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Potassium channels in epithelial transport

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Abstract Epithelial cells in the kidney, gastrointestinal tract and exocrine glands are engaged in vectorial transport of salt and nutrients. In these tissues, K^+ channels play an important role for the stabilization of membrane voltage and maintenance of the driving force for electrogenic transport. Luminal K^+ channels represent an exit pathway for the excretion of K^+ in secreted fluid, urine and faeces, thereby effecting body K^+ homeostasis. Indeed, the expression and function of several luminal K^+ channels is modulated by hormones regulating water, Na^+, and K^+ metabolism. In addition to net transport of K^+ in the serosal (or apical) direction, K^+ channels can be coupled functionally to K^+-transporting ATPases such as the basolateral Na^+/K^+ ATPase or the luminal H^+/K^+ ATPase. These ATPases export Na^+ or H^+ and take up K^+, which is then recycled via K^+ channels. This review gives a short overview on the molecular identity of epithelial K^+ channels and summarizes the different mechanisms of K^+ channel function during transport in epithelial cells.

Keywords K^+ channel · Potassium · Reabsorption · Secretion · Intestine · Kidney

Introduction

Transport of solutes, electrolytes and water across epithelia cells is essential for homeostasis of salt and water metabolism, reabsorption of nutrients, exocrine secretion and excretion of metabolic end-products. In epithelia, K^+ channels are involved in different cellular functions: (1) maintenance of a polarized cell membrane as a driving force for electrogenic transport; (2) cell volume regulation; (3) K^+ excretion according to metabolic needs; (4) K^+ recycling across luminal and basolateral membranes (functionally coupled to K^+-exchanging ion pumps); (5) cell fate: differentiation versus proliferation or apoptosis.

In the human genome around 80 different genes for K^+ channel α- and β-subunits have been described (http://www.gene.ucl.ac.uk/nomenclature/genefamily/KCN.shtml). In addition, hetero-oligomerization and splice variants yield a large number of structurally and functionally different native K^+ channels. Table 1 gives an, inevitably incomplete, overview of the epithelial expression of different K^+ channel genes. In recent years, the breathtaking progress of protein analysis and gene discovery has sped up our understanding of for K^+ channel structure and the role of these channels in genetically determined diseases. However, our knowledge of the tissue-specific expression pattern and its consequences for the function of native epithelia is still far from complete. The combination of molecular and biochemical techniques, genetically modified animals and functional methods will help to gain more insights into the diversity of epithelial K^+ channel physiology.

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Basolateral epithelial K^+ channels: driving force and cell volume regulation

In polarized epithelial cells basolateral K^+ channels hyperpolarize the cell membrane, thereby increasing the driving force for other electrogenic transport systems. Depending on the paracellular resistance, basolateral hyperpolarization leads also to hyperpolarization of the luminal membrane supporting transport across the luminal membrane. In epithelial cells from rat colonic crypts two distinct basolateral K^+ channels have been identified at the molecular level, exemplifying the physiological role of basolateral K^+ channels in general. Resting voltage of rat colonic enterocytes is mainly determined by KCNN4 (IK1, SK4 [17, 18, 40, 42, 65, 107]), a K^+ channel with a 10- to 20-pS single-channel conductance (Fig. 1C). KCNN4 bound to calmodulin [21, 43] is

Table 1 Epithelial K^+ channel genes and possible functions. [*OMIM* Online Mendelian Inheritance in Man database http://www.ncbi.nlm.nih.gov/omim/ classification No., Kv voltage-gated K+ channel, ROMK renal outer medullary K^+ channel, *Kir* inwardly rectifying K^+ channel, *TWIK* two-pore, weakly inwardly rectifying K^+ channel, *TREK* TWIK-related K^+ channel, *TASK* TWIK-related, acid-sensitive K^+ channel, *TOSS* TWIK-originated similarity sequence, *THIK* tandem pore domain, halothane-inhibited K^+ channel, *SLO* (slowpoke) large-conductance, Ca^{2+}-activated K^+ channel α-subunit, *SK* small-conductance K^+ channel, *SUR* sulphonylurea receptor)

