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Distal tubule basolateral potassium channels: cellular and molecular mechanisms of regulation

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Abstract

Purpose of review—Multiple clinical and translational evidence support benefits of high potassium diet; however, there many uncertainties underlying the molecular and cellular mechanisms determining effects of dietary potassium. $K_{ir}4.1$ and $K_{ir}5.1$ proteins form a functional heteromer ($K_{ir}4.1/K_{ir}5.1$), which is the primary inwardly rectifying potassium channel on the basolateral membrane of both distal convoluted tubule (DCT) and the collecting duct (CD) principal cells. The purpose of this mini-review is to summarize latest advances in our understanding of the evolution, physiological relevance and mechanisms controlling these channels.

Recent findings— $K_{ir}4.1$ and $K_{ir}5.1$ channels play a critical role in determining electrolyte homeostasis in the kidney and blood pressure, respectively. It was reported that $K_{ir}4.1/K_{ir}5.1$ serves as potassium sensors in the distal nephron responding to variations in dietary intake and hormonal stimuli. Global and kidney specific knockouts of either channel resulted in hypokalemia and severe cardiorenal phenotypes. Furthermore, knock out of $K_{ir}5.1$ in Dahl salt-sensitive rat background revealed the crucial role of the $K_{ir}4.1/K_{ir}5.1$ channel in salt-induced hypertension.

Summary—Here, we focus on reviewing novel experimental evidence of the physiological function, expression and hormonal regulation of renal basolateral inwardly rectifying potassium channels. Further investigation of molecular and cellular mechanisms controlling $K_{ir}4.1$ and $K_{ir}4.1/K_{ir}5.1$ mediating pathways and development of specific compounds targeting these channels function is essential for proper control of electrolyte homeostasis and blood pressure.

Keywords

collecting duct; distal convoluted tubule; $Kcnj10$; $Kcnj16$; $K_{ir}4.1/K_{ir}5.1$; NCC; ENaC

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Conflict of interest

There are no conflicts of interest.

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INTRODUCTION

Salt and water handling by the kidney directly impacts blood pressure. Ion channels and transporters in the distal tubules determine the transport rate and subsequently urinary excretion of electrolytes. The effect of sodium on blood pressure is dependent on diet composition, specifically on the sodium/potassium ratio. Diets supplemented with high potassium are associated with a lower risk of major cardiovascular events [1,2]. Despite highly relevant clinical and translational evidence supporting benefits of high potassium diet, there is a substantial lag in our understanding of the underlying molecular mechanisms. Inwardly rectifying K^+ channels, specifically $K_{ir}4.1$ and $K_{ir}4.1/K_{ir}5.1$ (encoded by *Kcnj10* and *Kcnj16* genes, respectively), play a dominant role in determining blood potassium level and serve as potassium sensors in the distal nephron [3–5]. This brief review discusses recent advances in our understanding of potassium homeostasis mediated by the basolateral K^+ channels in the distal nephron and mechanisms controlling the activity of these channels.

THE EVOLUTION OF K^+ CHANNELS

Potassium channels expressed in virtually all type of eukaryotic cells and involved in a plethora of physiological processes in both electrically excitable and non-excitable cells. The evolution and diversification of ion channels often provide important insights in the understanding of their function. From the structural characteristics and genome sequencing data majority of K^+ channels has been traced back to the prokaryotic world [6]. Potassium channels could be divided into three groups based on the principal structural components – two transmembrane helices inwardly rectifier (K_{ir}), two pore four transmembrane (K_{2p}) and six membrane helix voltage gated outward rectifier (K_v) (Figure 1). In the vertebrate, members of the K_{ir} family are further divided into the three main evolutionary groups – elementary, ATP-regulated (exhibit rundown in the absence of cytoplasmic ATP as a result of the net de-phosphorylation of the channel [7]), and G-protein-activated channels [8]. The last two evolutionary groups of K_{ir} genes are the major classes of the K_{ir} family, and their expression must be mutually exclusive according to phylogenetic analyses [9]. Indeed, G-protein-activated channels are expressed in the neuronal cells, and ATP-regulated K_{ir} channels are represented in the epithelial and glial tissues [10,11]. ATP-sensitive (K_{ATP}) channels composed of K_{ir} and sulfonylurea receptor (SUR) subunits set aside and not reviewed here. The ATP-regulated $K_{ir}4.1$ (encoded by *Kcnj10* gene), $K_{ir}1.1$ (renal outer medullary potassium channel (ROMK); encoded by *Kcnj1*) and $K_{ir}7.1$ (*Kcnj13*), and elementary $K_{ir}5.1$ (*Kcnj16*) channels are highly expressed in the distal kidney tubules. ROMK channels are expressed on the apical plasma membrane [12], and $K_{ir}7.1$ mRNA was found in the intercalated cells of cortical collecting duct (CCD) [13]. This brief review is focused on the mechanisms controlling expression and activity of the basolateral $K_{ir}4.1$ and $K_{ir}4.1/K_{ir}5.1$ channels expressed in distal convoluted tubule (DCT) and the collecting duct (CD) principal cells. It should be noted that these channels are highly expressed in CNS and contribute to a number of neurological disorders such as depression, epileptic seizure and others [14–18].

