Basolateral membrane K⁺ channels in renal epithelial cells

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Submitted 28 November 2011; accepted in final form 13 February 2012

Hamilton KL, Devor DC. Basolateral membrane K⁺ channels in renal epithelial cells. Am J Physiol Renal Physiol 302: F1069–F1081, 2012. First published February 15, 2012; doi:10.1152/ajprenal.00646.2011.—The major function of epithelial tissues is to maintain proper ion, solute, and water homeostasis. Transepithelial transport is not a simple feat; rather it is a well-orchestrated physiological process involving numerous membrane transport proteins. Epithelial cells are polarized and thus possess different patterns (distributions) of membrane transport proteins in the apical and basolateral membranes of the cell. K⁺ channels play critical roles in normal physiology. Over 90 different genes for K⁺ channels have been identified in the human genome. Epithelial K⁺ channels can be located within either or both the apical and basolateral membranes of the cell. One of the primary functions of basolateral K⁺ channels is to recycle K⁺ across the basolateral membrane for proper function of the Na⁺-K⁺-ATPase, among other functions. Mutations of these channels can cause significant disease. The focus of this review is to provide an overview of the basolateral K⁺ channels of the nephron, providing potential physiological functions and pathophysiology of these channels, where appropriate. We have taken a “K⁺ channel gene family” approach in presenting the representative basolateral K⁺ channels of the nephron. The basolateral K⁺ channels of the renal epithelia are represented by members of the KCNK, KCNJ, KCNQ, KCNE, and SLO gene families.

renal epithelia; KCNK; KCNJ; KCNQ; KCNE; SLO

THE MAJOR FUNCTION OF EPITHELIAL TISSUES IS TO MAINTAIN PROPER ION, SOLUTE, AND WATER HOMEOSTASIS. TRANSEPIHELIAL TRANSPORT IS NOT A SIMPLE FEAT; RATHER IT IS A WELL-ORCHESTRATED PHYSIOLOGICAL PROCESS INVOLVING NUMEROUS MEMBRANE TRANSPORT PROTEINS. EPITHELIAL CELLS ARE POLARIZED AND THEREFORE POSSESS DIFFERENT PATTERNS (DISTRIBUTIONS) OF MEMBRANE TRANSPORT PROTEINS IN THE APICAL AND BASOLATERAL MEMBRANES OF THE CELL DEPENDING UPON THE SPECIFIC FUNCTION OF A GIVEN EPITHELIUM (104, 108). FOR EXAMPLE, A CONCERTED EFFORT OF VARIOUS ION TRANSPORT PROTEINS MUST OCCUR IN A GIVEN EPITHELIUM TO CARRY OUT A SPECIFIC FUNCTION SUCH AS Na⁺ REABSORPTION (Fig. 1) OR Na⁺-GLUCOSE REABSORPTION, K⁺ REABSORPTION, K⁺ SECRETION, OR Cl⁻ SECRETION. THE HUMAN GENOME PROJECT HAS LED TO THE IDENTIFICATION OF NUMEROUS ADDITIONAL ION TRANSPORT PROTEINS AT THE MOLECULAR LEVEL. SUBSEQUENTLY, THE PHYSIOLOGICAL ROLES OF THESE PROTEINS IN TRANSEPIHELIAL ION/SOLUTE TRANSPORT HAVE BEEN ELUCIDATED, RESULTING IN THE IDENTIFICATION OF MANY DISEASES OF EPITHELIA CAUSED BY MUTATIONS OF ION CHANNELS AND TRANSPORTERS. THESE INCLUDE VARIOUS RENAL TUBULOPATHIES, INCLUDING BARTTER’S SYNDROME (42, 64, 136), GITELMAN’S SYNDROME (37, 88), EAST SYNDROME (FOR INFANT EPILEPSY, SEVERE ATAXIA, MODERATE SENSORENEURAL DEAFNESS AND RENAL SALT WASTING TUBULOPATHY) (2, 11), SESAME SYNDROME (FOR SEIZURES, SENSORENEURAL DEAFNESS, ATAXIA, MENTAL RETARDATION AND ELECTROLYTE IMBAL-

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The specific function of a given K⁺ channel is dependent upon the overall function of the epithelial cell and the membrane within which the K⁺ channel resides. In particular, the cellular functions of K⁺ channels of renal epithelial cells include 1) generation and maintenance of the negative cell membrane potential (76); 2) hyperpolarization of cell membrane potential during a physiological response, thereby providing a driving force for electrogenic transepithelial ion/solute transport (e.g., to drive Na⁺-glucose cotransport and Na⁺ reabsorption); 3) recycling of K⁺ across the basolateral membrane required for maintaining electroneutrality; for example, the basolateral K⁺ current is coupled with the Na⁺-K⁺-ATPase pump current to balance the charge movement across the apical membrane for Na⁺ reabsorption (18, 65, 109); 4) recycling of K⁺ across the apical membrane of the TAL cells for continuous function of the Na⁺-K⁺-2Cl⁻-cotransporter (NKCC2) (135); 5) providing a route for K⁺ secretion across the apical membrane (30); and 6) participating in tubular cell volume regulation (5).

This review does not presume to be a definitive survey of all the epithelial basolateral K⁺ channels but is focused on the recent past and advances in our knowledge (and molecular diseases) of basolateral membrane K⁺ channels of renal tubule epithelial cells. The reader is referred to a number of excellent review articles on epithelial K⁺ channels in both renal (28, 44, 71, 72, 136) and nonrenal tissues (1, 3, 9, 28, 38, 41, 45, 46, 56, 59, 94, 95, 105, 130, 132, 133). These articles include information pertaining to both apical and basolateral membrane K⁺ channels in a wide range of epithelial tissues.

There are numerous K⁺ channels located within the basolateral membrane of the epithelial cells of the various tubular segments of the nephron. It is our goal to provide an overview of these channels, as well as to provide potential physiological functions and pathophysiology of these channels, where appropriate. We have taken a “K⁺ channel gene family” approach in presenting the representative basolateral K⁺ channels of the nephron. However, before we present the specific K⁺ channels of the nephron, it is important to briefly discuss the major function(s) of the various segments of the nephron.