Gene	Aliases	Epithelial localization	Function	Disease	OMIM	References
KCNA10	Kv1.8	Kidney (proximal tubule, glomerular endothelium)	cGMP-activated, voltage-gated K^+ channel. Facilitation of proximal Na^+-coupled reabsorption (?)	Unknown	602420	[115, 116]
KCNJ1	Kir1.1, ROMK	Kidney (thick ascending limb, distal convoluted and connecting tubule, collecting duct)	K^+ recycling and K^+ secretion. Association with SUR2B in renal thick ascending limb is controversial	Severe renal salt and water loss, hypokalaemic alkalosis (antenatal Bartter syndrome type 2)	600359	[9, 19, 50, 67, 102, 112, 114]
KCNJ2	Kir2.1	Kidney (glomerulus, proximal tubule, thick ascending limb, collecting duct)	Tubular transport (?) Renal development (?)	Andersen syndrome (complex dysmorphism, cardiodysrhythmic periodic paralysis, kidney dysplasia)	600681	[2, 16, 84]
KCNJ4	Kir2.3	Placenta, kidney (cortical collecting duct, basolateral)	Associated with hLin-7b, inwardly rectifying K^+ conductance	Unknown	600504	[79]
KCNJ8	Kir6.1	Kidney (proximal tubule, basolateral)	ATP- and taurine-sensitive K^+ conductance, association with SUR2B/SUR2A	Unknown	600935	[3, 10]
KCNJ10	Kir4.1	Gastric parietal cells (luminal), kidney (distal convoluted tubule, basolateral)	K^+ recycling required for H^+/K^+ ATPase activity. Associated with Kir5.1 in renal distal convoluted tubules.	Impaired acid secretion (?)	602208	[28, 66]
KCNJ11	Kir6.2	Pancreatic β cells	Regulation of insulin secretion, association with SUR1	Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI)	600937	[39]
SUR1		Pancreatic β cells	Sulphonylurea receptor, regulation of insulin secretion	PHHI	600509	[1, 92]
SUR2B		Kidney (and widespread in other tissues)	Sulphonylurea receptor	Unknown	601439	[7]
KCNJ13	Kir7.1	Small intestine, colon, stomach, kidney (proximal tubule, basolateral)	Basolateral channel in proximal tubules. Luminal K^+ channel in colonocytes (?)	Unknown	603208	[15, 81]
KCNJ15	Kir4.2	Kidney (distal convoluted tubule, basolateral)	Associated with Kir5.1	Unknown	602106	[66]
KCNJ16	Kir5.1	Kidney (proximal and distal convoluted tubule, collecting duct), pancreas	Inwardly rectifying K^+ channel, probably forming heteromeric channels with Kir4.1 or Kir4.2	Unknown	605722	[16, 62, 66, 96]
KCNK1	TWIK	Kidney [proximal tubule (S1–2), thick ascending limb (?), collecting duct], intestine, pancreas	Luminal K^+ conductance (?), K^+ secretion in collecting ducts (?)	Unknown	601745	[13, 60, 61]
KCNK2	TREK1	Stomach, small intestine	stretch-regulated K^+ conductance	Unknown	603219	[22, 72]
KCNK5	TASK2	Kidney (proximal tubule, papillary collecting duct), intestine, airways, liver, pancreas	Activation by alkaline extracellular pH and changes in cell volume	Renal salt and water loss in KCNK5 knockout mice	603493	[73, 76, 86, 109]
KCNK6	TWIK2, TOSS	Lung, kidney, liver, colon, pancreas, lung, stomach	Inwardly rectifying, pH regulated K^+ channel	Unknown	603939	[12, 82,83, 87]
KCNK7	–	Pancreas, stomach, small intestine, colon, kidney, lung	Unknown (no channel activity in expression systems)	Unknown	603940	[72, 87]

Table 1 (continued)

