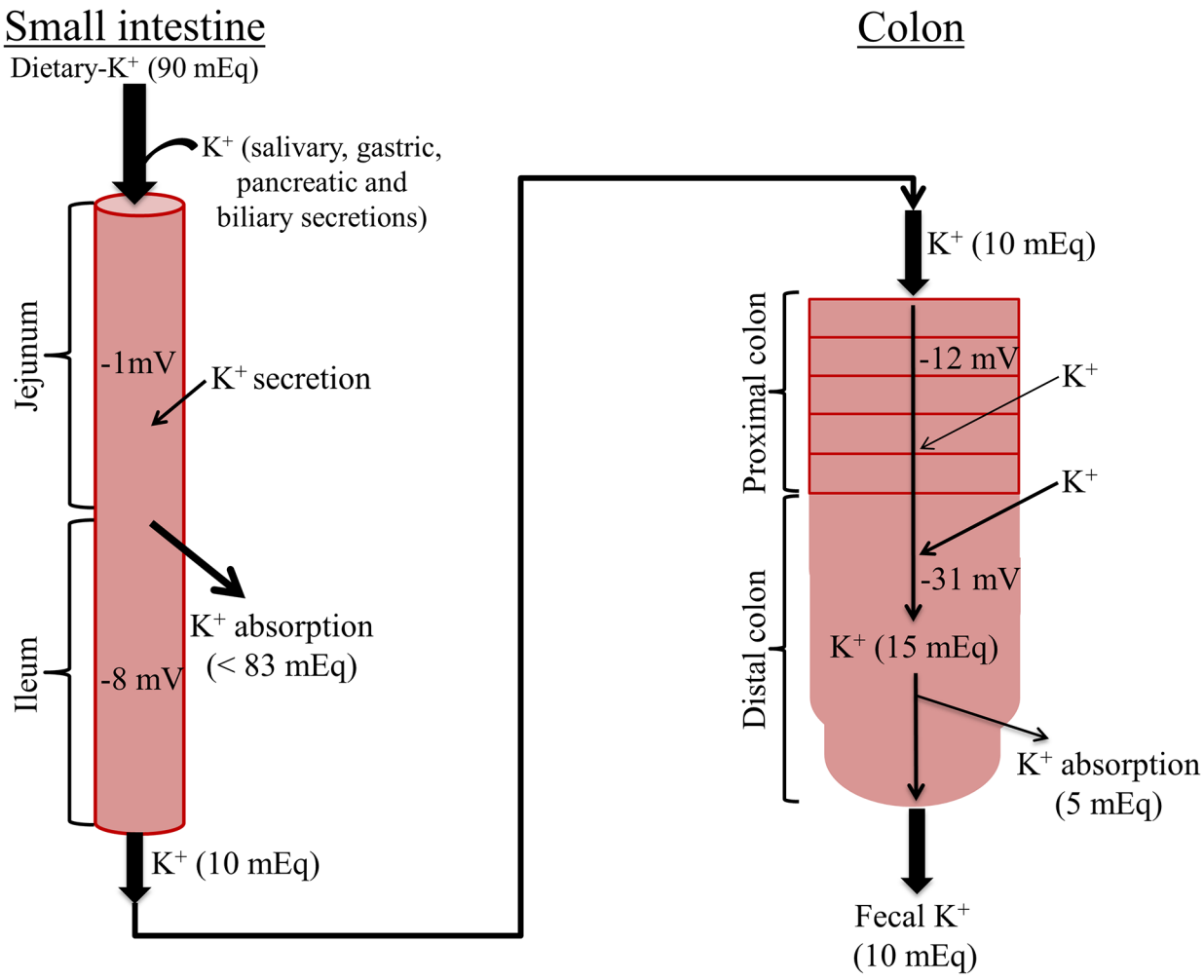

Figure 1: Role of normal human small intestine and colon in K^+ absorption and K^+ secretion.

Normal dietary K^+ intake is approximately 90 mEq/day. Salivary, gastric, pancreatic and intestinal secretions also contribute to the intestinal K^+ content. Thus, approximately 83 mEq K^+/day (i.e., 90%) is absorbed in the small intestine, and only 10 mEq K^+/day (i.e., ~10%) enters the colon. The colon secretes and absorbs 5 mEq K^+/day, and thus fecal K^+ excretion is 10 mEq/day. Small intestinal K^+ absorption occurs secondary to passive driving forces, such as solvent drag and/or membrane electrical potential. Proximal colon secretes K^+, while K^+ absorption occurs in distal colon. Average lumen-negative electrical potentials are −1, −8, −12 and −31 mV in the jejunum, ileum, proximal colon and distal colon, respectively (42). Outward and inward arrows indicate K^+ absorption and K^+ secretion, respectively. Thickness of arrows represent relative rate of absorption and secretion.

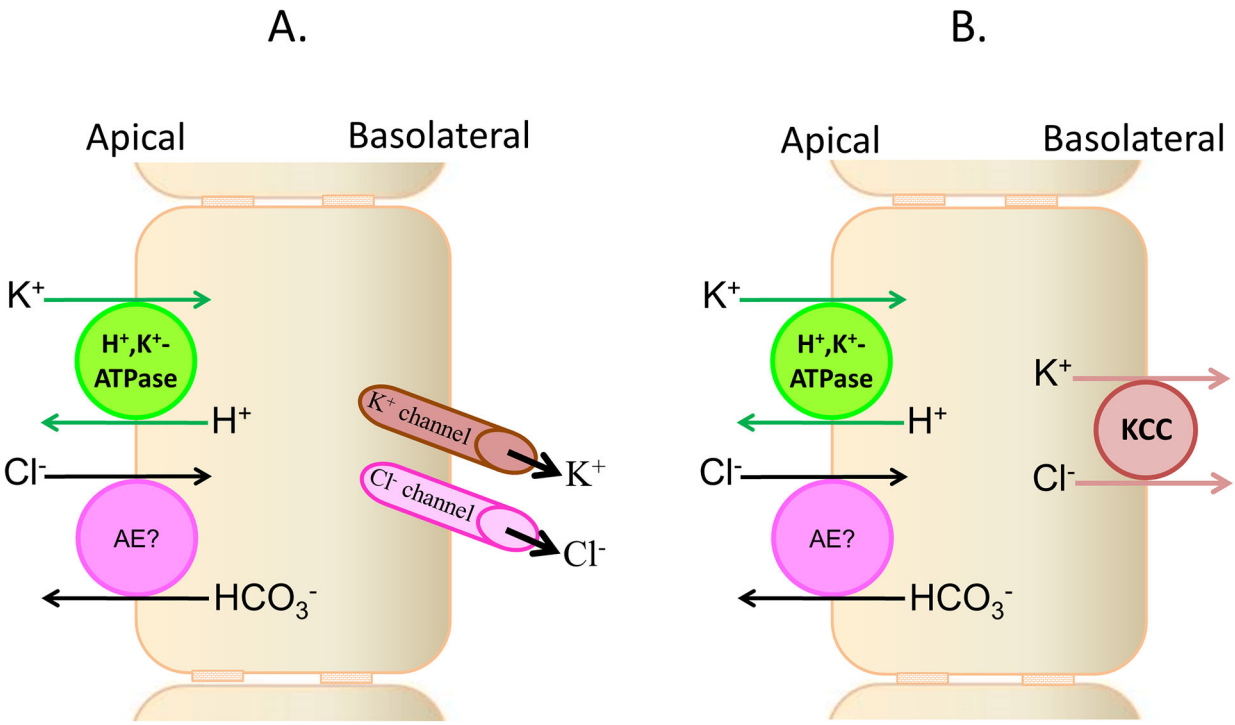

Figure 2: Cellular models of electroneutral K^+ absorption in animal (guinea pig, mouse and rat) distal colon.