BASOLATERAL CHANNEL CONDUCTANCE AND HETEROMERIZATION IN THE DISTAL TUBULES

ATP-regulated K_{ir} , such as apical ROMK and basolateral $K_{ir}4.1$ channels, are considered as “weak” inwardly rectifiers. Namely, “weak” indicates a notable persistent outward current when compared with “strong” rectifiers, where outward conductance is virtually abolished due to intracellular factors. $K_{ir}4.1$ can function as a homomeric channel or may form a heteromeric channel with $K_{ir}5.1$ [19]. $K_{ir}4.1/K_{ir}5.1$ heteromeric channel exhibit biophysical properties distinct from those of homomeric $K_{ir}4.1$ channel. This includes a larger single channel conductance and greater pH sensitivity [20,21]. It is important to note that $K_{ir}4.1/K_{ir}5.1$ is the predominant K^+ basolateral channel and a key determinant of the resting membrane potential in both DCT and CD principal cells [22,23]. This notion is supported by both electrophysiological and pharmacological methods. Thus, it was shown that $K_{ir}4.1$ homomeric channels are highly expressed in brain astrocytes and can be blocked with fluoxetine [24,25]. In contrast, fluoxetine has no effect on the macroscopic K^+ -selective conductance in CCD principal cells, which could be abolished by the tricyclic antidepressant nortriptyline [26] (nortriptyline inhibits both homomeric $K_{ir}4.1$ and heteromeric $K_{ir}4.1/K_{ir}5.1$ channels). Interestingly, the most common cardiovascular complication of nortriptyline, which is FDA-approved drug for the treatment of major depression, is hypotension [27,28].

A number of human mutations in *KCNJ10*, which underlie SeSAME/EAST syndrome, are characterized by salt wasting, renal tubulopathy, and autosomal recessive epilepsy, ataxia, sensorineural deafness [29,30]. Mutations in *KCNJ16* gene were reported to cause non-familial Brugada syndrome associated with sudden cardiac death [31]. Deletion of $K_{ir}5.1$ in mice strongly decrease sensitivity to intracellular pH and results in elevated open channel probability of compensatory overexpressed homomeric $K_{ir}4.1$ channel in the distal nephron [32]. Furthermore, it was recently reported that mutations in the hepatocyte nuclear factor 1 homeobox B (HNF1 β) cause autosomal dominant tubulointerstitial kidney disease [33]. As was shown in this study, compromised $K_{ir}5.1$, and potentially $K_{ir}4.1$ and the thiazide-sensitive sodium-chloride cotransporter (NCC; encoded by *SLC12A3*), drive these effects [33]. However, it should be noted that $K_{ir}5.1$ is less studied compared to $K_{ir}4.1$ and no human mutations in *KCNJ16* mimicking SeSAME/EAST syndrome have been identified up-to-date. One of the potential reasons for this is that in contrast to *KCNJ10*, *KCNJ16* gene is not included in the database of genes for the screening. Importantly, variations of the gene encoding the $K_{ir}4.1$ subunit results in a loss of function of both homomeric $K_{ir}4.1$ and heteromeric $K_{ir}4.1/K_{ir}5.1$ channels [34]. Furthermore, we recently reported that functional K^+ conductance mediated by basolateral K_{ir} channels requires $K_{ir}5.1$ subunit for trafficking of $K_{ir}4.1$ subunit towards the plasma membrane and compensatory overexpression of homomeric $K_{ir}4.1$ observed in $K_{ir}5.1$ knockout rats did not restore electrolyte balance [35]. Taken together these results indicate that both $K_{ir}4.1$ and $K_{ir}5.1$ are essential for proper inward rectification and basolateral potassium conductance along the distal nephron.