Gene	Aliases	Epithelial localization	Function	Disease	OMIM	References
KCNK9	TASK3	Kidney, lung, liver, stomach, colon	K^+ channel inhibited by extracellular acidosis	Unknown	605874	[47]
KCNK10	TREK2	Intestinal tract, pancreas (TREK2b splice variant), kidney (TREK2b, proximal tubule)	Volume- and stretch-activated K^+ conductance (?)	Unknown	605873	[33, 48]
KCNK12	THIK2	Lung, kidney, liver, pancreas, stomach	No functional channel in expression systems	Unknown	607366	[85]
KCNK13	THIK1	Lung, kidney, liver, stomach	Halothane-sensitive, weakly inwardly rectifying K^+ channel	Unknown	607367	[85]
KCNK15	TASK5	Pancreas, lung, kidney, liver	K^+ channel inhibited by extracellular acidosis	Unknown	607368	[5, 44]
KCNMA1	SLO	Colon (probably associated with KCNMB1 or 3), kidney (proximal tubule (?), thick ascending limb, collecting duct), parotid gland	Luminal K^+ conductance in mouse colon [aldosterone-regulated (?)]	KCNMA1 knockout mice lack purinergic receptor-mediated colonic K^+ secretion	600150	[8, 59, 75, 94, 105, 111]
		Kidney (probably associated with KCNMB3), lung (probably associated with KCNMB3)	Probably luminal K^+ conductance in distal nephron. K^+ secretion (?) aldosterone-regulated (?)	Hyperkalaemia (?)		[111]
KCNN4	SK4, IK1	Colon, intestine, stomach, lung, prostate, placenta (basolateral)	Ca^{2+}-regulated K^+ conductance	Defects in cholinergic receptor-mediated secretion (?)	602754	[34, 40, 42, 69, 91, 107]
KCNQ1	KvLQT1	Kidney: proximal tubule [luminal, associated with KCNE1 and KCNE2(?)] and collecting ducts [basolateral with KCNE3 (?)]	Repolarization of the luminal membrane restoring the driving force for electrogenic solute transport	Salt-wasting and hypokalaemia in KCNE1 knockout mice, no obvious human renal phenotype	–[1]	[20, 98, 103]
		Zona glomerulosa of adrenal gland (associated with KCNE1)	Regulation of aldosterone secretion	Increased aldosterone concentration (?)	176261	[4]
		Inner ear: marginal cells of the stria vascularis and vestibular dark cells	K^+ secretion into the endolymph	Deafness and impaired vestibular function (autosomal recessive Jervell-Lange-Nielsen syndrome)	220400	[25, 97]
		Gastric parietal cells (luminal, associated with KCNE2)	K^+ recycling required for H^+/K^+ ATPase activity	Reduced acid secretion in KCNQ1 knockout mice	–[2]	[14, 29, 58]
		Trachea, small and large intestine (basolateral, associated with KCNE3)	Important role for luminal Cl^- secretion	Constipation (?) Resistance against secretory diarrhoea such as cholera (?)	–[3]	[14, 30, 89, 90, 108]
		Pancreas, salivary glands (mainly associated with KCNE1)	Cl^- secretion (?)	Reduced exocrine secretion (?)	–	[45, 46, 56, 57, 108]

[1] Cardiac phenotype of KCNQ1 mutations: Long QT syndrome (Romano-Ward and Jervell-Lange-Nielsen syndromes [101]), OMIM 192500.
[2] Cardiac phenotype of KCNE2 mutations: Long QT syndrome, OMIM 603796
[3] Muscle phenotype of KCNE3 mutations: Periodic paralysis, OMIM 604433