Apical H^+,K^+-ATPase, and either basolateral parallel exit of K^+ and Cl^- through respective channels [**A**] or K^+-Cl^- cotransport (KCC) [**B**], mediate electroneutral K^+ absorption in animal colon. H^+,K^+-ATPase-mediated K^+ absorption is partially Cl^--dependent. It is not known whether anion exchanger-mediated Cl^--HCO_3^- exchange plays a role in Cl^--dependent K^+ absorption.

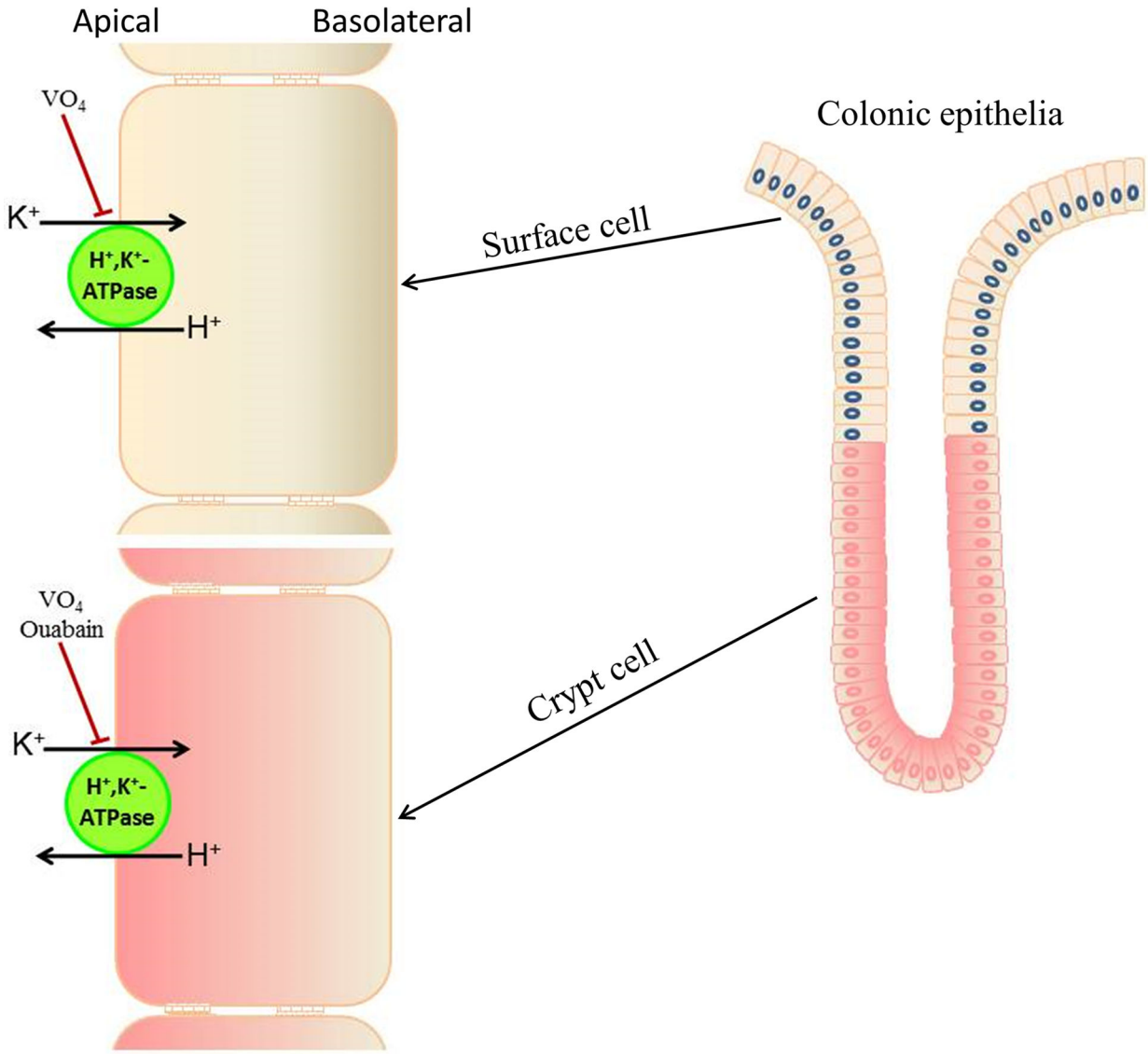

Figure-3: Distribution of ouabain-insensitive and ouabain-sensitive H^+,K^+-ATPase along the surface to crypt cell axis in rat distal colon.

Ouabain-insensitive H^+,K^+-ATPase is localized in surface cells and upper one-third of matured crypt cells (yellow colored cells), while ouabain-insensitive H^+,K^+-ATPase is localized mainly to crypt cells (red colored cells). Vanadate (VO_4, H^+,K^+-ATPase inhibitor) inhibits both ouabain-insensitive and ouabain-sensitive H^+,K^+-ATPase.