**Overview of the Transport Function of Segments of the Nephron**

PT. The PT is responsible for the reabsorption of approximately two-thirds of the ion, solute, and water filtered by the glomerulus. The epithelial cells of the PT are an example of a leaky absorptive epithelium in which the tight junctions have a low resistance, and thus the tight junctions of PT cells are important routes of paracellular transport (71). Ions and solutes reabsorbed by the PT cells include Na⁺, Cl⁻, K⁺, HCO₃⁻, phosphate, and sulfate, along with glucose, amino acids, and some organic acids, among other molecules. Many of these molecules are reabsorbed via luminal Na⁺-dependent transport proteins. For example, reabsorption of Na⁺ and glucose from the filtrate occurs via apically located Na⁺-glucose cotransporters (SGLT1, SLC5A1; or SGLT2, SLC5A2 depending upon the portion of the PT) driven by the Na⁺ gradient (Fig. 2). Na⁺ is moved across the basolateral membrane by the Na⁺-K⁺-ATPase while glucose is transported by either glucose transporter 1 (GLUT1, SLC2A1) or 2 (GLUT2, SLC2A2) depending upon the portion of the PT. Additionally, a considerable amount of secretion of organic acids and bases into the tubular filtrate occurs along the length of the PT. Many different ion channels and transporters, of which basolateral K⁺ channels play a critical role, are responsible for the transepacellular transport of ion and solute along the length of the PT. K⁺ channels of the KCNK and KCNJ gene families have been reported from the basolateral membrane of PT cells of various species.

TAL. The epithelial cells of the TAL are responsible for the reabsorption of 20–25% of filtered Na⁺, K⁺, and Cl⁻ each day. These ions are reabsorbed through both transcellular and paracellular routes. The apical step for the transcellular reabsorption of Na⁺, K⁺, and Cl⁻ is via the apical NKCC2...
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DCT. The cells of the DCT are responsible for reabsorption of nearly 5% of the Na⁺ and Cl⁻ from the filtrate. There is a gradation of physiological function of the DCT cells, with respect to the reabsorption of Na⁺, depending upon whether one is examining the epithelial cells of the early portion of the DCT (DCT1) or the late DCT (DCT2) (16, 79). The cellular entry step, in both portions of the DCT, for Na⁺ and Cl⁻ is via the apical Na⁺-Cl⁻ cotransporter (NCCT; SLC12A3) across the apical membrane of the DCT cell, utilizing the Na⁺ gradient (Fig. 4). Additionally, the apical amiloride-sensitive sodium channel (ENaC) has been reported in the DCT2 (ENaC is not shown in Fig. 4), as well as SLC12A3 (79). The reabsorbed Na⁺ exits the DCT cell by the Na⁺-/K⁺-ATPase, K⁺ exits via basolateral K⁺ channels, and Cl⁻ exits through a Cl⁻ channel (CLCKBA). Therefore, basolateral K⁺ channels, again, aid in the recycling of K⁺ across the basolateral membrane and for reabsorption of K⁺ ultimately back to the blood. There are a number of basolateral K⁺ channels that have been described for DCT cells, which include members of the KCNK, KCNN, KCNQ, and SLO gene families.

CNT and CD. The (principal) cells of the CNT and CD are responsible for ~10% of the reabsorption of Na⁺ and Cl⁻ from the daily filtrate. The process of reabsorption of Na⁺ for the CNT and the CD is similar. The entry step for Na⁺ is via (SLC12A1) while Na⁺ and K⁺ exit the cell by the Na⁺-/K⁺-ATPase and basolateral K⁺ channels, respectively (Fig. 3). Cl⁻ crosses the basolateral membrane via a Cl⁻ channel (CLCKBA). In the TAL, K⁺ channels play crucial roles in both the apical and basolateral membranes. The apical ROMK2 (Renal Outer Medullary K⁺; Kir1.1b) K⁺ channel aids in recycling K⁺ to the luminal solution to maintain the local K⁺ concentration for the proper function of SLC12A1 (136) while the basolateral K⁺ channels aid in recycling K⁺ back to the interstitium to provide K⁺ for proper Na⁺-/K⁺-ATPase function. There are a number of basolateral K⁺ channels that have been described for TAL cells, which include members of the KCNK, KCNJ, KCNQ, and SLO gene families.

Members of the KCNK Gene Family in the Nephron

The KCNK gene family is composed of a series of 18 channels (to date) whose subunits are composed of 4 trans-

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Fig. 3. Cellular model of Na⁺, K⁺, and Cl⁻ reabsorption by the thick ascending limb (TAL) of the loop of Henle. The apical entry step for these 3 ions is via the Na⁺-/K⁺-/2Cl⁻ cotransporter (SLC12A1). Na⁺ is transported across the basolateral membrane by the Na⁺-/K⁺-ATPase, and Cl⁻ exits the cell by a basolateral Cl⁻ channel (CLCKBA). There are a number of basolateral K⁺ channels, from 4 K⁺ channel gene families, which have been identified within the basolateral membrane of the TAL of various animals. The apical K⁺ channels are ROMK 2 (Kir1.1b) and ROMK3 (Kir1.1c) (136). Abbreviations of all K⁺ channels and transporters are provided in the text.

Fig. 4. Cellular model for NaCl reabsorption by early (DCT1) and late (DCT2) distal convoluted tubule cells. Na⁺ and Cl⁻ enter the cell via the Na⁺-/Cl⁻ cotransporter (SLC12A3). The reabsorbed Na⁺ and Cl⁻ exit DCT1 and DCT2 as described in Fig. 3. Cellular K⁺ leaves the cell via a number of K⁺ channels that have been described from 4 different gene families. Mg²⁺ enters the DCT1 and DCT2 cells by the Mg²⁺ channel (TRPM6) and exits the cell by the Na⁺-/K⁺-ATPase, after which K⁺ exits across the basolateral membrane via a number of K⁺ channels, respectively (Fig. 3). Cl⁻ exits the cell via a number of K⁺ channels belonging to 3 different K⁺ channel gene families. CNT and CD cells also have apical epithelial Na⁺ and Ca²⁺ channels and basolateral Ca²⁺ channels that aid in recycling Na⁺ and K⁺ back to the blood.