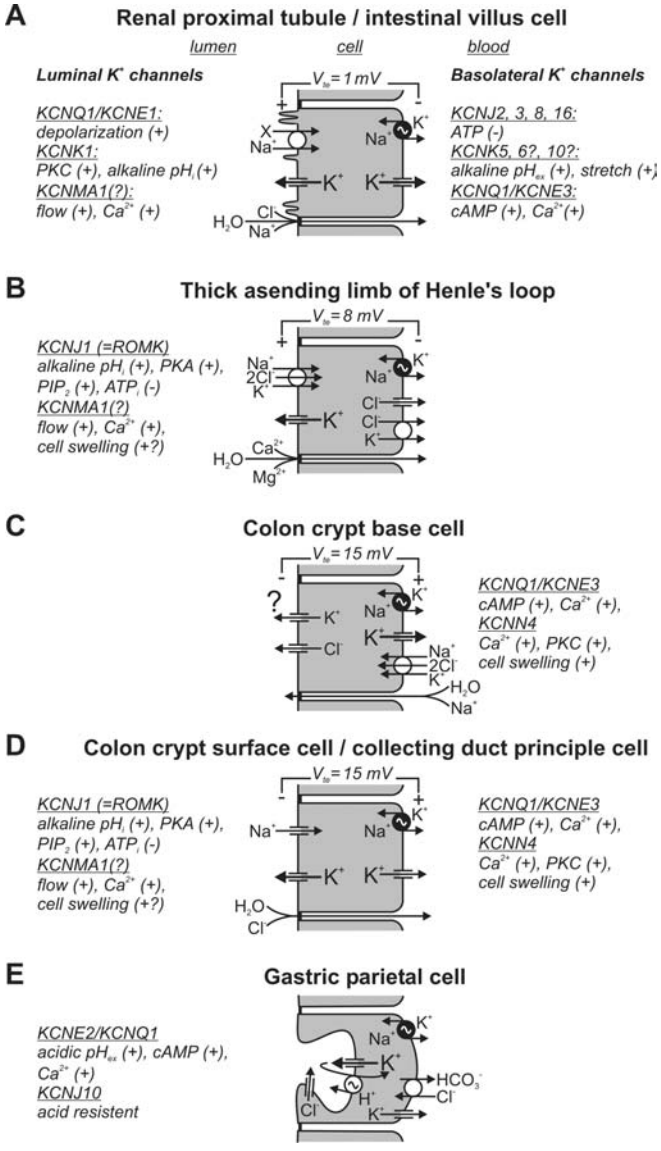

Fig. 1A–E Simplified models for K^+ channel function in different cell types. For simplicity, only one K^+ channel is drawn on basolateral or luminal side, although several different channels might be present. K^+ channel genes are named according to the Human Genome Organization (HUGO, http://www.gene.ucl.ac.uk/nomenclature/genefamily/KCN.shtml). Main regulation of K^+ channels is indicated as (+) for stimulation and (−) for inhibition (*PKA* protein kinase A, *PKC* protein kinase C, *PIP_2* phosphatidylinositol-4,5-bisphosphate)

regulated closely by Ca^{2+} in the latter's physiological range (100–500 nM) [100] and, therefore, Ca^{2+}-elevating agonists, such as acetylcholine or histamine, increase KCNN4 open probability. KCNN4 activation hyperpolarizes the basolateral and—depending on the permeability of the paracellular pathway—also the luminal membrane of enterocytes, thereby supporting electrogenic transport, e.g. luminal Cl^- secretion or Na^+ reabsorption (Fig. 1). KCNN4 is expressed abundantly in epithelial cells of colon [107] and of salivary glands [75, 95] and less in small intestine [34, 41]. However, during cAMP-mediated intestinal Cl^- secretion, KCNN4 activity is very low due to a reduction of intracellular Ca^{2+}. The driving force for Cl^- exit at the luminal side of the cell is maintained by a cAMP-stimulated basolateral K^+ conductance [106], which has been identified at the molecular level as KCNQ1 associated with its β-subunit KCNE3 [90]. Inhibition of KCNE3/KCNQ1 channel complex by the chromanol 293B or derivatives depolarizes the cell membrane, thereby diminishing the driving force for luminal Cl^- exit via the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel. Such a role for basolateral KCNE3/KCNQ1 channels in Cl^- secretion has been observed in various Cl^- secreting epithelia such as colon [53, 63, 90], small intestine [108] and airways [30, 70]. In addition, KCNE3 might assemble with KCNQ1 in distal nephron segments of the kidney.