DIETARY EFFECTS

The thiazide-sensitive NCC is sodium/chloride transporter localized to the apical membrane of the whole DCT, and ENaC channel, which expression begins at the late segments of DCT (DCT2; where both NCC and ENaC are present) and continues throughout the rest of the aldosterone-sensitive distal nephron, are the major contributors to sodium reabsorption at these sites and are involved in the final step of the blood pressure regulation in the kidney [36,37]. Dietary potassium intake has antihypertensive effects and improves cardiovascular outcomes [2,38]. Recent studies provide insights into the effect of high K^+ diet on the basolateral $K_{ir}4.1$ and $K_{ir}4.1/K_{ir}5.1$ channels in both DCT and CCD [39,40]. It was reported that high K^+ chow (5%; exact diet composition and chloride level were not disclosed) inhibited, and conversely, K^+ deficient chow (<0.001%) activated the $K_{ir}4.1/K_{ir}5.1$ heteromer in the DCT [40]. Furthermore, it was shown that high K^+ intake promoted an inhibition, whereas low K^+ intake increased the abundance of the expression in NCC and sodium transport in DCT. In contrast, dietary potassium did not have any effects on NCC expression in kidney-specific $K_{ir}4.1$ knockout mice [40]. Opposed to the inhibitory effects of high consumption on $K_{ir}4.1/K_{ir}5.1$ channels in DCT, treatment of mice with high K^+ chow (6% K^+ and either high (5%) or regular Cl^- (0.5%)) elicited an increase of $K_{ir}4.1/K_{ir}5.1$ channels activity as well as subsequent Na^+ transport through ENaC in the CCD principal cells (Table 1). Furthermore, stimulation of aldosterone signaling by Deoxycorticosterone acetate (DOCA) recapitulated the effects of high K^+ diet on $K_{ir}4.1/K_{ir}5.1$ channels in CCD [39]. The same studies also provide evidence that the increase in sodium content (from 0.3% to 1.6% NaCl) resulted in the reduction in basolateral K^+ -selective conductance in CCD likely reflecting reduced circulating aldosterone levels. Interestingly, earlier studies by Lachleb et al. showed that dietary potassium intake (either 8% K^+ , 0.3% Na^+ or 0% K^+ , 0.3% Na^+) had no influence on the properties of $K_{ir}4.1/K_{ir}5.1$ channels, when compared to the regular diet (0.6 K^+ , 0.3% Na^+), although there was a notable tendency of a higher $K_{ir}4.1/K_{ir}5.1$ activity on high K^+ compared to the low K^+ state. Furthermore, a Na^+ -depleted diet (0.09% Na^+ , 0.6% K^+) moderately increased its open probability [41].

MOLECULAR AND CELLULAR SIGNALING MECHANISMS CONTROLLING $K_{ir}4.1/K_{ir}5.1$ CHANNELS

Multiple factors regulate basolateral potassium channels coupled with the apical transport process in distal kidney tubules to regulate K^+ homeostasis in the body. Imbalance in basolateral potassium sensing promote strong changes in serum concentrations and often leading to hypokalemia, or hyperkalemia. Generally, basolateral K^+ conductance is higher than the apical one and possibly plays a dominant role in the control of potassium balance [42]. Functionally, $K_{ir}4.1/K_{ir}5.1$ channel recycles K^+ ions across the basolateral membrane, moved into the cell by the Na^+/K^+ -ATPase, and thus setting a negative basolateral membrane potential to drive Na^+ reabsorption and control K^+ secretion in DCT and CCD [3,4]. Using the specific deletion of $K_{ir}4.1$ gene in the kidney tubules (part of the thick ascending limb (TAL), DCT, the connecting tubule (CNT) and CCD) Cuevas et al. shows that $K_{ir}4.1/K_{ir}5.1$ channel is required to sense and control plasma K^+ as well as modulate NCC-mediated NaCl

transport in DCT [43]. Similarly, to $K_{ir}4.1$ knockout, the deletion of $K_{ir}5.1$ in mice promotes hypokalemia, associated with increased renal K^+ excretion [32].