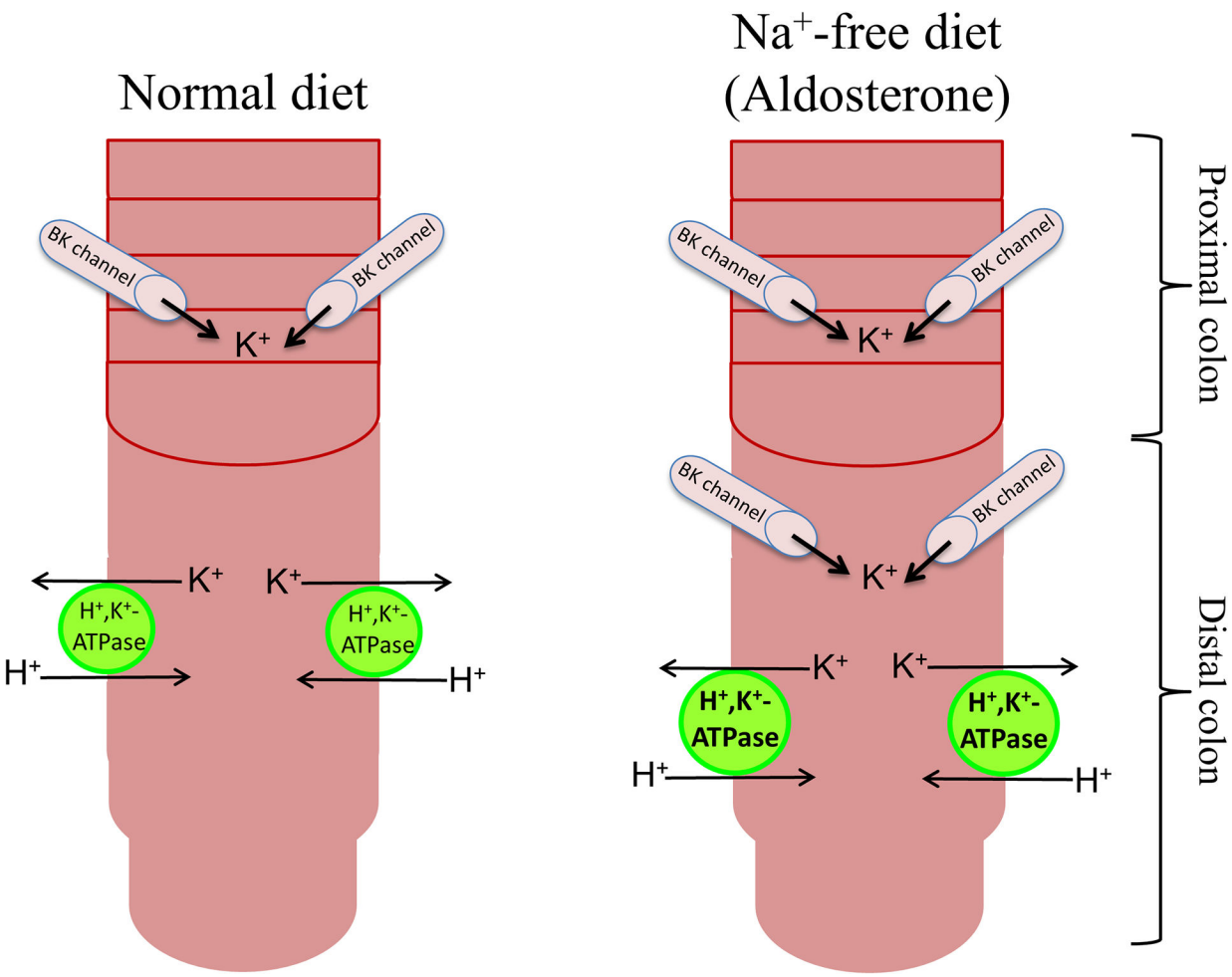

Figure-4: Effect of Na^+-free diet (aldosterone) on active K^+ absorption and active K^+ secretion in rat colon.

Active K^+ secretion and active K^+ absorption are present in proximal (lined segment) and distal segments of normal rat colon, respectively. Active K^+ absorption is mediated by H^+,K^+-ATPase, while active K^+ secretion is mediated via large conductance K^+ (BK) channels. Dietary Na^+ depletion induces active K^+ secretion in distal colon. Dietary Na^+ depletion also stimulates H^+,K^+-ATPase-mediated active K^+ absorption in distal colon. Dietary Na^+ depletion enhances BK channel and H^+,K^+-ATPase-specific protein expression in distal colon. It is not known whether dietary Na^+ depletion also stimulates active K^+ secretion in proximal colon.

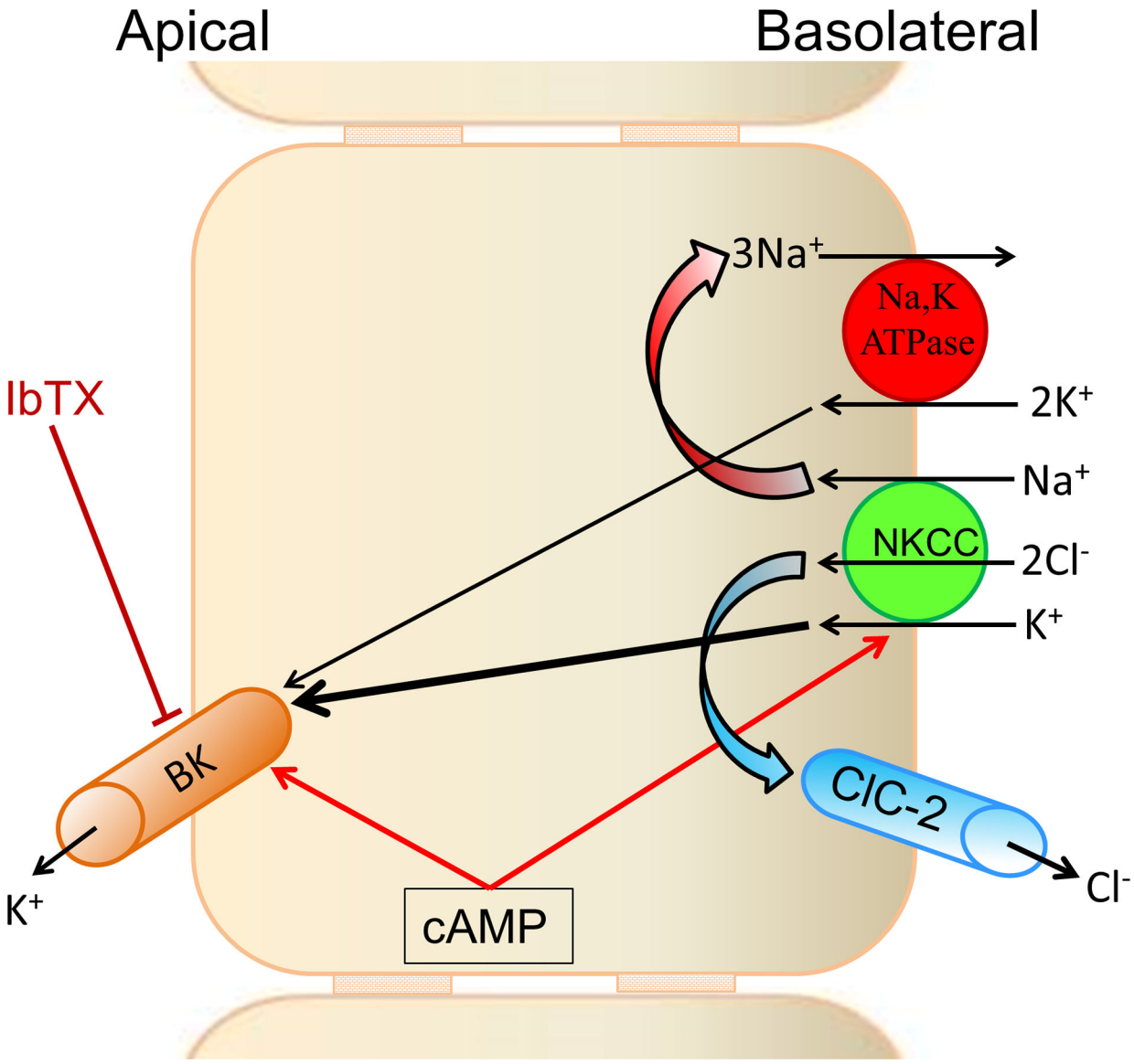

Figure-5: Cellular model of active K^+ secretion.

Coordinated activation of apical large conductance K^+ (BK) channels, and basolateral Na^+-K^+−$2Cl^-$ cotransporter (NKCC) and Cl^- channel 2 (ClC2) regulates active K^+ secretion. K^+ entering cells via basolateral NKCC (K^+ loader) exits via apical BK channels. K^+ entering via Na^+,K^+-ATPase also contributes to apical BK channel-mediated K^+ secretion. Continuous K^+ secretion depends on CLC2 and Na^+,K^+-ATPase maintaining low intracellular levels of Cl^- and Na^+, respectively. cAMP activates both basolateral NKCC and apical BK channel. Mucosal iberiotoxin (IbTX) inhibits active K^+ secretion. [Reproduced from (159)].

