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Topical Review

Function of K^+ Channels in the Intestinal Epithelium

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Introduction

Potassium channels play an important role for reabsorptive and secretory pathways in the gastro-intestinal tract. Over the last years molecular identification and functional characterization of K^+ channels led to a better understanding of physiology and disease of intestinal transport. In gastric parietal cells KCNJ10 (Kir4.1) and heteromeric KCNE2/KCNQ1 (MirP1/KvLQT1), K^+ channels co-localize with the acid-producing H^+/K^+ ATPase in the luminal membrane compartment. Specific K^+ channel blockage and genetical disruption of the KCNQ1 gene in mice inhibit acid secretion almost completely. In small intestine, K^+ channels provide the driving force for electrogenic reabsorption of nutrients in villus cells and secretion in intestinal crypt cells and they play an important role during cell volume regulation. In the colon, luminal K^+ channels repolarize the membrane and support electrogenic Na^+ reabsorption. In addition, they influence the final ionic composition of the feces. Ca^{2+}-regulated KCNN4 K^+ channels and KCNE3/KCNQ1 (MiRP2/KvLQT1) K^+ channels are localized in the basolateral membrane of crypt cells in small and large intestine. The KCNE3/KCNQ1 channel complex is activated by cAMP during secretory diarrhea, i.e., via cholera toxin. Tissue-specific modulation of intestinal K^+ channels could offer new therapeutic perspectives for the treatment of life-threatening forms of diarrhea or peptic ulcer disease.

Multifaceted Functions of K^+ Channels

Potassium channels are expressed in practically all mammalian cells. They are membrane proteins with two, four or six transmembrane domains and have in common a pore-forming loop that is part of the K^+-selective filter [22]. Additional regulatory subunits and hetero-multimerization are important for membrane targeting, pharmacology, and functional properties [1, 2, 5, 103, 114, 116, 140]. Very recently, fascinating structural data shed light on the molecular principles of K^+ channel structure and function [58, 59]. Helpful overviews on the molecular diversity and nomenclature of the about 85 different K^+ channel genes are available online at http://www. gene.ucl.ac.uk/nomenclature/genefamily/KCN.shtml and at http://www.ipmc.cnrs.fr/~duprat/.

This review focuses on the physiological and pathophysiological role of K^+ channels in epithelial cells of the gastro-intestinal tract. In intestinal epithelia K^+ channels are involved in different cellular function.

Hyperpolarization and Generation of Driving Force for Electrogenic Transport

Opening of basolateral K^+ channels leads to a shift of the membrane voltage towards the Nernst potential for K^+, which at the basolateral side is in the range of -90 mV. K^+ is then recycled by the Na^+/K^+ ATPase. The hyperpolarization increases the driving force for electrogenic transport: Since the paracellular pathway of the intestinal epithelium is relatively leaky and does not completely isolate the luminal from the basolateral side, a paracellular short-circuit current (I_{sc}) is induced by the transepithelial voltage difference (V_{te}) [36]. Thus, the basolateral K^+ channel-induced hyperpolarization is conducted to the luminal membrane and hyperpolarizes this membrane. By this mechanism, opening of basolateral K^+ channels supports basolateral and luminal electrogenic transport (Fig. 1) [41, 75]. Besides V_{te}, the paracellular ion flux depends on the specific ionic permeability of the paracellular barrier, which differs along the intestinal

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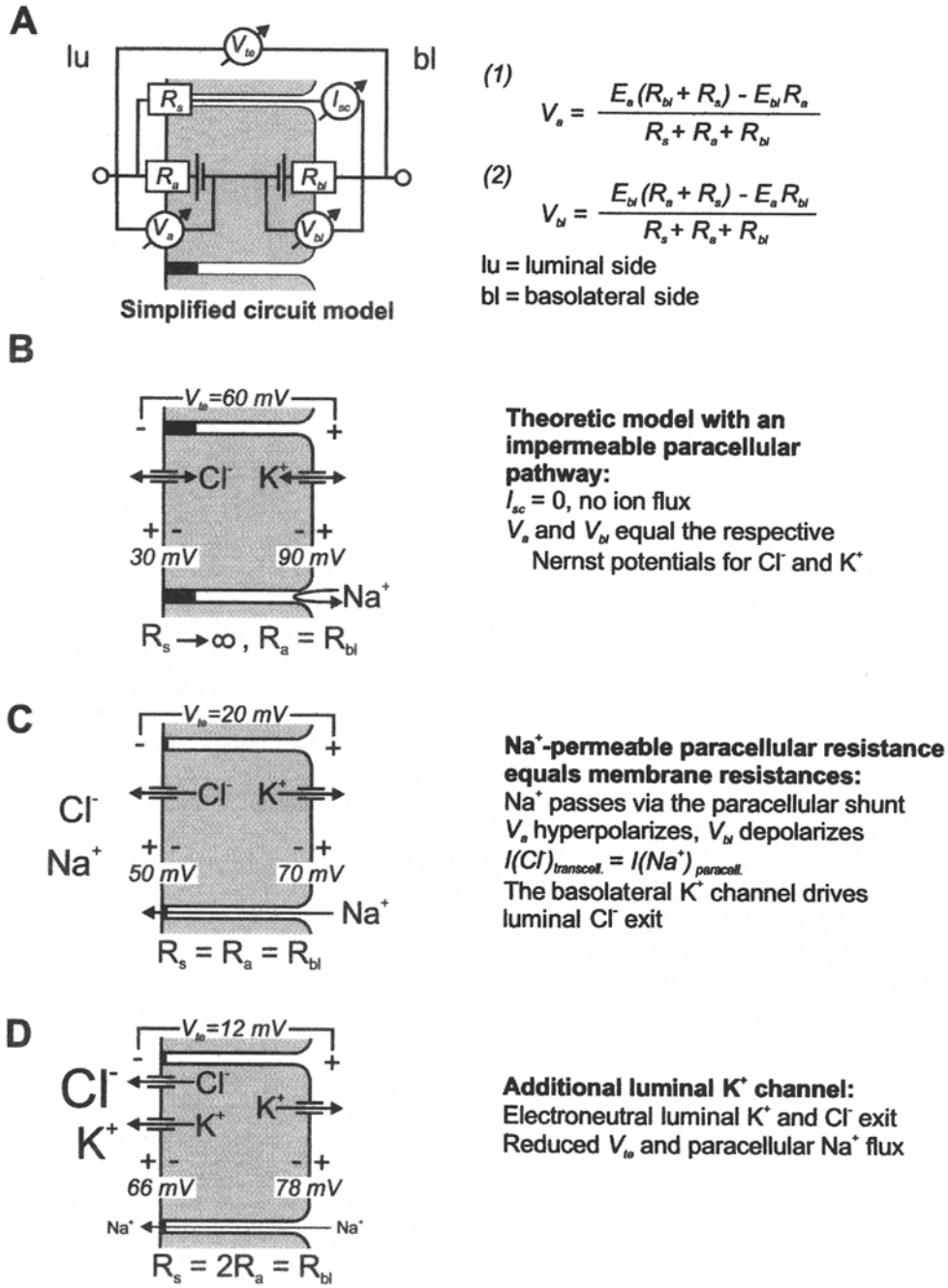