Phosphatidylinositol 4,5-bisphosphate (PIP_2) is considered as major specific physiological activator of almost all K_{ir} channels since these channels have several conserved PIP_2 -binding sites [44]. Interestingly, the deletion of 6 amino acids in the transmembrane domain 2 of $K_{ir}5.1$, which is localized within the region of the PIP_2 binding site, resulted in a complete knock out of this protein and a striking severe cardiorenal phenotype [35]. It was also reported that dopamine, that can induce stimulation of PIP_2 hydrolysis and subsequent activation of PKC [45], inhibits $K_{ir}4.1/K_{ir}5.1$ channels activity through the D2-like receptors [46]. PIP_2 and other phosphatidylinositides are essential regulators of renal ion channels [47–50], and additional studies are required to address potential modulation of $K_{ir}4.1$ and $K_{ir}4.1/K_{ir}5.1$ channels by phosphatidylinositides. Opposite to dopamine inhibitory effect, insulin and, to a lesser extent, IGF-1 can activate $K_{ir}4.1/K_{ir}5.1$ channel activity and increase open probability triggering hyperpolarization of the basolateral membrane and facilitating sodium reabsorption [26].

Angiotensin II (Ang II) and aldosterone, main components of the renin–angiotensin–aldosterone system are well known factors mediating apical K^+ channel excretion [51,52]. Both Ang II and aldosterone, regulate through corresponding receptors (angiotensin (AT_1 and AT_2) and mineralocorticoid (MR) receptors, respectively) extracellular fluid volume and plasma K^+ levels by controlling ion channels and transporters in the distal nephron. The plasma K^+ concentration is recognized as an important regulator of renal ion transport mechanisms, and it is believed that $K_{ir}4.1/K_{ir}5.1$ channels play important role in sensing the changes in plasma K^+ levels [43,53–56]. Importantly, changes in plasma K^+ levels can modulate sodium absorption, including NCC-mediated transport in DCT, independently of aldosterone. Wu et al. recently attempted to delineate a possible signaling pathway which mediates the effect of high K^+ diet on $K_{ir}4.1/K_{ir}5.1$ and NCC activity in DCT and tested contribution of Ang II-mediated pathway. While Ang II failed to affect channel activity at the baseline, the hormone inhibited $K_{ir}4.1/K_{ir}5.1$ in the presence of AT_1R blocker, losartan, suggesting that AT_2R is responsible for mediating the inhibitory effect of Ang II on basolateral K^+ channels in the DCT [57]. These data are consistent with previously reported findings from the same group that increased dietary K^+ intake inhibits the $K_{ir}4.1/K_{ir}5.1$ channels [40]. However, as discussed in the accompanying editorial commentary by Patel and Hussain [58], there seems to be a disconnect between the acute patch-clamp experiment and the 4-day *in vivo* renal clearance studies.

$K_{ir}4.1/K_{ir}5.1$ REGULATION OF BLOOD PRESSURE

The expression of $K_{ir}4.1/K_{ir}5.1$ channels in kidney tubules directly correlates with all main sodium pathways and functionally bound to sodium transport mediated by NKCC2 (in TAL), NCC (DCT) and ENaC (DCT2 and CCD). The full blockade or knockout of renal $K_{ir}4.1/K_{ir}5.1$ channels depolarize basolateral membrane in all described nephron segments and could be considered as equivalent to antihypertensive treatment by three types of diuretics (loop (TAL; furosemide), thiazide (NCC; hydrochlorothiazide) and potassium-sparing (CCD; amiloride)) at the same time. Recent studies using genetically modified

animal research models reveal relation of these channels to the blood pressure regulation. On the genetic level, silencing of $K_{ir}4.1$ gene strongly associated with neurological pathologies, like ataxia and other, as well as early mortality. In contrast, the mutation in $K_{ir}5.1$ did not result in mortality or any visible neurological pathologies present in $K_{ir}4.1$ phenotype [32,35]. To demonstrate the functional importance of $K_{ir}4.1/K_{ir}5.1$ in blood pressure regulation and potential treatment of hypertension, we created the knockout of $K_{ir}5.1$ in Dahl salt-sensitive (SS) rats [35]. The deletion of $K_{ir}5.1$ channel promotes not only the attenuation in basal mean arterial pressure in Dahl SS rats but completely prevent from the development of salt-induced hypertension and renal damage following high salt diet when animal's diet was supplemented with high potassium. High potassium nutritional content is necessary for $K_{ir}5.1$ knockout survival, since the deletion of the $K_{ir}4.1/K_{ir}5.1$ channel triggered salt wasting phenotype resulted in hypokalemia, similarly to the phenotype observed in $K_{ir}4.1$ knockout, which further in combination with elevated diuresis triggered rapid mortality during a high salt challenge. Overall, these results indicate that the combination of two key factors, high potassium diet and control of renal basolateral conductance or $K_{ir}4.1/K_{ir}5.1$ channel activity, have enormous potential as a means to reduce blood pressure and control hypertension. The broad significance of this study is the identification of the indispensable importance of $K_{ir}4.1/K_{ir}5.1$ channels in the development and pathology of salt-sensitive hypertension.