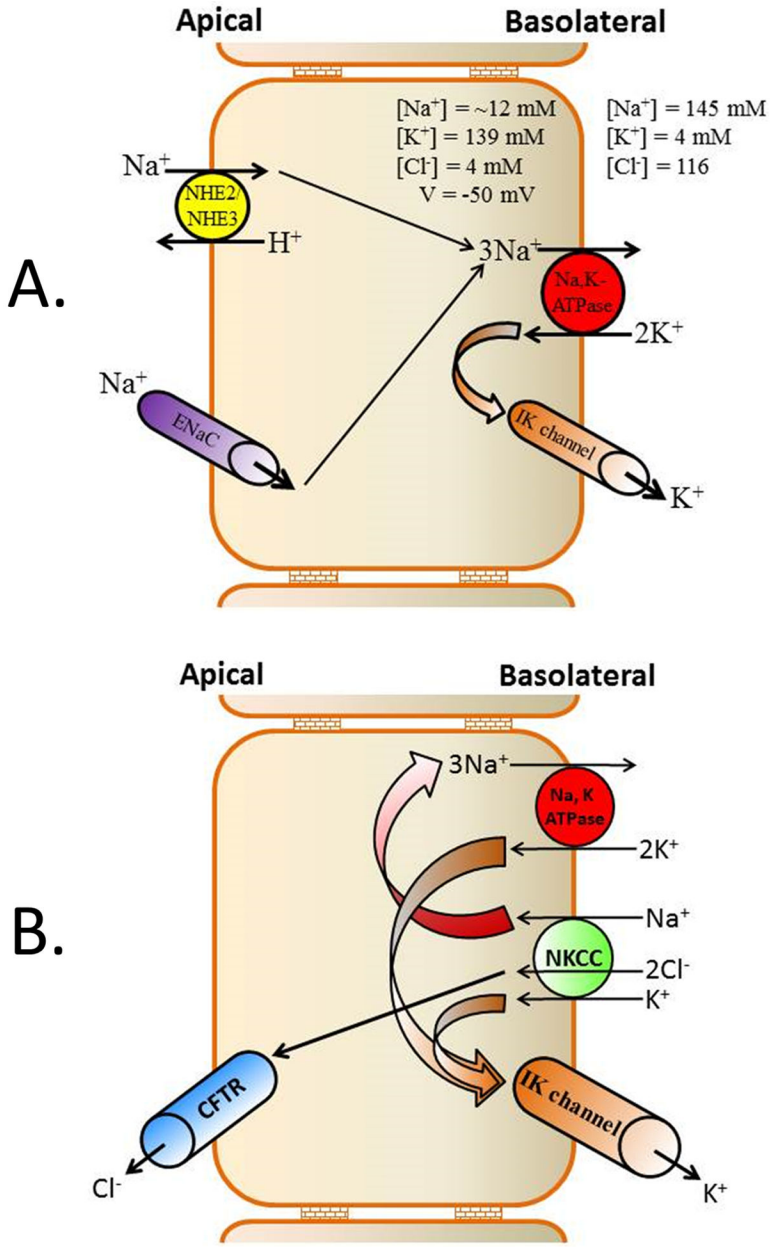

Figure-6: Colonic epithelial cell models for basolateral membrane K^+ channel-regulated transport processes.

[**A**] Under basal conditions, K^+ recycling across basolateral membranes via K^+ channels operating in concert with Na^+,K^+-ATPase, contributes to the favorable electrochemical gradient (reflecting high intracellular Na^+ and low intracellular K^+ concentrations, and a negative membrane potential) necessary for the secondary Na^+ absorption mediated by apical Na^+-H^+ exchanger isoforms 2 and 3 (NHE2/NHE3) and epithelial Na^+ channel (ENaC). NHE2 and NHE3 mediate electroneutral Na^+ absorption, while ENaC mediates electrogenic Na^+ absorption [**B**] Under stimulated condition (e.g., cholera), apical Cl^- exit via CFTR (cystic fibrosis transmembrane regulator) Cl^- channels following Na^+-K^+ $-2Cl^-$ (NKCC) transporter-mediated basolateral Cl^- uptake tends to depolarize cells.

This is counter-balanced by the hyperpolarizing effect of K^+ exit through basolateral intermediate conductance K^+ (IK) channels, thus maintaining the electrical gradient required for sustained Cl^- secretion.

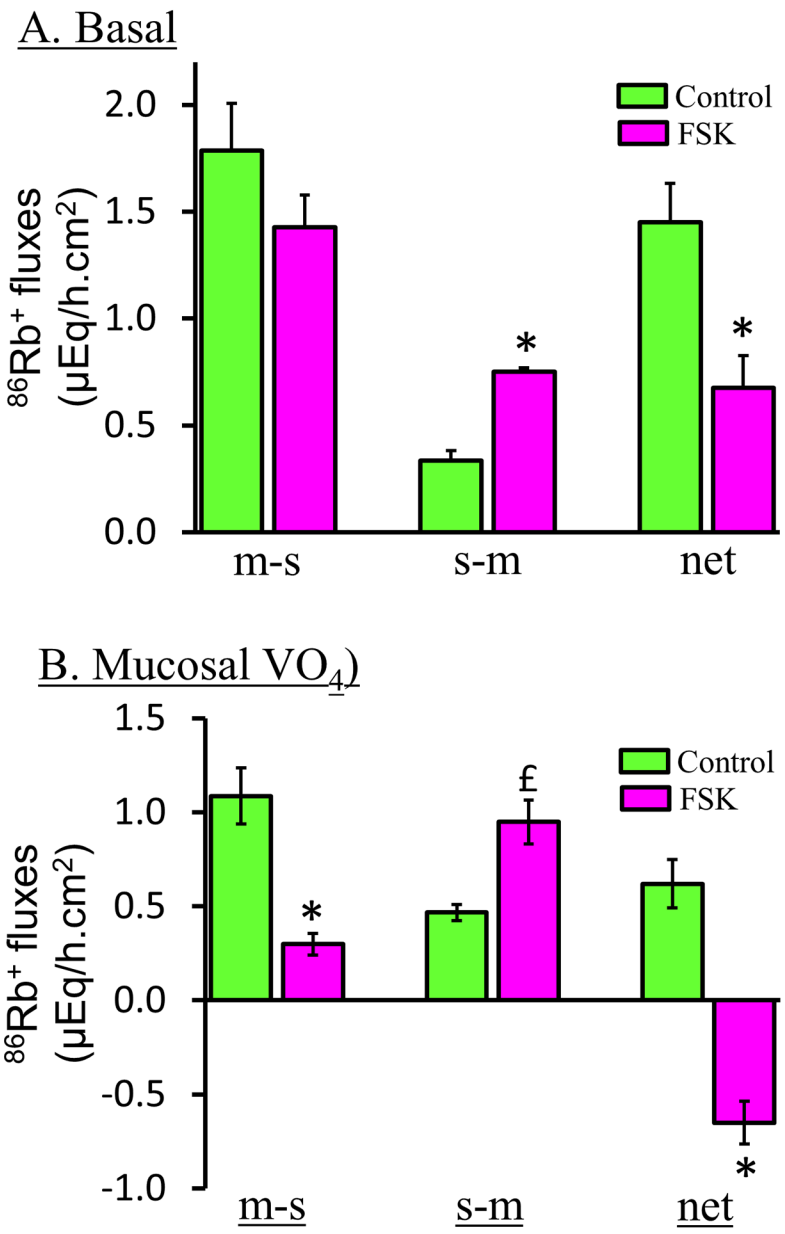

Figure-7: Effect of cellular cAMP increased by forskolin (FSK, adenylate cyclase activator) on K^+ fluxes in the presence and absence of mucosal VO_4 (P-type ATPase inhibitor) in rat distal colon.