Besides the stabilization of membrane voltage during electrogenic transport, basolateral K^+ channels are engaged in maintenance of cell volume, which represents a continuous challenge for transporting cells. In colonic crypts, cell swelling induces activation of KCNN4 K^+ channels, probably via increases in intracellular Ca^{2+} activity. The enhanced K^+ conductance leads to an exit of K^+ as an osmolyte, stabilizes the membrane voltage and supports Cl^- secretion. Together these mechanisms underlie the regulatory volume decrease [110]. Na^+-coupled reabsorption of sugars and amino acids depolarizes the membrane of small intestinal enterocytes and is paralleled by osmotic water influx. Depolarization, changes in the metabolic state and cell swelling activate basolateral (and luminal) K^+ channels, which in turn repolarize the membrane voltage needed for ongoing transport and regulatory volume decrease [31, 68]. Similar mechanisms of K^+ channel activation have been described in renal proximal tubular cells which perform mass transport of solutes and water similar to small intestinal enterocytes. Reabsorption of glucose and phenylalanine has been shown to activate (probably via cell swelling [99]) basolateral K^+ channels in proximal tubular cells [11] and there is good evidence for an ATP-regulated K^+ conductance that allows recycling of K^+ taken up by Na^+/K^+-ATPase [54, 55, 71, 78] (Fig. 1A). The pH-regulated and cell volume-sensitive K^+ channel KCNK5 (TASK2) is expressed strongly in renal proximal tubules. KCNK5 is—among others—a good candidate channel for activation by transport-associated changes in cell metabolism, cell volume and extracellular pH (possible activation by increase in basolateral $NaHCO_3$ extrusion) [6, 76, 77, 86, 109]. The precise function and subcellular localization of renal KCNK5 channels, however, remains to be established.

Furthermore, inwardly rectifying ATP-sensitive K^+ channels (members of the KCNJ family), cyclic nucleotide-regulated K^+ channels and maxi K^+ channels (KCNMA1 associated with β-subunits) have been described or proposed as basolateral K^+ channels in various epithelial tissues on the basis of immuno-localization

studies and functional characteristics of native channels [10, 35, 49, 66, 68, 79].

Luminal K^+ channels: repolarization, fine tuning of K^+ excretion and K^+ recycling

In renal proximal tubules, and probably in the small intestine, luminal K^+ channels play an important role for restoring the driving force of Na^+-coupled transport systems (amino acids, sugars), which depolarize the luminal membrane (Fig. 1A). Some of these luminal K^+ channels are activated directly by the transport-associated depolarization (i.e. KCNE1/KCNQ1 and KCNA10 in renal proximal tubules [98, 116]), others are regulated by mediators, second messenger pathways and cell volume [36, 37, 93]. Since the epithelia of small intestinal villi and renal proximal tubules have a low paracellular resistance [27], basolateral K^+ channels act in concert with luminal channels and hyperpolarize both basolateral and luminal membranes. However, the direction of the paracellular short circuit current differs, depending on luminal or basolateral K^+ channel activation [104].

In more "tight" epithelia, such as distal colon and renal collecting duct, the relative importance of luminal K^+ channels for repolarization is enhanced compared with "proximal" epithelia: in the presence of a high paracellular resistance, activation of basolateral K^+ channels does not suffice to hyperpolarize the luminal membrane. Moreover, the luminal K^+ channel activity in "distal" epithelia directly affects the ionic composition of urine and faeces: i.e. activation of luminal K^+ channels during colonic Cl^- secretion results in electroneutral KCl secretion; activation of basolateral K^+ channels, however, leads to electrogenic luminal Cl^- exit followed by paracellular Na^+ flux (NaCl secretion) [32, 52]. Therefore, luminal K^+ channel activity in the distal colon and renal collecting ducts is adjusted tightly according to body K^+ homeostasis. In the distal colon, luminal K^+ conductance is enhanced by the mineralocorticoid aldosterone and dietary K^+ intake [64, 88]. Very recently, it has been shown in colonic mucosa, that luminal purinergic receptor stimulation regulates luminal K^+ channels, identified molecularly as maxi-K^+ channels (KCNMA1) [51, 59] (Fig. 1D).