Fig. 1. Role of K^+ channels during electrogenic transport. (*A*) A simplified circuit model for an epithelial cell layer (modified from [40, 41]). For simplification, Na^+/K^+ ATPase pump current and paracellular diffusion potential have been omitted. Abbreviations: V_{te}, transepithelial voltage; V_a, apical membrane voltage, V_{bl}, basolateral membrane voltage; I_{sc}, short circuit current over the paracellular resistance; R_a apical membrane resistance; R_{bl}, basolateral membrane resistance; R_s, paracellular shunt resistance; E_a, electrochemical driving force of the apical membrane; E_{bl}, electrochemical driving force of the basolateral membrane. (*B*) In a theoretic epithelium having only luminal Cl^-, basolateral K^+ channels, and no paracellular conductance, I_{sc} equals 0. V_a and V_{bl} are determined by the Nernst equilibrium for Cl^- and K^+, respectively. Neither Cl^- nor K^+ leaves the cell because the driving force is missing. Despite a high V_{te} no transepithelial ion flux can occur. (*C*) Addition of a paracellular Na^+ permeability to model ***B*** leads to Na^+ flux to the lumen driven by V_{te}. This I_{sc} attenuates V_{te}, hyperpolarizes the luminal and depolarizes the basolateral membrane, resulting in Cl^- and K^+ exit to the luminal and basolateral side, respectively: The epithelium secretes NaCl. (*D*) Additional activation of a luminal K^+ conductance ensues in electroneutral transcellular KCl secretion and further reduces V_{te}, thereby diminishing paracellular Na^+ flux. For a reabsorptive epithelium the luminal Cl^- conductance in models *C* and *D* has to be replaced by electrogenic transport systems such as Na^+-dependent glucose or amino-acid transport. In such an epithelium, a Cl^--selective paracellular conductance would cause paracellular Cl^- reabsorption, resulting in transepithelial reabsorption of substrates, Na^+, and Cl^-. Water follows along the osmotic gradient.

tract, depending on the composition of barrier-forming proteins [23, 105].

K^+ Secretion and Fine-tuning of Salt Metabolism

Luminal K^+ channels directly hyperpolarize the apical membrane and lead to K^+ secretion into the lumen. In contrast to basolateral K^+ channels, activation of luminal K^+ channels decreases V_{te}, thereby reducing the driving force for paracellular transport of ions. Luminal K^+ channel activity in distal colon and distal renal nephron segments plays an important role for K^+ excretion and Na^+ reabsorption [3, 76]. These segments determine the final ion composition of feces and urine and are mainly regulated by the mineralocorticoid aldosterone and K^+ intake.

Recycling of K^+ across the Luminal Membrane

In gastric parietal cells and to less extent in colonic surface cells, luminal K^+ channels are required to recycle K^+ that has been taken up by H^+/K^+ ATPases [37, 137]. In gastric glands, inhibition of the K^+-recycling channel blocks H^+/K^+ ATPase activity and hence gastric acid secretion almost completely [38].

Cell Volume Regulation

Transport of osmolytes and osmotic gradients across the luminal membrane represent a continuous challenge for volume regulation in intestinal cells. Upon hypotonic swelling, activation of K^+ channels allows reduction of the concentration of intracellular osmolytes, thereby performing regulatory volume decrease [121]. In contrast, cell shrinkage leads to inhibition of K^+ channels. Thus, volume regulation-induced changes of K^+ channel activity can directly affect transepithelial ion transport [109, 137]. Several cloned K^+ channels that are expressed in intestinal epithelium are affected by changes in cell volume (i.e., KCNN4 [44, 137], KCNK5 [96], and KCNQ1 [73]). An excellent review on cell volume regulating mechanisms is given in [68].

Proliferation and Differentiation

K^+ channel activity is dependent on cell cycle, proliferation and differentiation. There is some evidence that K^+ channels might be directly involved in the regulation of these processes [100, 141] and that pharmacological modulation of K^+ channels can change cellular fate [60]. Recently, activation of K^+ channels was observed in intestinal epithelial cells after wounding, which probably plays an important role for epithelial cell migration [107, 131]. During cancer genesis in colonic epithelium, changes in ion channel expression have been observed [12]. It is of great interest to gain more insight into the mechanisms regulating the rapid cell renewal in the gastrointestinal tract. However, at present it is not clear whether the changes in ionic conductances are mainly secondary effects or whether the ionic properties interfere with the cellular fate in a more direct way.

Although all of the above mentioned different functions of K^+ channels are of importance, we will focus in this review on the major task of the gastrointestinal epithelium: transport of substrates, salt and water.