Fig. 5. Cellular model of Na⁺ reabsorption by the CNT and the CD. Na⁺ enters CNT and CD cells via the epithelial sodium channel (ENaC), going down its electrochemical gradient. The reabsorbed Na⁺ is transported across the basolateral membrane by the Na⁺-/K⁺-ATPase. K⁺ is transported out across the basolateral membrane via a number of K⁺ channels belonging to 3 different K⁺ channel gene families. CNT and CD cells also are capable of K⁺ secretion utilizing the entry of K⁺ via the Na⁺-/K⁺-ATPase, after which K⁺ exits across the apical membrane via ROMK (136). Abbreviations of all K⁺ channels and transporters are provided in the text. *ROMK2 (Kir1.1b) is located in the cortical collecting duct, but not in the outer medullary collecting duct (136).
membrane domains and 2 pore regions. Lazdunski and colleagues (75) described KCNK1 (TWIK-1; Tandem Weak Inward Rectifying K⁺ Channel), the first member of the KCNK gene family. This group of channels is considered as “leak” K⁺ channels, which stabilize the cellular negative resting membrane potential (28), additionally, some members are sensitive to pH, temperature, volume, and/or membrane stretch (28, 34, 35).

Levy et al. (76) provided significant insight into the segmental expression the KCNK K⁺ channels within the human nephron. Using RT-PCR, Levy and colleagues identified KCNK1, KCNK3, KCNK5, KCNK10, and KCNK13 within the nephron and KCNK3, KCNK6, and KCNK10 within the glomerulus (76). Unfortunately, the study by Levy et al. (76) did not determine the membrane location of the KCNK channels, nor were the authors able to differentiate the three segments of the PT or to tease out the K⁺ channels between the DCT and the CD of the distal nephron. Nonetheless, that study provided a framework of the possible KCNK K⁺ channels present within the nephron.

There have been at least three members of the KCNK gene family identified in the basolateral membrane of cells from the nephron in a range of studies encompassing tubules from humans, rats, mice, and rabbits.

**KCNK5 in the nephron.** KCNK5 (TASK-2; TWIK-Related Acid Sensitive K⁺ Channel) which is now classified as a TALK (TWIK-Related Alkaline pH-Activated K⁺ Channel) was identified as the first member of the TASK subfamily of KCNK channels and was cloned from the human kidney and identified in the PT, distal tubule, and CD by Lazdunski and coworkers (110). The KCNK5 K⁺ channel is a noninactivating, outward rectified, acid-sensitive K⁺ channel whose gating is modulated by extracellular pH (110). Since its initial discovery, Poujol and coworkers, (5, 77, 78), using primary cell cultures of PT cells from control and KCNK5 knockout (KO) mice, have demonstrated that basolateral KCNK5 plays significant roles in volume regulation. Indeed, Barriere et al. (5) identified swelling-activated K⁺ currents attributable to KCNK5 in PT cells, and cells cultured from KO mice exhibited completely impaired volume-regulatory responses. Therefore, KCNK5 plays a critical role in cell volume regulation within PT cells.

Furthermore, Warth et al. (134) suggested, based on electrophysiological experiments coupled with pH and HCO₃⁻ measurements of PT cells from control and KO KCNK5 mice, that the basolateral KCNK5 K⁺ channel senses the basolateral external pH resulting from HCO₃⁻ transport. They further suggested that KCNK5 served as a “molecular switch” that modulates the K⁺ conductance relative to the rate of basolateral HCO₃⁻ transport (134). Recently, it has been reported that heterologously expressed KCNK5 can be modulated by intracellular pH (pHᵢ) and that a lysine (Lys²⁴⁵) in the fourth transmembrane domain of KCNK5 is the specific residue that is responsible for the pHᵢ gating of KCNK5 (92). These studies certainly provide exciting evidence for a major role of KCNK5 in pH homeostasis of PT cells and its potential role in renal proximal tubular acidosis (134).

**KCNK12 and KCNK13 in the nephron.** Derr and colleagues (106) first reported the KCNK12 (THIK-2; Tandem Pore Domain Halothane Inhibited K⁺ Channel) and KCNK13 (THIK-1) K⁺ channels of the THIK subfamily of KCNK K⁺ channels from rat kidney and brain among other tissues. Similarly, Lazdunski and coworkers (31) identified a human homolog of KCNK12 predominantly expressed in the pancreas. However, recently, Theilig et al. (124) reported that KCNK12 and KCNK13 were abundantly expressed in the nephron of both mice and rats. They clearly identified KCNK12 in the basolateral membrane of PT, TAL, DCT, CNT and CD cells of mice by immunostaining; furthermore, they suggested that KCNK12 contributes to recycling of K⁺ across the basolateral membrane, aiding the function of the Na⁺-K⁺-ATPase. Additionally, Theilig et al. (124) reported expression (RT-PCR) of KCNK13 within the PT, TAL, and CD cells and KCNK12 within the CD cells of human renal tissue. Theilig et al. (124) suggested that these KCNK channels might play a role in energy efficiency by modulating Na⁺ and Cl⁻ transport during hypoxic conditions.

Certainly, the numbers of and roles of basolateral KCNK K⁺ channels of the nephron are increasing (28). Further excitement with respect to the KCNK gene family has arisen by the implication of KCNK5 in renal proximal tubular acidosis (134). Indeed, Bayliss and Barrett (6) have suggested that two-pore channels are emerging as potential therapeutic targets for renal-related disorders.

**KCNJ Gene Family Members in the Nephron**

Many members of the KCNJ gene family, encoding Inward Rectifying K⁺ channels (Kir), have been identified in the recent molecular physiological era. The first member of the KCNJ gene family cloned was the ATP-dependent, inwardly rectified ROMK1 (KCNJ1; Kir1.1) K⁺ channel isolated from the rat kidney by Hebert and coworkers (50). To date, there are 18 members of the KCNJ gene family that include epithelial K⁺ transport channels, classic Kir channels, G protein-gated K⁺ channels, and ATP-sensitive K⁺ channels (46). Members of this gene family are characterized by two membrane-spanning domains linked by a pore-forming region and have intracellular NpH₂- and COOH-terminal domains (46). KCNJ1 (3 splice variants: ROMK1, Kir1.1a; ROMK2, Kir1.1b; ROMK3, Kir1.1c) is a predominant apical membrane K⁺ channel in various segments of the nephron and has been elegantly reviewed by Welling and Ho (136). The basolateral KCNJ K⁺ channels play a role in K⁺ homeostasis and contribute to the resting cellular membrane potential and recycling of K⁺ across the basolateral membrane of renal epithelial cells.