In native collecting duct cells, at least two different types of luminal K^+ channels have been identified, small-conductance (25–35 pS) and large-conductance (80–140 pS) channels [111]. The abundance of the small-conductance channel is increased with a K^+-rich diet, but not with a low-Na^+ diet [26, 80]. The small-conductance K^+ channel is probably encoded by the KCNJ1 gene (ROMK) [38, 67], which is defective in antenatal Bartter syndrome type 2 [Online Mendelian Inheritance in Man (OMIM) database http://www.ncbi.nlm.nih.gov/omim/ classification No. 600359). The large-conductance K^+ channel (maxi-K channel, KCNMA1) is activated by flow-induced membrane stretch and by rises in cytosolic Ca^{2+}. This might contribute to the increase in K^+ excretion at high urinary flow rate [74, 111].

In K^+-excreting epithelial cells, luminal K^+ channels underlie vectorial transport of K^+ across the epithelium. On the other hand, luminal and basolateral K^+ channels can also mediate K^+ recycling. For example, in renal thick ascending limb (TAL) cells, KCNJ1 (ROMK) plays a crucial role for K^+ recycling across the luminal membrane. This K^+ recycling is needed for Na^+ reabsorption via the $Na^+2Cl^-K^+$ cotransporter (NKCC2) (Fig. 1B). In patients suffering from KCNJ1 mutations, Na^+ reabsorption by the NKCC2 is markedly diminished, resulting in a life-threatening salt wasting syndrome (antenatal Bartter syndrome type 2).

In the small intestine and renal proximal tubule, basolateral K^+ channels are coupled to Na^+/K^+ ATPase activity. This allows K^+ to recycle, thus ensuring hyperpolarization, lowering of intracellular $[K^+]$, ongoing Na^+/K^+ ATPase activity and reabsorption of Na^+ and Na^+-coupled substrates [31, 71].

Gastric parietal cells secrete fluid containing 150 mM HCl. The acid-producing enzyme is a P_2-type ATPase, which pumps H^+ into the lumen coupled to uptake of K^+ [23, 24]. Therefore, a continuous supply of luminal K^+ is required for sustained acid production by parietal cells (Fig. 1E). Almost 20 years ago, it was postulated that the K^+ recycling pathway is a K^+ conductance, but the molecular identity of the K^+ channel(s) remained unclear [113]. The observation of impaired gastric acid secretion paralleled by massive gastric hyperplasia (probably due to high gastrin levels) in KCNQ1 knockout mice indicated that KCNQ1 might be involved in acid secretion [58]. In fact, KCNQ1 co-assembles with KCNE2 to form a luminal K^+ channel in gastric parietal cells [14, 29]. Inhibition of KCNQ1 by the chromanol 293B almost completely inhibits acid secretion in mouse, rat and dog in vivo and in isolated rabbit gastric glands in vitro [29]. These pharmacological data and the gastric phenotype of KCNQ1 knockout mice suggest that KCNQ1 is required for K^+ recycling across the luminal membrane for sustained H^+/K^+ ATPase activity. In addition to KCNQ1, KCNJ10 is located in the luminal membrane of parietal cells and probably acts together with KCNQ1 to recycle K^+ [28].

Conclusions

K^+ channels fulfil a variety of different tasks in epithelial cells and are regulated precisely so as to adapt to cellular needs. In recent years we have gained greater insight into K^+ channel genetics and the functional properties of the channels in expression systems. Elucidation of the function of molecularly identified K^+ channels in native tissue, their subunit compositions and interactions with regulatory proteins and macromolecular complexes is needed for a better understanding of the physiological roles of epithelial K^+ channels and possible clinical implications. Specific pharmacological modulation of

epithelial K^+ channels will offer new perspectives for the treatment of epithelia-linked diseases such as diarrhoea, peptic ulcer and metabolic disorders.

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