Luminal K^+ Channels Are Required for Acid Secretion in Gastric Parietal Cells

In stomach mucosa, acid secretion occurs in a specialized cell type, the parietal cell. These mitochondria-rich cells have a unique morphology with invaginations of the luminal membrane into the cytoplasm and complex vesicular structures, so-called tubulocisternae, which amalgamate with the luminal membrane upon secretory stimuli [31]. The acid-producing enzyme H^+/K^+-ATPase is localized in these tubulocisternae. After amalgamation with the luminal membrane, the H^+/K^+-ATPase pumps H^+ out of the cell, paralleled by an uptake of K^+. Cl^- is secreted into the lumen via apical ClC-2 Cl^- channels [82, 123]. To avoid K^+ depletion of the luminal fluid due to H^+/K^+ ATPase activity, a recycling pathway for K^+ is required (Fig. 2*A*). There is good experimental evidence that K^+ channels are the respective pathway [46, 138, 139]. In immunofluorescence experiments the KCNQ1 K^+ channel (formerly named KvLQT1) showed an H^+/K^+-ATPase-like distribution pattern in human parietal cells (Fig. 2*B*) [24, 38]. Its pharmacological inhibition by the chromanol 293B abolished acid secretion almost completely in vitro and in vivo. Most likely, KCNQ1 is associated with its regulatory subunit KCNE2 (MiRP1) to form the native channel complex [24, 38]. The functional role of KCNQ1 for acid secretion was underlined by observations in KCNQ1 knockout mice, which have an impaired acid secretion leading to hypergastrinemia and glandular gastric hypertrophy [69]. At present, it is not known whether homozygous KCNQ1 mutations in patients suffering from so-called Jervell-Lange-Nielsen syndrome [95] also lead to defects in gastric acid secretion. Very recently, another K^+ channel was described in parietal cells: Immunofluorescence experiments and electron microscopy revealed a localization of KCNJ10 (Kir4.1) in the H^+/K^+-ATPase-containing membrane compartment, suggesting that besides KCNQ1 also KCNJ10 might play a role during acid secretion [37]. To date no data are available concerning the gastric