**KCNJ2 (Kir2.1, IRK1) and KCNJ16 (Kir5.1) in the nephron.** Jan and colleagues (68) originally cloned KCNJ2 (Kir2.1) from the mouse macrophage. KCNJ2 is generally found in cardiac, skeletal muscle, and nervous tissue (46). However, Derst et al. (22) identified both KCNJ2 and KCNJ16 (Kir5.1, discussed further below) by RT-PCR in human PT cells, and furthermore they demonstrated that KCNJ2 and KCNJ16 colocalized on chromosome 17q. KCNJ16 is known to form heteromeric channels with other members of the KCNJ gene family (103), and it has been identified in the basolateral membrane of DCT and CD cells (69, 98, discussed later). Indeed, Derst et al. (22) reported that KCNJ2 coassembled with KCNJ16 when expressed in Xenopus laevis oocytes. Additionally, Tucker et al. (126) and Tanemoto et al. (121) reported that heteromeric channels composed of KCNJ16 and KCNJ10 (Kir4.1) are inhibited by pHᵢ and the pH sensitivity of the heteromeric channel is dependent upon KCNJ16. This further suggests that...
KCNJ16 is crucial for maintenance of pH by proximal tubular cells. Last, Derst and coworkers (22) suggested these Kir subunits form channels and reside within the basolateral membrane of PT cells; however, the basolateral localization remains to be determined.

KCNJ4 (Kir2.3, IRK3, HIR, HRK1, hIRK2) in the CD of the nephron. The KCNJ4 K⁺ channel was originally described from human and murine brain, specifically from the hippocampus, but this channel was also shown to be within heart and skeletal muscle by the groups of Kurachi (89), Vanderberg (101), and Nichols (83). This channel is an inward rectifier with a single-channel conductance of ~10 pS and inhibited by known K⁺ channel blockers (e.g., Ba²⁺, Cs⁺, TEA) as characterized by expressing KCNJ4 in the X. laevis oocyte expression system. These initial studies did not demonstrate KCNJ4 within kidney tissue.

Welling (135) presented the first comprehensive study of KCNJ4 (reported by Welling as CCD-IRK3) of renal epithelial cells. Welling isolated KCNJ4 from the established mouse CD cell line, M1 (119). He demonstrated the presence of KCNJ4 within the M1 cell line by Northern blotting, but KCNJ4 was not present within either Madin-Darby canine kidney (MDCK) or pig kidney (LLC-PK1) cell lines, both of distal nephron origin. Additionally, Welling (135) provided the first evidence of KCNJ4 in native mouse kidney by RT-PCR. The characteristics of this channel, expressed in X. laevis oocytes, were a strongly inward rectified channel, with a conductance of 14.5 pS, high open probability, and inhibition by Ba²⁺ (135). Based on sequence homology, Welling suggested that the channel he characterized was the channel reported by Kurachi (89), Vanderberg (101), and Nichols (83) and their colleagues. Subsequently, Welling and coworkers (73, 74) established that KCNJ4 was targeted to the basolateral membrane in a polarized epithelium and at that time suggested that KCNJ4 was the channel that encoded for the small-conductance K⁺ channel of CD principal cells and it played a physiological role in K⁺ homeostasis.

Consistent with Welling’s work, Millar et al. (87) identified the presence of KCNJ4 in both whole mouse cortex and cortical CDs by RT-PCR. Additionally, Millar et al. patched the basolateral aspect of single, isolated CD tubules and demonstrated that the KCNJ4 had a similar biophysical profile (strong inward rectification, sensitivity to Ba²⁺, half-maximum at 0 mV for Ba²⁺ block, for example) to the channel reported by Welling (135). Furthermore, Millar et al. (87) implied that the dominant nature of the conductance associated with KCNJ4 suggested that this channel played an important part in K⁺ handling in the principal cells of the cortical CD.

KCNJ8 (Kir6.1) in the nephron. The ATP-dependent K⁺ channel (K_{ATP}) was first described by Noma (93) from cardiac tissue using patch-clamp experiments. Since then, K_{ATP} channels have been reported from pancreatic β-cells, skeletal muscle, vascular smooth muscle, and renal tubule cells (46, 56). The KCNJ8 K⁺ channel was first cloned from rat pancreatic cells (55). KCNJ8 plays a multitude of roles in various tissues, including shortening of the action potential, cellular loss of K⁺ during metabolic complications of the heart, insulin secretion, regulation of smooth muscle function, regulation of skeletal muscle excitability, and release of neurotransmitters (56).

Zhou et al. (142) demonstrated robust labeling of KCNJ8 in the basolateral membrane of DCT and CD cells as well as weak expression of KCNJ8 in PT cells of the rat by immunohistochemistry. Maurer et al. (85, 86) described, by electrophysiological experiments, an ATP-sensitive K⁺ channel from the basolateral membrane of PT cells of the salamander (Ambystoma) that was modulated by PKA, PKC, and pH, yet was not affected by stretch or a swelling-activated response. In contrast, Brochiero et al. (13) reported that the KCNJ8 K⁺ channel of rabbit PT cells was taurine sensitive and suggested that KCNJ8 played a role in osmoregulation as taurine was a known exportable osmolyte (70). Therefore, the loss of intracellular taurine and the activation of KCNJ8 would act collectively to regulate cell volume of PT cells (13). KCNJ8 certainly plays a role in volume regulation; however, further investigation is required to elucidate the role of KCNJ8 in proximal tubular physiology.

KCNJ10 (Kir4.1, Kir1.2, K_{AR}-2) and KCNJ16 (Kir5.1, BIR9) in the nephron. Adelman and colleagues (12) first described the inwardly rectified potassium channels KCNJ10 and KCNJ16 cloned from brain, heart, and skeletal muscle tissues. Kurachi and coworkers (57) examined the distribution of KCNJ10 within the rat nephron. They clearly identified KCNJ10 within the basolateral membrane of cells of the DCT, CNT, and CD segments of the rat nephron by immunohistochemistry and immunogold electron microscopy (57). KCNJ10 exists as a homeric channel, but it can form a heteromeric channel with KCNJ16 (103). Subsequently, Paulais et al. (100) identified a basolateral K⁺ channel in the TAL of mice that had similar electrophysiological properties to that of a K⁺ channel described by Hurst et al. (54) from rabbit TAL cells, and strikingly similar to the heteromeric KCNJ10/KCNJ16 K⁺ channel reported by Pessia et al. (103). Additionally, Lourdel et al. (81) identified KCNJ10 and KCNJ16 along with KCNJ15 (Kir4.2) by mRNA expression from mouse DCT cells, and they demonstrated immunolocalization of KCNJ10 in the basolateral enfoldings of DCT cells. They characterized, by patch clamping isolated DCT tubules, the biophysical properties of a K⁺ channel that strongly resembled KCNJ10/KCNJ16. Furthermore, Lachheb et al. (69) reported significant mRNA expression for KCNJ10 and KCNJ16 from mouse CD cells. Also, Lachheb et al. (69) patched the basolateral membrane of CD cells, and one of the K⁺ channels exhibited many characteristics of KCNJ10/KCNJ16. They further suggested that the K⁺ channel reported by Paulais et al. (100) was actually the heteromeric KCNJ10/KCNJ16 K⁺ channel (69). Finally, Derst et al. (22) demonstrated the expression of KCNJ16 within the human TAL and reported that KCNJ16 formed heteromeric channels with KCNJ2 when expressed in X. laevis oocytes.