[**A**] In the absence of mucosal VO_4, forskolin (FSK) significantly inhibits active K^+ absorption (i.e., net K^+ absorption) by stimulating s-m K^+ fluxes. [**B**] Presence of 1 mM mucosal VO_4 unmasks FKS-induced active K^+ secretion. It is to be noted that mucosal VO_4 also inhibits basal K^+ absorption in normal colon (see Figure–11). Mucosal to serosal (m-s) and serosal to mucosal (s-m) $^{86}Rb^+$ fluxes (K^+ surrogate) were measured under voltage clamp condition in the absence (**green bars**) and presence (**red bars**) of forskolin. Net K^+ fluxes were calculated by subtracting s-m fluxes from m-s fluxes. Positive and negative fluxes represent active K^+ absorption and active K^+ secretion, respectively. *$p < 0.001$ –

compared to respective fluxes in the absence of FSK; $^{£}p < 0.05$ – compared to in the absence of FSK. [Reproduced from ref. (159)].

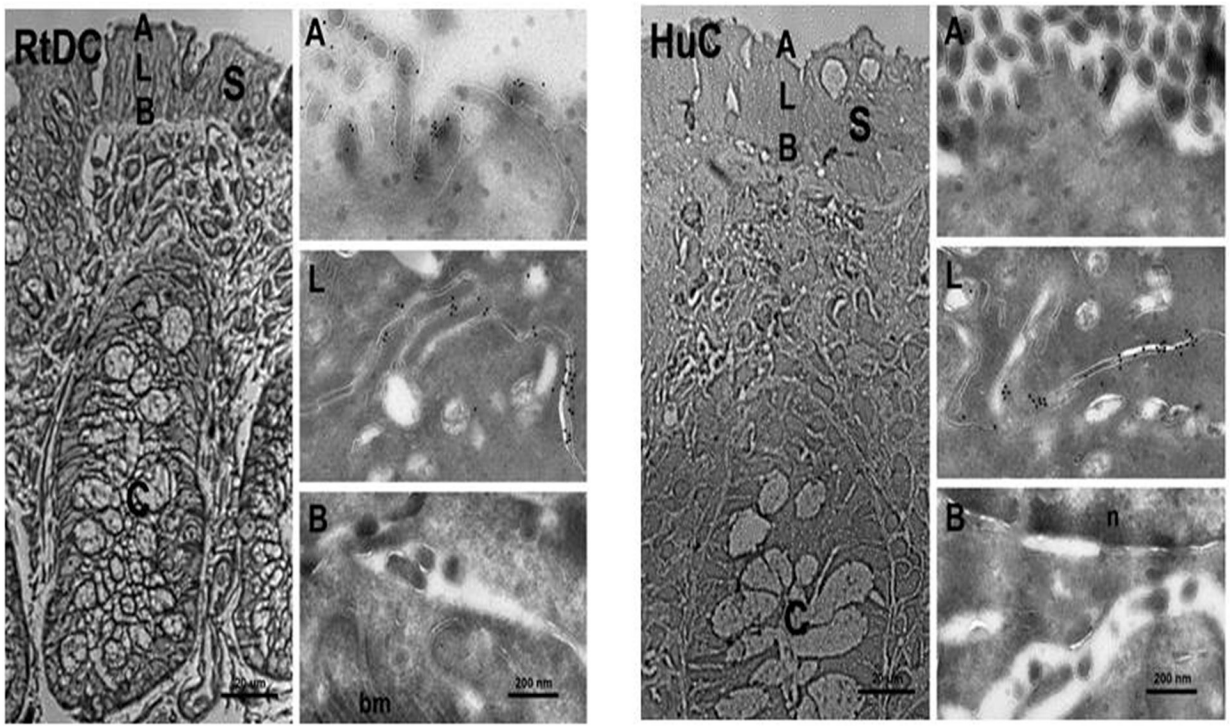

Figure-8: Immunogold labeling of intermediate conductance K^+ (IK) channels in colonic surface epithelial cells of normal rat distal colon (RtDC) and normal human colon (HuC).

Cryosemithin sections were prepared and trypan blue-stained for orientation (left column of each panel). Tissue specimens were ultratrimmed for cryothin sectioning, focusing on small areas of interest in the colonic surface epithelium to characterize plasma membrane domain-specific localization of IK channel proteins at the ultrastructural level. Cryothin sections were immunolabeled with anti-IK_{abc} and detected with a secondary donkey anti-rabbit 10 nm gold-labeled antibody. Anti-IK_{abc} localized IK-like proteins in apical [A], and lateral [L] plasma membrane domains of rat and human colonic epithelial cells, but not in basal plasma membranes [B] of surface epithelial enterocytes. These results using high resolution immunogold electron microscopy confirm our earlier results using confocal microscopy. [S] Surface epithelium; [C] crypts; [n] nucleus; [bm] basal plasma membrane. Images were acquired either at 400x primary magnification (cryosemithin section, bar = 20 μm) by light microscopy, or at 21,000x primary magnification (cryothin sections, bar = 200 nm) by electron microscopy. Similar results were obtained with two and three different human and rat tissues, respectively. [Reproduced from ref. (12)].