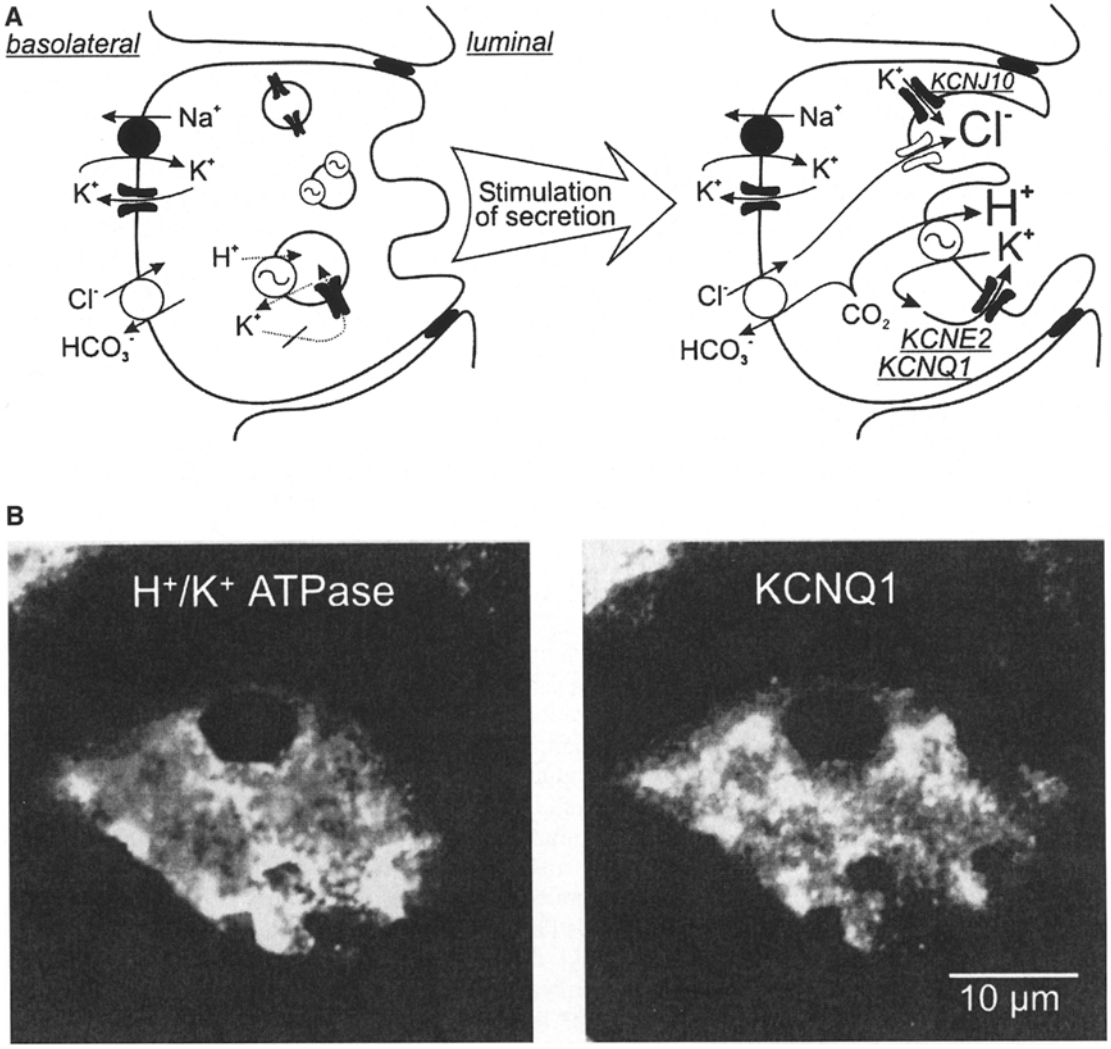

Fig. 2. K^+ recycling is required for acid secretion in parietal cells. (*A*) Functional and morphological changes of a parietal cell during stimulation of acid secretion. In the absence of secretory stimuli H^+/K^+ ATPase is located in intracellular vesicular structures (so-called tubulocisternae [31]). At present, it is not known whether K^+ channels, required for K^+ recyling, are located in H^+/K^+ ATPase-containing vesicles or in separate vesicular structures. A connection of the tubulocisternae to the lumen does not yet exist. Upon stimulation via cAMP and IP_3/Ca^{2+} pathways, tubulocisternae get fused with the luminal membrane, thereby enlarging the luminal surface and targeting H^+/K^+-ATPases and K^+ channels to the apical side. Now K^+ channels get activated by increasing concentrations of cAMP and cytosolic Ca^{2+}, and allow K^+ recycling, which is necessary for ongoing H^+/K^+-ATPase activity. (*B*) Immunofluorescence of a resting human parietal cell with labeling of H^+/K^+-ATPases (*left*) and KCNQ1 K^+ channels (*right*). Both show a granular distribution pattern within the cell, suggesting a localization of the proteins in vesicles and tubulocisternae, which belong to the luminal membrane compartment.

phenotype of KCNJ10 knockout mice [85]. Further studies are required to elucidate nature, function and membrane targeting of luminal K^+ channels during gastric acid secretion.

In the basolateral membrane the Cl^-/HCO_3^- exchanger serves Cl^- uptake and HCO_3^- extrusion. Basolateral Na^+/H^+ exchangers stabilize intracellular pH and cell volume [110, 118]. With the patch-clamp technique, K^+ conductances have been observed in the basolateral membrane and in whole-cell experiments [25, 90]; in whole-cell experiments [63], however, it is at present not clear whether they provide the driving force for voltage-dependent basolateral transport or for luminal Cl^- exit. For the latter function paracellular permeability would be required (*see* Fig. 1), which has been shown to be rather low [36].

Function of K^+ Channels for Reabsorption and Secretion in Small Intestine

In small intestine most of the nutrients are digested and consecutively absorbed. The largest part of the