KCNJ13 (Kir7.1, Kir1.4) in the nephron. Krapivinsky et al. (67) first described the KCNJ13 K⁺ channel from the kidney, small intestine, prostate, testis, and brain. This channel is quite unique with characteristics different from most Kir K⁺ channels such as: a very small conductance of 50 fS, not sensitive to ATP, low sensitivity to barium (a nonspecific blocker of K⁺ channels) and the inward rectification of the channel is independent of extracellular K⁺ (26, 67). KCNJ13 shares only 38% homology with its closest member (KCNJ15) of the KCNJ gene family (67).

Ookata et al. (96) reported KCNJ13 within PT cells of rat tubules by Western blotting and further demonstrated KCNJ13 within the basolateral membrane of rat DCT, CNT, and CD cells by immunostaining. Additionally, Derst et al. (21) dem-

AJP-Renal Physiol • doi:10.1152/ajprenal.00646.2011 • www.ajprenal.org
demonstrated the presence of $\text{KCNJ13}$ $K^+$ channels in isolated PTs from human and guinea pig kidneys based on RT-PCR experiments. Using immunohistochemistry, Derst et al. clearly demonstrated the presence of $\text{KCNJ13}$ in the basolateral membrane of guinea pig PT cells. The electrophysiological data of the guinea pig $\text{KCNJ13}$, expressed in $\text{X. laevis}$ oocytes, was consistent with previously reported data on human $\text{KCNJ13}$. Derst et al. suggested that the $\text{KCNJ13}$ $K^+$ channel was well suited to mediate $K^+$ exit across the basolateral membrane of the PT cells because the channel has a very low dependence on $K^+$ permeation by external $K^+$ (21). Therefore, $\text{KCNJ13}$ maintains a high efflux of $K^+$ at low interstitial $K^+$ concentrations (21). $\text{KCNJ13}$ warrants further study to uncover the role this channel plays in renal physiology.

$\text{KCNQ}$ gene family member $\text{KCNQ1}$ ($K_{LQT1}$, $K_{7.1}$) and $\text{KCNE}$ family members $\text{KCNE1}$ (MinK) and $\text{KCNE3}$ (MIRP2) in the nephron. The members of the $\text{KCNQ}$ gene family are voltage-activated $K^+$ channels. Wang and coworkers (131) cloned $\text{KCNQ1}$, the first member of this gene family indentified. This channel was found in a number of tissues, including cardiac muscle, skeletal muscle, and epithelia (59). Subsequently, two groups demonstrated that $\text{KCNQ1}$ coassembled with a $\beta$-subunit, $\text{KCNE1}$, a purported one-transmembrane domain channel first described from the rat kidney by Nakani-shi and colleagues (127), to form a slow outwardly rectifying $K^+$ channel characteristic of the cardiac $I_K$, $K^+$ channel that aids in the repolarization of the cardiac cells (4, 114). In addition to coassembling with $\text{KCNE1}$, $\text{KCNQ1}$ can coassemble with the $\beta$-subunit $\text{KCNE3}$ in a variety of epithelial tissues, including the intestine (19, 116). The $\text{KCNQ1}/\text{KCNE3}$ $K^+$ channel was characterized as a cAMP-dependent channel exhibiting a linear current-voltage relationship that is different from the $\text{KCNQ1}/\text{KCNE1}$ $K^+$ channel (116). Mutations within $\text{KCNQ1}$ give rise to a number of diseases, including long QT syndrome (LQT1) and deafness (58, 91).

The presence of $\text{KCNQ1}$ and $\text{KCNE1}$ within the kidney was verified by RT-PCR, in situ hybridization, and immunofluorescence (20, 120, 128). In fact, $\text{KCNQ1}$ and $\text{KCNE1}$ are expressed in the apical membrane of mammalian PT cells (120, 128), and it was suggested that $\text{KCNQ1}$ plays a role in $Na^+$ reabsorption by the PT cells of the mouse (129). Nevertheless, Wingo and colleagues (141) determined the distribution of $\text{KCNQ1}$ in the mouse kidney. Using Northern blot analysis, they reported the presence of $\text{KCNQ1}$ from the whole kidney, after which they conducted RT-PCR on isolated tubule segments and detected $\text{KCNQ1}$ within the DCT, CNT, and CD and weak signals for the early PT and the cortical TAL. Using immunostaining, they demonstrated clear basolateral membrane labeling of $\text{KCNQ1}$ in cells from the TAL, DCT, CNT, and CD. However, Wingo and coworkers did not have any experimental evidence for $\text{KCNQ1}$ within the basolateral membrane of the PT cells and further suggested that the discrepancy between their data and the study by Vallon et al. (128) might result from different $\text{KCNQ1}$ isoforms. Recently, Cirovic et al. (17) confirmed basolateral $\text{KCNQ1}$ within the DCT cells of frog kidney. However, those authors did not mention a possible $\beta$-subunit that aggregates with $\text{KCNQ1}$ within the frog DCT.

The function(s) of basolateral $\text{KCNQ1}$ within the various segments of the nephron is still to be determined; however, these channels could certainly be responsible for recycling of $K^+$ across the basolateral membrane as described above for other basolateral $K^+$ channels. Additionally, $\text{KCNQ1}$ would be well positioned to play a role in $K^+$ reabsorption during times of a low-$K^+$ diet, for instance.

Interestingly, Duranton et al. (27) identified the $\beta$-subunit $\text{KCNE3}$ within cultured mouse DCT cells. Furthermore, they examined the involvement of $\text{KCNQ1-KCNE3}$ in the LPS-induced apoptosis of mouse DCT cells and revealed there is an activation of $\text{KCNQ1-KCNE3}$ conductance by LPS. Duranton et al. put forth the possibility that the $\text{KCNQ1-KCNE3}$ channel may play a crucial role in LPS-mediated pathogenesis of renal disease during sepsisemia. This report is quite exciting, as the role of basolateral $K^+$ channels in renal epithelia is gaining more clinical relevance.