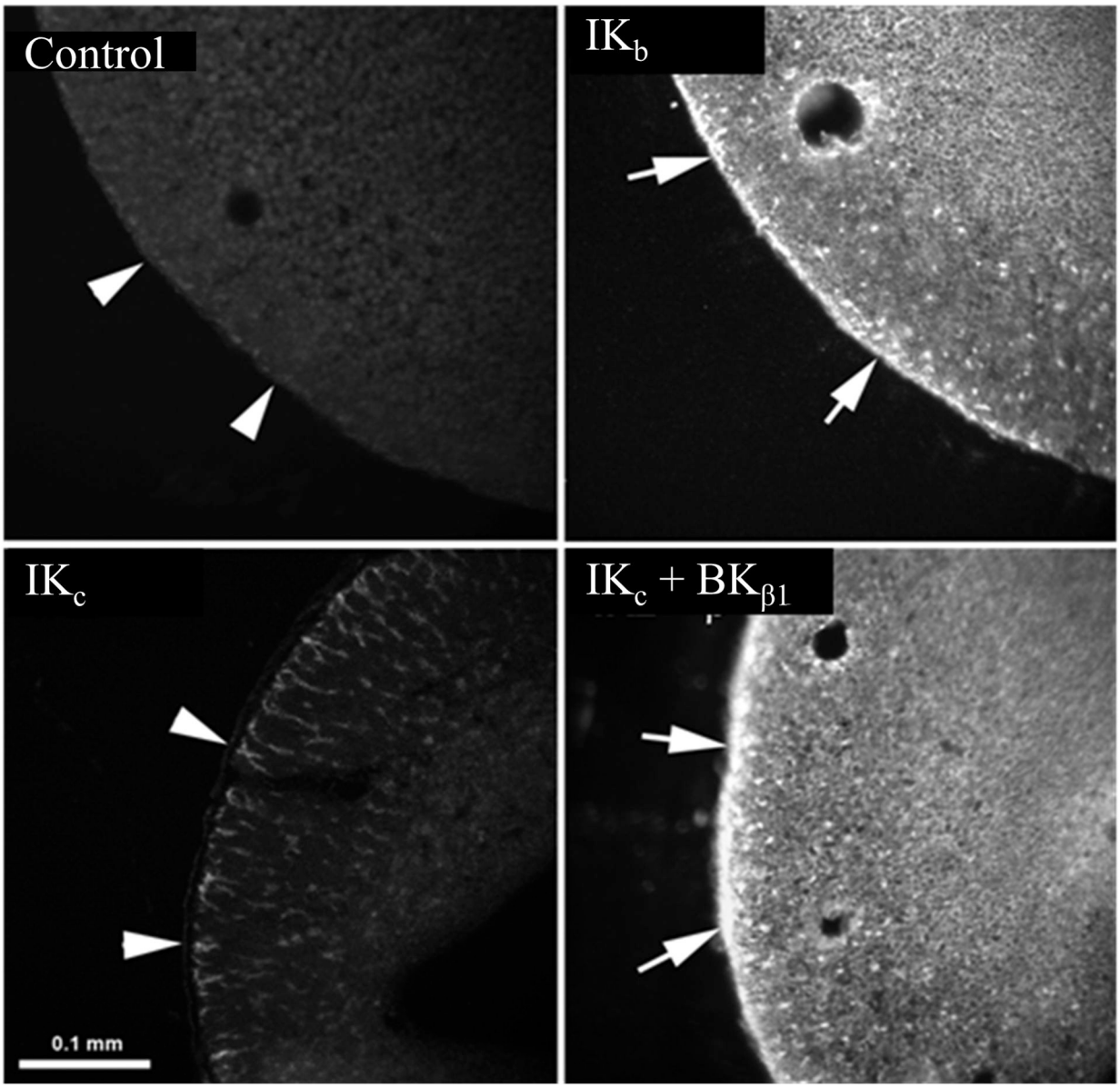

Figure-9: Indirect immunofluorescence imaging of intermediate conductance K^+ (IK) channel protein in cRNA-injected *Xenopus oocytes*.

Anti-IK_{abc} antibody localized IK channel proteins to the plasma membrane of IK_b cRNA-injected oocytes (IK_b), but not water injected (control) oocytes. IK protein was identified only in the cytoplasm, but not in the plasm membrane of IK_c cRNA-injected oocytes (IK_c). Plasma membrane targeting of IK protein was substantially enhanced in oocytes coinjected with IK_c and the $BK_{\beta 1}$-subunit (i.e., large conductance K^+ channel β-subunit) cRNAs (IK_c + $BK_{\beta 1}$). Arrowheads indicate the absence (or minimal presence) of IK cahnnel proteins (left panels), while arrows indicate the presence of IK channel proteins (right panels) on the plasma membrane of oocytes. Fluorescence images were acquired using Nikon light microscope. Bar = 0.1 mm. [Adapted from ref. (12)].

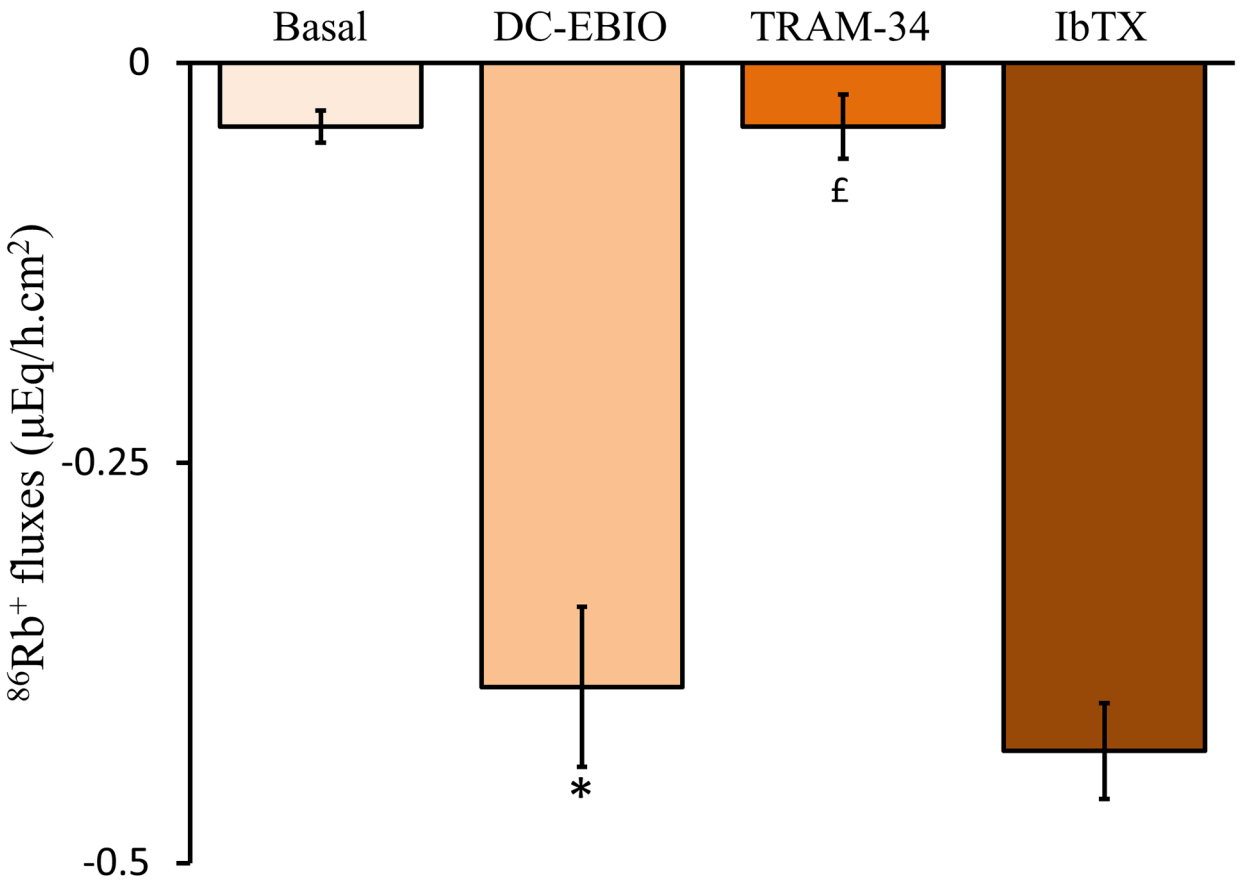

Figure-10: Mucosal DC-EBIO [intermediate conductance K^+ (IK) channel opener] activates IK channel mediated K^+ secretion in normal rat distal colon.

Minimal K^+ secretion is present under basal conditions. Mucosal DC-EBIO (IK channel opener) stimulates active K^+ secretion. Mucosal TRAM-34 (IK channel blocker) inhibits DC-EBIO-stimulated K^+ secretion. DC-EBIO-stimulated K^+ secretion is not inhibited by mucosal iberiotoxin [IbTX, large conductance K^+ (BK) channel blocker). [Reproduced from ref. (124)].