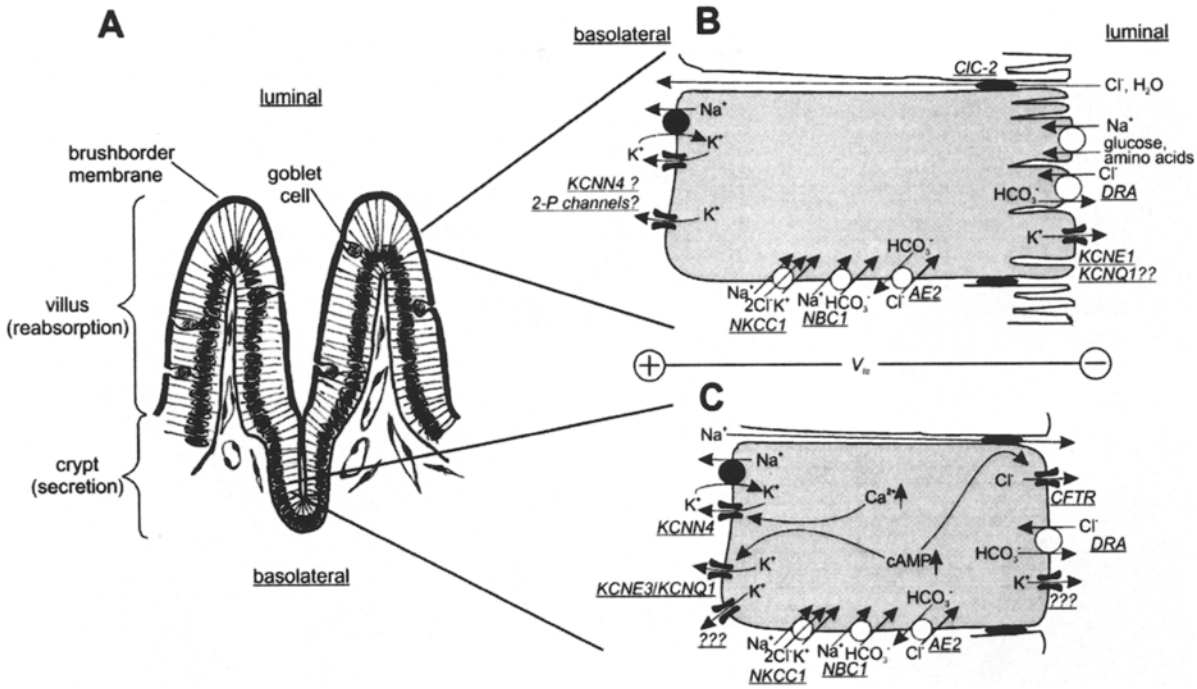

Fig. 3. Electrogenic transport in small intestine. (*A*) The mucosa of small intestine consists of crypt and villus cells. Reabsorption takes mainly place at the brushborder membrane of villus enterocytes. Goblet cells produce mucus, crypt cells secrete HCO_3^--rich fluid to neutralize gastric acid. Stem cells for the rapid regeneration of enterocytes are localized at the crypt basis. (*B*) In the luminal membrane of villus cells, glucose and amino acids are reabsorbed in a secondary active way together with Na^+. This depolarizes the luminal membrane, leading to the generation of a lumen-negative transepithelial voltage (V_{te}), which can drive reabsorption of anions via the paracellular pathway. Luminal K^+ channels could play a role for repolarization [134]. There is also some evidence for an H^+/K^+ exchange mechanism, probably via H^+/K^+ ATPase [9]. The molecular identity of luminal and basolateral K^+ channels is not known. The intermediate-conductance K^+ channel is probably less expressed in the basolateral membrane of villus cells when compared with crypt cells [47]. ClC-2 Cl^- channels seem to mediate paracellular Cl^- fluxes [45] driven by the electro-chemical gradient. (*C*) Secretion in crypt cells requires activation of luminal Cl^- channels (CFTR), basolateral (and luminal) K^+ channels, NKCC1 and Na^+/K^+ ATPase [42, 125]. Heteromultimeric KCNE3/KCNQ1 channels represent a cAMP-activated K^+ conductance. Their inhibition largely attenuates electrogenic Cl^-/HCO_3^- secretion. The intermediate-conductance K^+ channel (probably KCNN4) is activated via increases in cytosolic Ca^{2+}. HCO_3^- leaves the cell via CFTR and via luminal anion exchangers (probably DRA). On the basolateral side, Cl^- can be taken up by NKCC1 and by Na^+-dependent and -independent anion exchangers (AE2 and NBC) [130]. Luminal Cl^- and basolateral K^+ conductance create a lumen-negative V_{te}, that possibly induces paracellular Na^+ fluxes. The mechanisms for HCO_3^- secretion are probably present in villus cells, too (*B*).

fluid is reabsorbed by the small intestinal mucosa and only some 20% enter the colon. The mass transport in the small intestine involves both transcellular and paracellular transport of solutes, ions and water. In order to fulfill different physiological demands, the reabsorptive capacity of small intestinal mucosa is regulated by transcriptional and non-transcriptional mechanisms. Thus, expression of transporters and ion channels can vary over a broad range, depending on the needs [53, 64, 97, 99].

Among the transcellular mechanisms, secondary active transport allows absorption of substrates even against a concentration gradient, i.e., by Na^+-coupled transporters for glucose and amino acids. Many of the transporters use the chemical gradient for Na^+ or H^+ and the negative membrane voltage as driving forces [86, 98]. The entry of a positive net charge via these systems depolarizes the luminal membrane of enterocytes, leading to a transepithelial voltage difference (V_{te}, *see* Fig. 1 and Fig. 3) and consecutively to paracellular electrogenic transport, i.e., transport of Cl^- [8, 45]. However, the depolarization of the luminal membrane reduces further voltage-dependent transcellular transport. To restore the transport capacity of the enterocytes, K^+ channels are required to repolarize the membrane voltage. They can be localized in either the luminal or the basolateral membrane of villus cells (Fig. 3). It has been shown that activation of basolateral K^+ channels by pinacidil or BRL 38227 increases NaCl reabsorption, paralleled by an enhanced short-circuit current [51]. Strong activation of luminal K^+ channels, e.g., by cell swelling [80], could even produce a lumen-positive transepithelial voltage, which in turn would invert the direction of paracellular ion fluxes [45]. In another study, a nitric oxide-activated basolateral K^+ conductance was described, whose activation by the K^+ channel opener cromakalim enhanced net fluid reabsorption

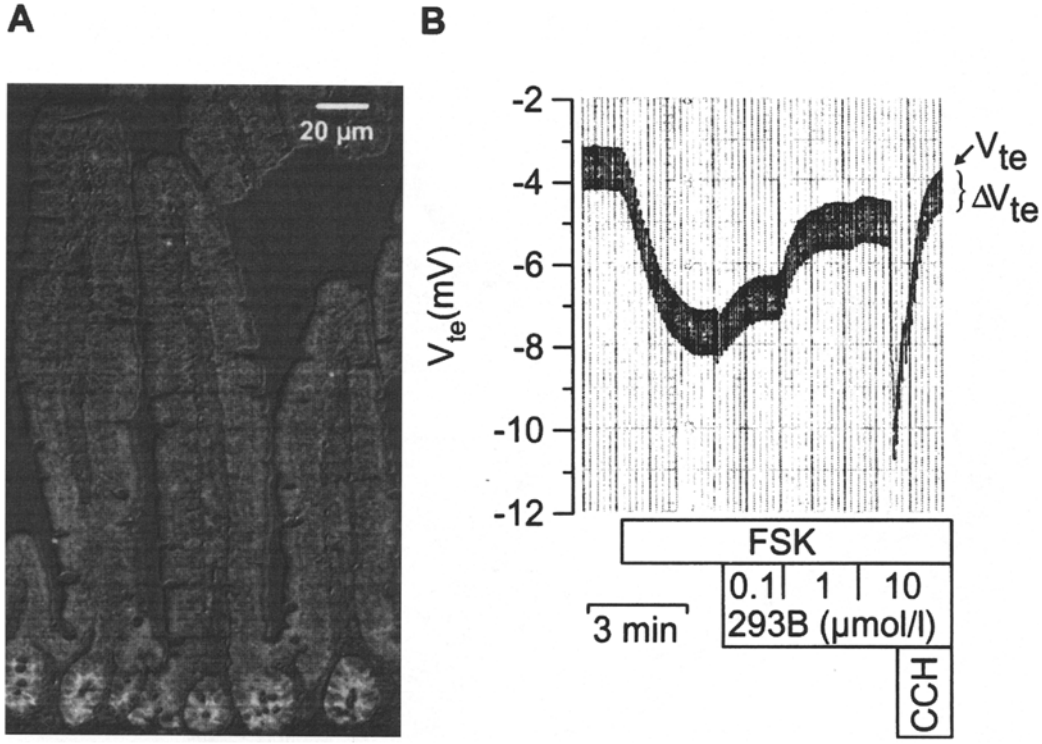

Fig. 4. KCNE3/KCNQ1 K^+ channels in mouse jejunum. (*A*) Immunolocalization of KCNQ1 in mouse jejunum (overlay with differential interference contrast image). The KCNQ1-specific antibody [134] preferentially labeled the basolateral membrane of jejunal crypts cells. (*B*) Effect of the chromanol 293B on cAMP-activated secretion in mouse jejunum. Forskolin at 5 µM (FSK) increased transepithelial voltage (V_{te}) mainly by activation of luminal Cl^- and basolateral KCNE3/KCNQ1 K^+ channels. 293B reduced V_{te} concentration-dependently by some 70%. Carbochol 100 µM (CCH) led to a rise in V_{te} by transiently activating Ca^{2+}-activated K^+ channels (probably KCNN4). ΔV_{te} is a measure for transepithelial resistance.