$\text{SLO}$ gene family member $\text{SLO2.2}$ in the TAL of the nephron. The $\text{SLO}$ mammalian gene family is composed of four members (113), and the first member cloned was $\text{SLO1}$, better known as the maxi-$K$ channel (also $K_{Ca1.1}$, $BK$, $KCNMA1$) (15). The members of this gene family have a large single-channel conductance (60–270 pS), exhibit several subconductance states, and $Ca^{2+}$, $Na^+$, $Cl^-$, and pH can modulate most members of the $\text{SLO}$ gene family. $\text{SLO2.2}$ ($K_{Ca1.1}$, $K_{Na}$, $K_{Ca4.1}$, SLACK, $\text{Sequence Like A Calcium-Activated K}$) is a $Na^+$- and $Cl^-$-activated $K^+$ channel that was first reported from cardiac myocytes (61) and cloned by Kaczmarek and colleagues (60) and Salkoff and coworkers (138, 139). Generally, these $K^+$ channels are found in excitable tissues.

Recently, Paulais et al. (99) reported the first occurrence of the $Na^+$-sensitive $K^+$ channel $\text{SLO2.2}$ from renal epithelial cells. In fact, $\text{SLO2.2}$ was identified in only the TAL cells of the mouse using RT-PCR. Using single-channel patch-clamp experiments, Paulais et al. described the functional identification of the basolateral $150$-$pS$ $Na^+$, $Cl^-$-activated $K^+$ channel that was neither pH nor ATP sensitive. The physiological role of $\text{SLO2.2}$ is still yet to be established. However, Paulais et al. suggested, based on the $Na^+$ sensitivity of $\text{SLO2.2}$, that this channel could participate in the apical/basolateral “physiological crosstalk” coupling of basolateral $K^+$ conductance to $Na^+$ entry across the apical membrane which has been debated for many years (8, 23, 43, 117). Interestingly, the $Na^+$-regulatory sensor motif of $\text{SLO2.2}$ has been recently identified within the $\text{RAC2}$ ($\text{Regulators of Conductance of K}$) domain, which is intriguing as RAC domains are designed to couple specific ion-sensing mechanisms to channel gating (140). Additionally, $\text{SLO2.2}$ can play a role in maintaining the membrane potential and recycling $K^+$ across the basolateral membrane. This report by Paulais et al. (99) appears, to our knowledge, to be the only report of $\text{SLO2.2}$ in renal epithelial tissues. This channel certainly requires additional investigation to determine its physiological role in the function of ion transport physiology of the TAL.

Other basolateral $K^+$ channels within the nephron. In addition to the $K^+$ channels described above, there have been many $K^+$ channels identified within the basolateral membrane of renal epithelial cells from a number of animals (frog, salamander, rabbit, rat, $\text{X. laevis}$). However, the authors have been unable to ascertain to which specific $K^+$ channel gene families these $K^+$ channels belong. Unclassified channels are reported in the basolateral membrane of PT cells (7, 32, 33, 51–53, 62, 63, 97, 111, 125), TAL cells (24, 39, 40), DCT cells (123), and CNT/CD cells (36, 47–49, 82).
Renal Pathophysiology and Basolateral K⁺ Channels

The molecular physiological era has ushered in many opportunities for determining the molecular basis of diseases, and thus our understanding of renal tubular diseases has blossomed over the past two decades. We have identified, in the introduction to this paper, a number of molecular diseases that are specific to the kidney; however, those diseases do not involve basolateral K⁺ channels of the nephron.

Here, we will focus on two related “renal” syndromes, SeSAME and EAST, which have been recently described, involving renal basolateral K⁺ channels that elicit physiological complications with tubular function, but also afflict other organ systems based on the distribution of these K⁺ channels. As we presented earlier, KCNJ10 (Kir4.1) exists as a homomeric channel, but it can form heteromeric channels with KCNJ16 (Kir5.1) (103) and is found predominantly within the DCT, CNT, and CD cells (57, 69, 81, 84, 100). Additionally, these channels are found within a wide range of tissues, including brain, cochlea, heart, and skeletal tissues (57, 81, 84). Therefore, mutations in these channels can lead to clinical manifestations in multiple tissues as has been recently reported for SeSAME and EAST. These syndromes have similar symptoms that are described below. However, we present these syndromes separately based on their original descriptions (11, 115).

SeSAME syndrome-KCNJ10. Lifton and colleagues (115) described a previously unreported human autosomal recessive syndrome which was characterized by seizures, sensorineural deafness, ataxia, mental retardation and electrolyte imbalance (named SeSAME) coupled with hypokalemia, metabolic alkalosis, and hypomagnesemia. This study entailed examining individuals of four kindreds from Afghan, Great Britain, and Canadian ancestries. The original patient exhibited general seizures, developmental delay, atrophy in the lower limbs, marked ataxia, progressive hearing loss, hypokalemia, metabolic alkalosis, and hypomagnesemia (115). Additionally, other patients exhibited elevated renin and aldosterone, further suggesting a salt-wasting complication within the kidney. By linkage analysis, Scholl et al. (115) localized the putative causative gene to a 2.5-Mb segment of chromosome 1q23.2–23.3. The case for the original patient showed no homozygosity to any known loci of Bartter’s or Gitelman’s syndromes, both well-described syndromes of the TAL and DCT, respectively (37, 64, 115).

Scholl et al. (115) suspected that the gene of interest in this syndrome would be expressed in the brain, inner ear, and kidney, at least, as reports that KCNJ10 knockout mice exhibited neurological and renal phenotypes similar to those of their patients (25, 66, 90). Thus KCNJ10 was the candidate gene to pursue. Using direct DNA sequencing of KCNJ10, Lifton’s group identified six previously unidentified nonsense and missense mutations (R65P, C140R, T164I, A167V R199stop, and R297C; widely expressed in the N terminus, external loop, transmembrane domain 2, and the C terminus) on both alleles in all patients. These mutations occurred at positions that were completely conserved among all vertebrate species examined. Furthermore, Scholl et al. (115) stated that a number of those mutations had previously been shown to play a role in loss of function in related K⁺ channels. Additionally, recent reports have further characterized mutations of KCNJ10 reported by Lifton and colleagues (107, 112, 122, 137).