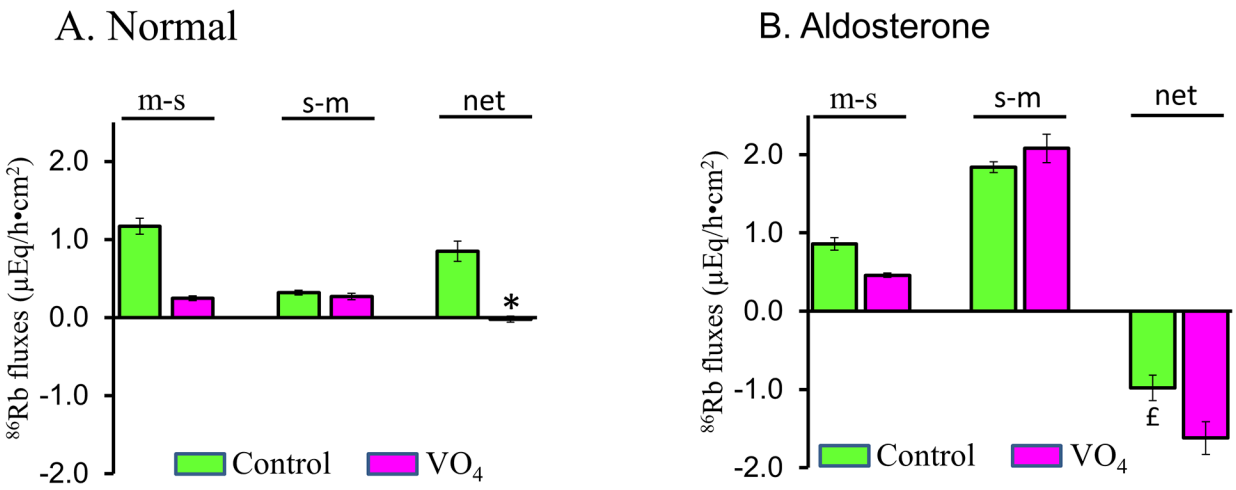

Figure-11: Active K^+ transport in normal and aldosterone-treated (dietary Na^+ depleted) rat distal colon.

Net K^+ transport was determined from the difference between mucosal to serosal (m-s) and serosal to mucosal (s-m) unidirectional fluxes measured under voltage clamp conditions. Net positive value represent active K^+ absorption, while net negative value represent active K^+ secretion. [**A**] Active K^+ absorption present in normal rat distal colon (green bars) was inhibited by mucosal vanadate (VO_4; P-type ATPase inhibitor; red bars). [**B**] Active K^+ secretion in aldosterone-treated rat distal colon was further stimulated by mucosal VO_4. *$p < 0.001$- compared to Control; $^{£}p < 0.001$ – compared to Control; $^{‡}p < 0.001$ – compared to Control. [Reproduced from ref. (176)].

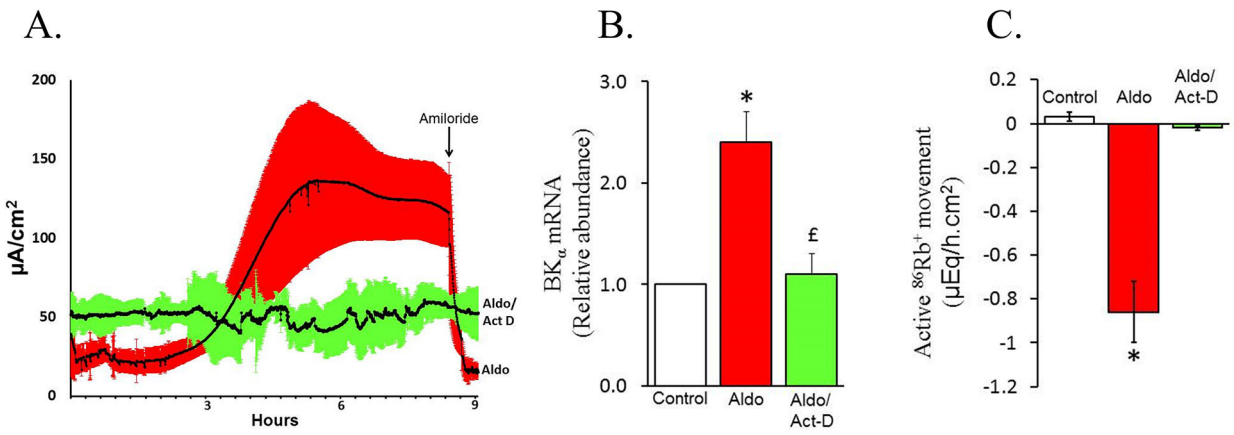

Figure-12: Effect of actinomycin D on aldosterone-induced Isc in normal rat distal colon *in vitro*.

[**A**] Normal rat distal colonic mucosal layers were mounted under voltage clamp condition in Ussing chambers. Immediately after mounting, either aldosterone (**aldo**) or aldosterone plus actinomycin D (transcriptional inhibitor) (**aldo/act-D**) was added to the serosal bath. Isc was measured for up to 9 hr. At the end of 8½ hr, 10 μM amiloride was added to mucosal bath. Enhanced Isc and inhbition of Isc by amiloride indicates that aldosterone induced epithelial Na^+ channel (ENaC)-mediated Na^+ absorption (aldo). Absence of amiloride-sensitive Isc in the presence of actinomycin D (aldo/act-D) indicates that aldosterone-induced ENaC-mediated Na^+ absorption is regulated at transcriptional level. [**B**] RT-qPCR analyses indicated that aldosterone enhanced the abundance of large conductance K^+ channel α-subunit (BK_α)-specific mRNA (aldo) , while this change was prevented by actinomycin D (aldo/act-D). [C] K^+ fluxes measured under voltage clamp condition indicate that aldosterone stimulated active K^+ secretion (aldo), whereas this response was blocked by actinomycin D (aldo/act-D). [Reproduced from ref. (176)].