[115], indicating that luminal and basolateral K^+ conductances support reabsorption in small intestinal villus cells.

In the crypts of the small intestine, net secretion of bicarbonate, mucus, salt and water occurs, which allows buffering of acidic gastric content and facilitates propulsion of the intestinal content. Under pathological conditions, overwhelming activation of secretion, i.e., by cholera toxin, can lead to severe diarrhea. Transcellular transport in crypt cells is mainly a serosal-mucosal flux of Cl^-, HCO_3^- and K^+ [130], which is activated via cAMP and Ca^{2+} pathways and to some extent via nitric oxide/cGMP [6]. Bicarbonate secretion plays an important role for mucosal protection and neutralization of gastric acid. However, the luminal pathway for bicarbonate exit is controversially discussed: It probably involves electrogenic systems such as CFTR channels (cystic fibrosis transmembrane conductance regulator) [21] and electroneutral Cl^-/HCO_3^- exchangers such as DRA (down-regulated in adenoma) [50, 55, 93, 104]. The amount of HCO_3^- secreted via electrogenic transport systems is dependent on the membrane voltage and, thus, on K^+ channel activity. For the maintenance of electro-neutrality, Na^+ enters the lumen via the paracellular pathway driven by the transepithelial voltage, and K^+ can be secreted via luminal K^+ channels (Fig. 3*C*).

Transcellular mass transport of nutrients, salt, and water is a continuous challenge for cellular volume regulation of enterocytes in small intestine. There is good evidence that K^+ channels play a role during regulatory volume decrease after swelling of villus enterocytes [79]. Moreover, it has been shown that Na^+-dependent absorption of amino acids in enterocytes leads to activation of Na^+/K^+ ATPase and of basolateral K^+ channels. The increase in basolateral K^+ conductance prevents rises in intracellular K^+ concentration (due to enhanced Na^+/K^+ ATPase activity) and counteracts the depolarization caused by luminal electrogenic transport activity [39].

Compared with colonic K^+ channels, relatively little is known about the functional properties and the molecular identity of K^+ channels in the small intestine (Fig. 3) [124]. With electrophysiological methods several basolateral K^+ channels could be distinguished: an abundant large conductance "maxi" K^+ channel (90 to 250 pS) [15, 92, 122], an intermediate-conductance, Ca^{2+}-activated K^+ channel, small-conductance channels [15], K_{ATP}-like channels [30] and a chromanol 293B-sensitive K^+ conductance [134]. The regulation of the large-con-