Molecular basis of renal manifestations of SeSAME-KCNJ10. Similar to other salt-wasting diseases (Bartter’s, Gitelman’s syndromes), renal complications of SeSAME can be better understood by examining the ion transport cellular models of the various segments of the nephron. Based on the location of KCNJ10 within the nephron and the clinical manifestations of SeSAME, the function of DCT, CNT, and CD cells are critical in understanding the molecular basis of SeSAME. The general ion transport functions of the DCT cells (Fig. 4) include 1) Na⁺ and Cl⁻ reabsorption by luminal SLC12A3, 2) luminal uptake of Mg²⁺ by TRPM6 (Transient Receptor Potential Melastatin subtype 6), and 3) luminal Ca²⁺ reabsorption by TRPV5 (Transient Receptor Potential Vaniloid member 5) (not shown in Fig. 4) in the DCT2 cells (2, 115). The basolateral Na⁺-K⁺-ATPase plays a number of crucial roles in the overall transport function of the DCT cell by transporting Na⁺ out of the cell for the exchange with interstitial K⁺. Furthermore, the continued operation of the Na⁺-K⁺-ATPase maintains the proper electrochemical gradient for the apical influx of Na⁺ (and thus Cl⁻) and maintaining the cell’s negativity for enhanced ion transport function. Cellular K⁺ exits the basolateral membrane via KCNJ10 and maintains the cell’s negative potential, contributing to electrical driving forces for transcellular ion transport. The absorbed Cl⁻ exits the cell via the basolateral CLCKB/A channel aided by the electrochemical gradient. Finally, intracellular Mg²⁺ is transported across the basolateral membrane by putative Mg²⁺ transporters (shown in Fig. 4 but not Fig. 6). Loss of KCNJ10 function (Fig. 6) coupled with the potentially reduced activity of the Na⁺-K⁺-ATPase can have a number of downstream effects on ion transport, including 1) diminished Na⁺ and Cl⁻ entry across the apical membrane of the DCT cell, leading to salt-wasting; 2) reduced cell negative potential,

![Fig. 6. Molecular model of altered ion transport in SeSAME/EAST syndromes](http://ajprenal.physiology.org/)

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which lowers the driving force for entry of Mg$^{2+}$ via TRPM6 or the exit of cellular Cl$^{-}$ by CLCKB/A across the basolateral membrane, resulting in reduced reabsorption of Mg$^{2+}$ and Cl$^{-}$; and 3) reduced Na$^{+}$ and Cl$^{-}$ reabsorption by the DCT, leading to the increase of renin and aldosterone, as reported in some patients (115), which will ultimately lead to increased Na$^{+}$ reabsorption and K$^{+}$ secretion by the CNT and CD cells, resulting in hypokalemia and metabolic alkalosis, as seen in Bartter’s and Gitelman’s syndromes (37, 64).

Here, we have only examined the renal complications of SeSAME. Our understanding of this syndrome is just being realized, and future studies are required to fully elucidate the large ramifications of SeSAME in nonrenal tissues.

**EAST syndrome-KCNJ10.** Kleta and colleagues (11) reported another autosomal recessive syndrome involving KCNJ10 shortly after Scholl et al. (115), in which five children from two consanguineous families of Pakistan descent exhibited infant epilepsy, severe ataxia, moderate sensorineural deafness and renal salt wasting tubulopathy, which has been named EAST syndrome. These individuals exhibited seizures in infancy; also, these children experienced speech and motor delay, gate ataxia, intention tremor, and dysdiadochokinesia (inability to perform rapid, alternating movements), which are all consistent with cerebellar dysfunction (11). All children (inability to perform rapid, alternating movements), which are named EAST syndrome. These individuals exhibited seizures in infancy; also, these children experienced speech and motor delay, gate ataxia, intention tremor, and dysdiadochokinesia (inability to perform rapid, alternating movements), which are all consistent with cerebellar dysfunction (11). All children displayed renal symptoms of elevated renin, hypokalemic metabolic acidosis, and renal salt wasting tubulopathy, which has been named EAST syndrome. These individuals exhibited seizures in infancy; also, these children experienced speech and motor delay, gate ataxia, intention tremor, and dysdiadochokinesia (inability to perform rapid, alternating movements), which are all consistent with cerebellar dysfunction (11). All children displayed renal symptoms of elevated renin, hypokalemic metabolic acidosis, and hypocalciuria, again suggesting altered renal tubular function, in addition to the neurological symptoms. Again, KCNJ10 was the candidate gene screened by linkage analysis. Bockenhauer et al. (11) screened the complete coding region of KCNJ10, which revealed a homozygous missense mutation R65P (within the N terminus just before transmembrane domain 1) in four of the children and another homozygous missense mutation G77R (within transmembrane domain 1) in the last child. The R65 and G77 amino acids were conserved among all 21 species determined by a protein-homology analysis.

Bockenhauer et al. (11) further heterologously expressed the wild-type KCNJ10 channel and two mutant KCNJ10 channels in X. laevis oocytes and reported that the wild-type channel exhibited robust currents typical of an inward rectifier K$^{+}$ channel. However, current from the mutant R65P KCNJ10 channels were reduced to 25% and current from mutant G77R KCNJ10 channels were reduced to only 5% of the current exhibited by wild-type control channels (11). Thus the decrease in function of mutant KCNJ10 channels could result in an altered electrochemical driving force for transcellular NaCl reabsorption, resulting in the similar alteration of ion transport function of the DCT cells as described above for the molecular basis of SeSAME syndrome.

Recently, Warth and colleagues (107) described a new mutation of KCNJ10 (R175Q) that could play a role in altered renal function in EAST syndrome patients. When this mutation was heterologously expressed in HEK cells, Reichold et al. (107) noted that the mutated channel only exhibited channel flickering with no clear single-channel level and had only 10–15% the open probability of the wild-type channel. Additionally, they examined the pH sensitivity of wild-type KCNJ10 and the R175Q mutant channel in excised inside-out patches. The wild-type channel had a half-maximal activity observed at pH 6.3, as previously described (102). However, the R175Q mutant channel was inactive at physiological pH, but shifted to a half-maximal activity at pH 9.35. So, the single point mutation of KCNJ10 dramatically shifted the pH sensitivity of the channel to quite alkaline conditions. In addition to the molecular channel evidence, Reichold et al. (107) also examined the distal tubular morphology of an EAST syndrome patient by using material from kidney biopsies. Electron microscopy studies revealed that the DCT cells had reduced numbers of mitochondria and diminished basolateral infoldings. With a view of these results coupled together, EAST syndrome patients would exhibit compromised reabsorptive capacity of DCT cells based on morphology and channel function (107).