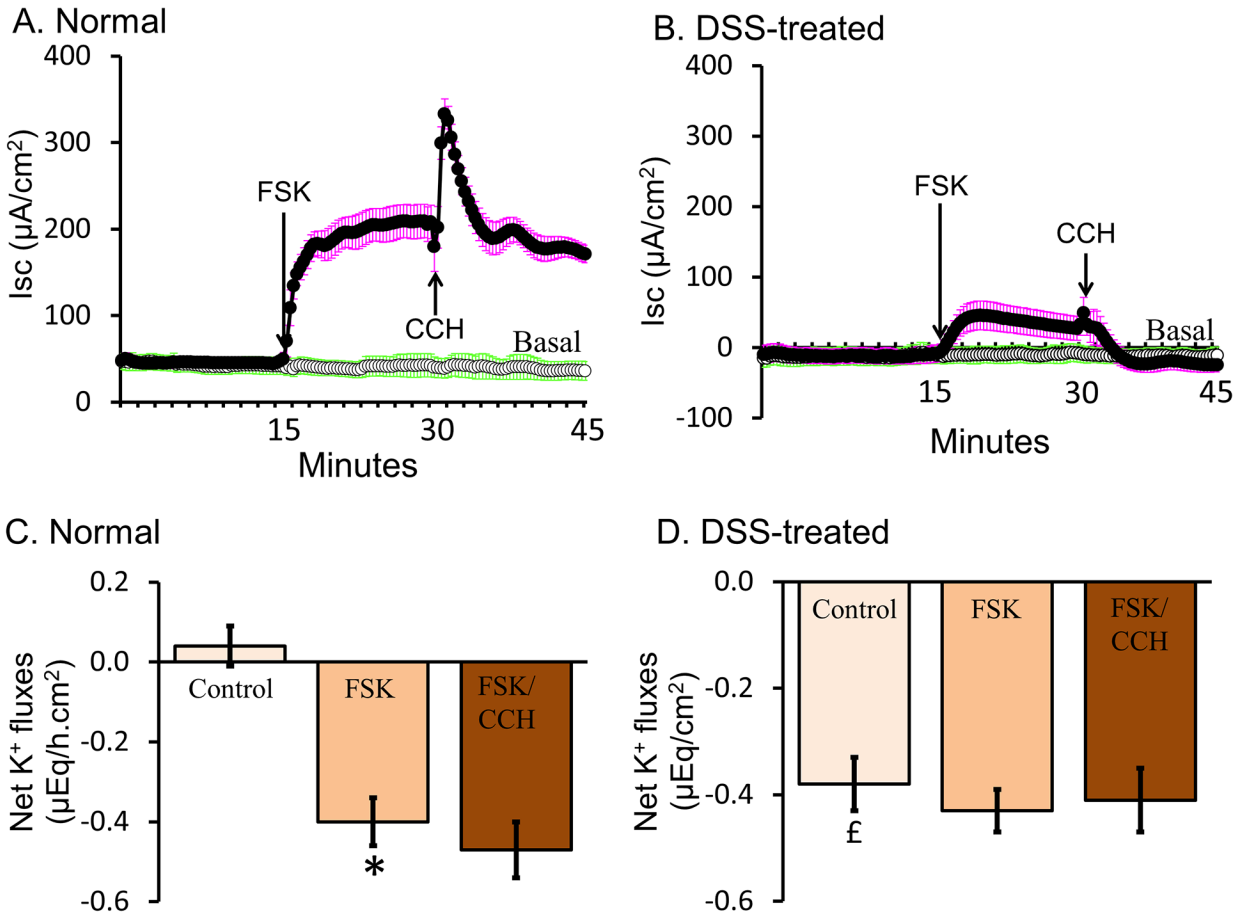

Figure-13: Dextran sulfate sodium (DSS)-induced inflammation stimulates active K^+ secretion and abolishes agonist (cAMP and Ca^{2+})-stimulated Cl^- secretion in rat distal colon.

[**A**] Positive Isc (short circuit current) represents the presence of anion (Cl^-/HCO_3^-) secretion under basal conditions. Increasing intracellular cAMP by forskolin (FSK; adenylate cyclase activator) stimulated active Cl^- secretion. Increasing intracellular Ca^{2+} by carbachol (CCH; adrenergic agonist; FSK/CCH) further transiently stimulated active Cl^- secretion. [**B**] Negative Isc indicates induced cation secretion and absence of anion secretion under basal conditions in DSS-inflamed colon. The minimal increase in Isc induced by FSK, and the absence of a FSK/CCH-induced Isc, indicated that Cl^- secretory processes were abolished in DSS-inflamed colon. [**C**] In the presence of mucosal ortho-VO_4 (H^+,K^+-ATPase inhibitor), minimal K^+ absorption was present in normal colon (control). In normal colon, FSK stimulated active K^+ secretion, while FSK/CCH had no additional effect on K^+ secretion. [**D**] In DSS-inflamed colon (control), active K^+ secretion was present under basal conditions, but neither FSK nor FSK/CCH stimulated active K^+ secretion. [Reproduced from (94)].

Table-1:
Functional expression of HKC_{α} cDNA in heterologous expression systems.

Functional activity of the putative colonic H^+-K^+-ATPase α-subunit (HKC_{α}) was determined *in vitro* using heterologus expression systems. The baculovirus-*Sf9* and HEK293, and *Xenopus* oocyte expression systems, utilized H^+,K^+-ATPase and ^{86}Rb uptake measurements, respectively. Individually expressed HKC_{α} exhibited ouabain-insenstivie H^+,K^+-ATPase activity in the Baculovirus-*Sf9* expression system (101). cRNA transcribed from HKC_{α}, plus either HKG_{β} or $NaK_{\beta 1}$, exhibited both partial ouabain-sensitive and partial ouabain-insensitive ^{86}Rb uptake in *Xenopus* oocytes (37). HKC_{α} and HKG_{β} (and torpedo $NaK_{\beta 1}$) coexpression exhibited ouabain-sensitive H^+,K^+-ATPase (9), while HKC_{α} coexpressed with HKC_{β} exhibited ouabain-insensitive H^+,K^+-ATPase activities in HEK293 cells (165). Human HKC_{α} coexpressed with $NaK_{\beta 1}$ in baculovirus-*Sf9* exhibited ouabain-sensitive H^+,NH_4^+-ATPase activity (188, 189). HKC_{β} – Colonic H^+,K^+-ATPase β-subunit; HKG_{β} – Gastric H^+,K^+-ATPase β-subunit; NaK_{β} – Na^+,K^+-ATPase β-subunit.

HKC_{α}	β-subunit	Expression system	Function	Ouabain		Reference
				Sensitive	Insensitive	
Rat	none	Baculovirus-*Sf9*	K^+-ATPase	-	Yes	(101)
Rat	HKG_{β}	Xenopus oocytes	^{86}Rb uptake	Yes	Yes	(37)
Rat	$NaK_{\beta 1}$	Xenopus oocytes	^{86}Rb uptake	Yes	Yes	(37)
Rat	TB_{β}	Xenopus oocytes	^{86}Rb uptake	Yes	-	(38)
Guinea pig	HKG_{β}	HEK-293 cell	H^+,K^+-ATPase	Yes	-	(9)
Guinea pig	Torpedo NaK_{β}	HEK-293 cell	H^+,K^+-ATPase	Yes	-	(9)
Rat	HKC_{β}	HEK-293 cell	H^+,K^+-ATPase	-	Yes	(165)
Human	$NaK_{\beta 1}$	Baculovirus-*Sf9*	NH_4^+-ATPase	Yes	-	(188, 189)

Table-2:

Electrophysiological and pharmacological characteristics of basolateral K^+ channels in animal and human colon.

Patch clamp studies characterized cAMP- and Ca^{2+}-activated K^+ channels with different conductances in basolateral membranes of colon from rat, rabbit, human and the T84 cell line (a human colon carcinoma cell line). cAMP-activated small conductance (< 3 − 6.8 *pS*) K^+ channels are inhibited by chromanol 293B, while Ca^{2+}-activated large conductance (138 − 220 *pS*) K^+ channels are inhibited by Ba^{2+} and TEA (non-specific K^+ channel blockers). Both cAMP and Ca^{2+} activated intermediate conductance (12 − 28 *pS*) K^+ channels, which are inhibited by Ba^{2+}, TEA and clotrimazole (CLT; an IK channel blocker) in rat and human colon, and inhibited by CLT in T84 cells. Similar detailed information about apical K^+ channels are not available in the litrature.

Species	Agonist	Conductance (*pS*)	Inhibitor	Reference
Rat	cAMP	< 3	Chromanol 293B	(205)
	Ca^{2+}	12	Ba^{2+} and TEA	(27)
	Ca^{2+}	187	Ba^{2+}	(27)
	Non-selective	27	Not known	(174)
Rabbit	Ca^{2+}, cAMP	90 – 220	Ba^{2+} and TEA	(110)
Human	cAMP	6.8	Not known	(4)
	cAMP, Ca^{2+}	23	Ba^{2+}, quinidine and DPC	(109, 157)
	Ca^{2+}	138	Ba^{2+}, quinidine and TEA	(109)
T84 cell line	cAMP, Ca^{2+}	28	CLT	(48)
	Ca^{2+}	161	Ba^{2+}	(47)