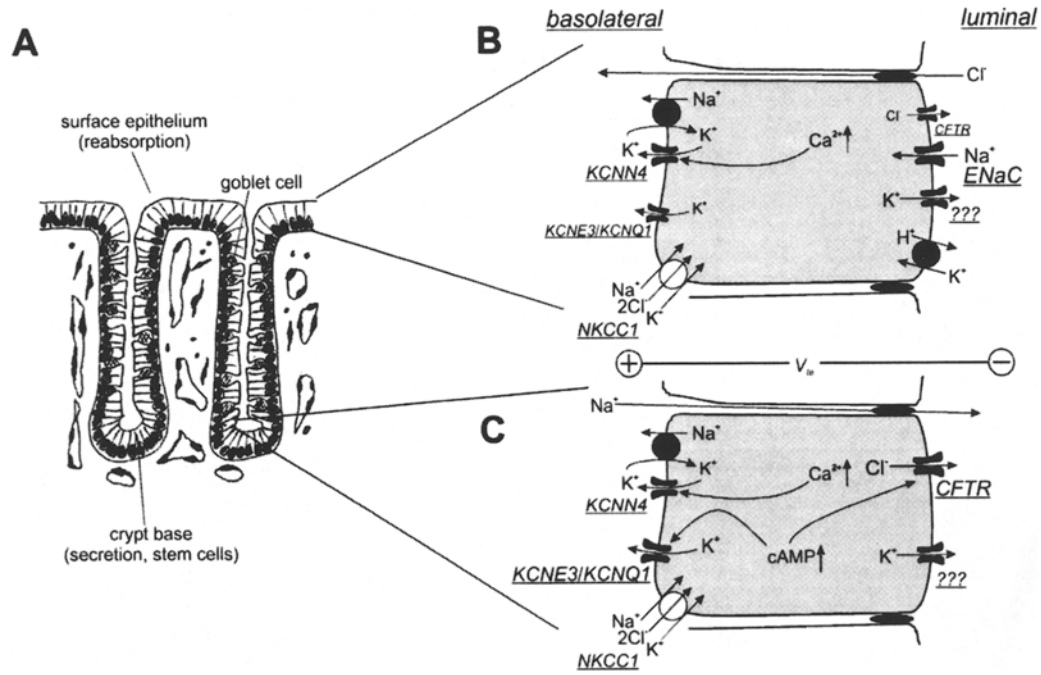

Fig. 5. Role of K^+ channels for secretion and absorption in distal colonic mucosa. (*A*) Colonic crypts consist of enterocytes, enteroendocrine cells and goblet cells. Absorption of short-chain fatty acids, salt, and water takes place in surface cells and the upper part of the crypt. At the crypt base, secretion and mitosis take place. (*B*) In surface cells Na^+ enters the cell via ENaC and is exported via basolateral Na^+/K^+ ATPase. CFTR Cl^- channels are less abundant than in crypt base cells. Without luminal K^+ channel activity, ENaC-induced luminal depolarization leads to Cl^- reabsorption via CFTR. Activation of luminal K^+ channels results in K^+ secretion paralleled by luminal hyperpolarization. If the luminal membrane voltage is more negative than the Cl^- equilibrium potential, the direction of the CFTR Cl^- flux would invert: the cell secretes KCl and reabsorbs Na^+. Luminal H^+/K^+ ATPase serves mainly K^+ reabsorption. Basolateral K^+ channels provide a part of the driving force for luminal ion movement. (*B*) In crypt base cells, secretion requires cAMP-dependent activation of luminal CFTR Cl^- channels and of basolateral KCNE3/KCNQ1 K^+ channels. Ca^{2+} leads to activation of basolateral KCNN4 K^+ channels but requires a certain level of luminal CFTR activity to induce Cl^- secretion, because CFTR seems not to be directly Ca^{2+}-activated. Ca^{2+}-activated Cl^- channels play a minor role in normal tissue but can be observed during tumor genesis in colonic mucosa [12]. Driven by the transepithelial voltage, Na^+ follows via the paracellular pathway.

ductance K^+ channel by cAMP and Ca^{2+} is controversially discussed [15, 87, 92, 122]. The intermediate-conductance K^+ channel is strongly activated by rises in cytosolic Ca^{2+} and by 1-ethyl-2-benzimidazolinone (1-EBIO) and shows functional characteristics similar to cloned IK1 channels (KCNN4) [47], suggesting that KCNN4 is the intermediate-conductance K^+ channel as found in rat colonic crypts [135]. There is some evidence for a regulation of the intermediate-conductance K^+ channel by cAMP [87], however, in another study no such regulation was observed [15]. Activation of this channel by 1-EBIO leads to a strong increase in Cl^- secretion but does not affect phloridzin-sensitive glucose absorption indicating that the 1-EBIO-activated K^+ channel is mainly expressed in intestinal crypts and not or only little in villus cells [47].

The 293B-sensitive conductance is mainly located in crypt cells and formed by KCNQ1/KCNE3 channel proteins (Figs. 3*C* and 4*A*) [24, 134]. The KCNE3/KCNQ1 channel complex is activated during cAMP-stimulated secretion. Its inhibition blocks electrogenic jejunal secretion by some 50–70% (Fig. 4*B*). Thus, KCNE3/KCNQ1 channels are a possible target for the treatment of life-threatening forms of secretory diarrhea, such as cholera. The 293B derivative IKs224 was shown to inhibit jejunal secretion with an IC_{50} in the nanomolar range [134]. However, clinical use of KCNE3/KCNQ1 blockers would require subunit specificity and/or locally restricted delivery of the drug, since one has to avoid inhibition of KCNE1/KCNQ1 channels in heart and inner ear.

K^+ Channels in Colonic Mucosa

In contrast to mass transport in small intestine, the colonic mucosa serves the fine tuning of salt and water metabolism. Under physiological conditions absorption largely exceeds secretion: Some 90% of 1.5 l of intestinal content entering the colon are absorbed and only 150–200 g are excreted under physiological conditions. However, a certain level of secretion of mucins, electrolytes and water is

Table 1. Expresssion of K^+ channels in the gastrointestinal tract

Channel	HUGO symbol	Aliases	Stomach	Small intestine	Colon	Method/References
Large-conductance Ca^{2+}-activated K^+ channels	**KCNMA1**[1]	**KCa1, 1, SLO**	h+, rb+++	h+	h++, rb++	DB [7], N, P [91], [70]
	KCNMB1[2]	hslo-beta	h++	h++	h++	DB [7]
	KCNMB2[2]				h(−)	DB [7]
	KCNMB3[2]		h++	h++	h++	DB [7]
	KCNMB4[2]				h+	DB [7]
MinK-related proteins (co-assembly with KCNQ1)	**KCNE1**	**IsK, minK**	m+, h−	h(+)	m(+)	N [20], P [132]
	KCNE2	**MiRP1**	h+++, m+++	m−	m(+)	N, IS [24], P [38], P [132]
	KCNE3	**MiRP2**	h++, m++	m++	m+++	N [24], P [38], [117]
Inward rectifier	**KCNJ1**	**Kir1, 1f, ROMK6**		r+	r+	P [62]
	KCNJ10	**Kir4.1**	r++			P [37]
	KCNJ13	Kir7.1	h++, r++	h+++	h(+)	N [101], N [94], P [37]
	KCNJ15	Kir4.2	r++			P [37]
2-p-Domain K^+ channels	KCNK1	TWIK1	h(+), m++	h(+), m++	h(+), m++	P [71], QP [88], P [4, 108]
	KCNK2	TREK1	h++	h+	h−	P [71, 72], QP [88]
	KCNK3	TASK1	m+	h(+), m+	h(+)	N [32], P [71], N [61]
	KCNK5	TASK2	h+	h+		QP [88]
	KCNK6	TWIK2	h++, m+++	h++, m+	h++, m++	QP [88], N [19], P [112]
	KCNK7		h+++	h++		QP [88]
	KCNK10	TREK2	h(+)	h+	h+	P [72], QP [88]
	KCNK12	THIK2	r+			P [106]
	KCNK13	THIK1	r+			P [106]
Intermediate-conductance Ca^{2+}-activated K^+ channel	**KCNN4**	**SK4, IK1, Kca4**	h++, m++	h+	h+++, r++, m++	DP [56], P [135], N [54], N [74], P [128]
KCNQ K^+ channels	**KCNQ1**	**KvLQT1**	m+++, h+++	m+, h++	m++, r++, h+	N [24], P [66], P [38], N [20], P, IS [26]

[1] Expression perhaps restricted to smooth muscle cells.

[2] Probably localized in neurons; h, human tissue; r, rat tissue; m, mouse tissue; rb, rabbit tissue; P, PCR; QP, Quantitative PCR; N, Northern blot; DB, RNA dot blot; IS, in situ hybridization; in bold letters: experimental evidence for function in native intestinal mucosa.

required for normal transport and composition of feces. Thus, defects in secretion, i.e., in cystic fibrosis, can lead to severe constipation. On the other hand, impairment of colonic reabsorption leads to diarrhea, affecting salt/water and acid/base metabolism [67].