Very recently, Zdebik and coworkers (29) described three new mutations of KCNJ10 (R65C, F75L, and V259stop) from patients clinically diagnosed with EAST syndrome. These mutations were heterologously expressed in X. laevis oocytes, and all mutant channels exhibited significantly impaired channel function, suggesting these mutations caused reduced basolateral membrane K$^{+}$ conductance and abnormal distal nephron function.

SeSAME/EAST and KCNJ16. Much attention has been paid to the role of KCNJ10 in the complications of SeSAME and EAST syndromes as discussed above. Of course, KCNJ10 forms both homomeric channels and can also form heteromeric channels with KCNJ16 (103). Recently, Paulais et al. (98) examined the renal phenotype of mice that lacked KCNJ16 (knockout; KCNJ16−/−), and thus in those animals the homomorphic KCNJ10 channel would presumably be a primary basolateral K$^{+}$ channel in the TAL, DCT, CNT, and CD (11, 81, 100, 107). Interestingly, compared with SeSAME/EAST patients, the KCNJ16−/− mice exhibited, barring hypokalemia and K$^{+}$ wasting without NaCl wasting, very few symptoms of SeSAME or EAST syndromes. The KCNJ16−/− mice exhibited normal NaCl reabsorption by the TAL, metabolic acidosis, hyperchloremia, hypermagnesemia, and hypercalciuria.

Paulais et al. (98) examined the pharmacological and electrophysiological characteristics of KCNJ16+/+ and KCNJ16+/− mice to begin to understand the renal phenotypic differences between the knockout mice and SeSAME/EAST patients. Paulais et al. studied the physiological function of the tubules by determining the effects of diuretics, which inhibit specific Na$^{+}$-dependent transporters or ENaC, on ion transport function of the TAL and distal nephron. The effects of furosemide (inhibitor of SLC12A1) and amiloride (inhibitor of ENaC) on ion transport function were the same for tubules from both KCNJ16+/+ and KCNJ16+/− mice. These results suggested that the loss of KCNJ16 did not alter ion transport of the TAL and distal nephron (98). Next, Paulais et al. examined the effects of hydrochlorothiazide (HCTZ), an inhibitor of SLC12A3 in the DCT, and demonstrated that HCTZ induced a significantly greater increase in Na$^{+}$ in the urine of KCNJ16+/− mice compared with urine Na$^{+}$ levels of KCNJ16+/+ mice. Paulais et al. concluded that the genetic loss of KCNJ16 leads to a stimulation of NaCl reabsorption by the DCT cells in the knockout mice. Additionally, using single-channel experiments with DCT cells, Paulais et al. demonstrated the single-channel properties of KCNJ16+/+ (i.e., KCNJ10+KCNJ16) had a conductance of 44 ± 1 pS and an open probability of 0.31 ± 0.05 while channel properties of KCNJ16−/− had a conductance of 23 ± 1 pS and an open probability of 0.74 ± 0.04, which supported previous findings...
of heteromeric and homomeric KCNJ10 channels (81, 103, 121).

Furthermore, Paulais et al. demonstrated, with single-channel studies, that the 44-pS KCNJ16+/+ channel was sensitive to pH over the range of pH 6.8–8; as has been reported (69, 81, 100, 102, 103, 121, 126), while the KCNJ16−/− channel was not pH sensitive over that same pH range. As Tucker et al. (126) had proposed “a novel functional role in pH-dependent regulation of renal K+ buffering and recycling” for KCNJ16, Paulais et al. (98) now provided dramatic proof, with the KCNJ16−/− mouse, supporting Tucker’s proposed function for KCNJ16. Therefore, the results from the pH and electrophysiological studies suggested that, for the KCNJ16−/− mouse, the K+ channels (presumably KCNJ10) responsible for basolateral K+ conductance would be highly active and have altered pH sensitivity.

How does the loss of KCNJ16 lead to the symptoms exhibited by the KCNJ16−/− mouse? Paulais et al. (98) focused on the normal/abnormal function of the DCT as a means of explaining the symptomology of the knockout mouse. As can be seen in Fig. 7A, the normal function of the DCT is for NaCl reabsorption across the DCT epithelial cells. However, with the loss of KCNJ16, the homomeric KCNJ10 channel is thus expressed within the basolateral membrane of the DCT cells; however, the homomeric channel does not exhibit the pH sensitivity as the heteromeric KCNJ10/KCNJ16 channel does, leading to an enhanced activity. Therefore, there is an increased basolateral K+ conductance (i.e., KCNJ10), leading to increased Na+-K+-ATPase function, with increased activity of the apical SLC12A3, and an increased driving force for Cl−/exit by CLCKB/A; this ultimately leads to increased NaCl reabsorption across the DCT cell (Fig. 7B) (98).

At the time of this writing, we have been unable to locate any published paper(s) that describe a mutation within KCNJ16. It is very exciting to envision how our knowledge of SeSAME and EAST syndromes will blossom once specific mutations of KCNJ16 are discovered.

Concluding Remarks

Basolateral K+ channels play critical roles in the epithelial ion/solute transport physiology of the nephron and aid in overall homeostasis of the body. There is a wide variety of K+ channels from a number of gene families that have been described and are found in specific locations throughout the segments of the nephron. Our understanding of the roles these K+ channels play in overall renal homeostasis and pathophysiology is still emerging. The possible role of KCNK5 as a “molecular switch” in renal proximal tubular acidosis is an exciting development in the field of proximal tubule physiology. The SeSAME and EAST syndromes, involving KCNJ10 and KCNJ16, have only recently been described and have certainly opened new and exciting research avenues for many renal molecular physiologists. The renal research future is certainly bright, and we anticipate major strides in our understanding of the role of basolateral K+ channels in renal tubulopathies during the next decade.

ACKNOWLEDGMENTS

This paper is presented in memory of our friends Dr. James K. Bubien and Dr. Dale J. Benos, both of whom contributed much to our understanding of the physiology and pathophysiology of the kidney. We want to apologize to all authors whom we were unable to reference due to space limitations. We thank Dr. Corina M. Balut for comments on this manuscript. We also thank Dr. Thomas E. Kleyman for discussions on the transport proteins of the DCT.

GRANTS

This work was supported by National Health, Lung, and Blood Institute Grants HL-083060 and HL-092157 to D. C. Devor and an Aims grant from the Department of Physiology of the University of Otago to K. L. Hamilton.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.
AUTHOR CONTRIBUTIONS


REFERENCES