In the proximal part, Na^+ is mainly reabsorbed via Na^+/H^+ exchangers and in distal colon, via Na^+ channels (ENaC). Depending on the needs of metabolism and hormone concentrations, K^+ can be net-secreted via channels or reabsorbed by a luminal H^+/K^+-ATPase (Fig. 5) [10, 34, 89, 120]. A detailed list of hormones and mediators regulating colonic transport is given in [133]. Moreover, bacterial degradation of undigested nutrients leads to generation of short-chain fatty acids and ammonia, which are taken up by cells located at the surface of colonic crypts [17, 18, 48].

K^+ channels play a role for secretory and reabsorptive pathways. In particular the activity of luminal K^+ channels affects the K^+ balance of the body and therefore is regulated via K^+ intake and different hormones. In the presence of high potassium diet [16, 113] or high aldosterone concentrations [35, 43, 76, 81], K^+ channels hyperpolarize the luminal membrane of crypt cells, leading to electroneutral transcellular secretion of KCl instead of transcellular Cl^- exit and paracellular Na^+ flux (Fig. 1*D*). In surface epithelial cells, the K^+ channel-induced hyperpolarization increases the driving force for Na^+ uptake via ENaC in distal colon. These K^+ conductances are modulated by cholinergic and cAMP-mediated pathways [29, 49, 84, 119]. Direct functional characterization of luminal K^+ channels with the patch-clamp technique is hampered by mucus and microvilli, which make measurements very difficult. There is evidence for large-conductance K^+ channels with single-channel conductances from 120–230 pS [16, 113, 133] and for a pH-sensitive ROMK-type channel [52, 62, 133]. Data from KCNMA1 knockout mice indicate that maxi K^+ channels play a role in K^+ secretion after purinergic receptor stimulation [70]. The inhibitory effect of the chromanol 293B on cAMP-activated serosal-to-mucosal Rb^+ flux suggests that KCNQ1 might be localized in luminal and basolateral membranes [29]. In the luminal membrane, KCNQ1 could co-assemble with the small regulatory proteins KCNE1 or KCNE2 [132].

In the basolateral membrane of colonic mucosa at least three different types of K^+ channels are present: (1) a large-conductance K^+ channel that is very abundant in rabbit colon [77, 78, 127]; (2) KCNN4 underlying the intermediate-conductance Ca^{2+}-activated K^+ channel [14, 27, 135], and (3) KCNQ1, a very small-conductance K^+ channel that is stimulated via cAMP and blocked by 293B [11, 24, 26, 65, 75, 117, 136].

Upon cholinergic stimulation of rat colonic mucosa, a strong but transient opening of KCNN4 channels is observed, leading to hyperpolarization of the basolateral membrane. The basolateral hyperpolarization increases the transepithelial potential difference if the luminal membrane is depolarized by Cl^- channels [13, 49]. Interestingly, the Ca^{2+} pathway alone seems not to activate sufficiently the luminal Cl^- conductance in normal colonic mucosa: in the absence of cAMP-mediated activation of luminal Cl^- channels, cholinergic stimulation by carbachol inverts the polarity of the V_{te} and leads to a lumen-positive transepithelial voltage via activation of luminal K^+ channels [83]. However, during carcinogenesis, Ca^{2+}-activated Cl^- channels are expressed, counteracting the hyperpolarizing effect of KCNN4 channel opening [12] and thereby mimicking the effect of carbachol in some colonic cell lines. Colonic KCNN4 channels are potently blocked by the antifungal drug clotrimazole and activated by 1-EBIO [28, 102, 129, 135]. Pharmacological activation and inhibition of colonic KCNN4 channels have been discussed as strategies for the treatment of cystic fibrosis and diarrhea, respectively [28, 57, 111, 126]. Basolateral K^+ channel inhibition was claimed to mediate the effect of the antidiarrheal drug loperamide [33].

In large intestine cAMP-mediated secretion plays an important role for normal transport of feces, which is impaired in cystic fibrosis. On the other hand, some bacterial toxins, such as cholera toxin, induce an overwhelming secretion in small and large intestine [133]. It has been shown that cAMP decreases intracellular Ca^{2+} activity of colonocytes via depolarization-induced reduction of Ca^{2+} influx. Thus, KCNN4-type Ca^{2+}-dependent K^+ channels are closed during cAMP-mediated secretion [13]. Under these conditions, the driving force for luminal Cl^- exit mainly depends on cAMP-activated KCNQ1 K^+ channels. The KCNQ1 inhibition by 293B was shown to block the electrogenic part of Cl^- secretion (Fig. 1*C*) [75] and the minor electroneutral secretion of KCl (Fig. 1*D*) [29]. Like in small intestine, KCNQ1 is associated with its regulatory subunit KCNE3 in the basolateral membrane of colonic enterocytes. In contrast to the cardiac KCNE1/KCNQ1 channel complex, which is voltage-dependent and slowly activating, KCNE3/KCNQ1 channels are voltage-independent and constitutively open [117].

More Intestinal K^+ Channels in the Future?

During the last years a number of new K^+ channel transcripts, i.e., for several maxi K^+ channels and 2-p-domain K^+ channels, have been found in the gastrointestinal tract and the list of intestinal K^+ channel genes (Table 1) is probably not complete.

On the other hand, for expression analysis, often commercially available samples of total tissue cDNA or RNA (including muscle layers and neuronal cells) were used. In these cases it is not proven that the respective K^+ channels are localized in the epithelial cells. Only for a very limited number of channels epithelial expression, cellular localization and a functional role in the native tissue could be shown. However, these data led to a better understanding of transport in the intestinal tract and these channels could be targets of drug development for the treatment of transport-related diseases.

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