CONCLUSION

The blood pressure associated with the renal regulation of fluid and electrolyte balance. As was discussed above, remodeling of inward rectifier K^+ channels function and particularly basolateral $K_{ir}4.1/K_{ir}5.1$ has the potential for tuning chronic blood pressure and, thus, developing new pharmacological tools for treatment of hypertension. Renal basolateral $K_{ir}4.1/K_{ir}5.1$ channels represent potential targets for therapeutic intervention in the fight against serum potassium disturbances. Despite all recent knowledge in our understanding of the importance of the basolateral $K_{ir}4.1/K_{ir}5.1$ channel for K^+ homeostasis, the molecular mechanisms and complete scheme of the regulation of this channel function along the distal nephron in health and disease conditions requires future extensive attention.

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REFERENCES AND RECOMMENDED READING

1. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med* 2014, 371:601–611. [PubMed: 25119606]
2. Staruschenko A Beneficial effects of high potassium: contribution of renal basolateral K^+ channels. *Hypertension* 2018, 71:DOI: 10.1161/HYPERTENSIONAHA.118.10267.* This is a recent review

summarizing effects of high K^+ diet, including DASH, specifically focusing on its effects on $K_{ir}4.1/K_{ir}5.1$ channels.

3. Palygin O, Pochynyuk O, Staruschenko A. Role and mechanisms of regulation of the basolateral $K_{ir}4.1/K_{ir}5.1$ K^+ channels in the distal tubules. *Acta Physiol* 2017, 219:260–273.
4. Wang WH. Basolateral Kir4.1 activity in the distal convoluted tubule regulates K secretion by determining NaCl cotransporter activity. *Curr Opin Nephrol Hypertens* 2016.
5. Su XT, Wang WH. The expression, regulation, and function of $K_{ir}4.1$ (Kcnj10) in the mammalian kidney. *Am J Physiol Renal Physiol* 2016, 311:F12–15. [PubMed: 27122539]
6. Miller C An overview of the potassium channel family. *Genome Biol* 2000, 1:reviews0004.1
7. McNicholas CM, Wang W, Ho K, Hebert SC, Giebisch G. Regulation of ROMK1 K^+ channel activity involves phosphorylation processes. *Proc Natl Acad Sci U S A* 1994, 91:8077–8081. [PubMed: 8058760]
8. Tanaka-Kunishima M, Ishida Y, Takahashi K, Honda M, Oonuma T. Ancient intron insertion sites and palindromic genomic duplication evolutionally shapes an elementally functioning membrane protein family. *BMC Evol Biol* 2007, 7:143. [PubMed: 17708769]
9. Pattnaik BR, Asuma MP, Spott R, Pillers DA. Genetic defects in the hotspot of inwardly rectifying K^+ (Kir) channels and their metabolic consequences: a review. *Mol Genet Metab* 2012, 105:64–72. [PubMed: 22079268]
10. Hebert SC, Desir G, Giebisch G, Wang W. Molecular diversity and regulation of renal potassium channels. *Physiol Rev* 2005, 85:319–371. [PubMed: 15618483]
11. Mark MD, Herlitz S. G-protein mediated gating of inward-rectifier K^+ channels. *Eur J Biochem* 2000, 267:5830–5836. [PubMed: 10998041]
12. Welling PA. Roles and Regulation of Renal K Channels. *Annu Rev Physiol* 2016, 78:415–435. [PubMed: 26654186]
13. Chen L, Lee JW, Chou C- L et al. Transcriptomes of major renal collecting duct cell types in mouse identified by single-cell RNA-seq. *Proc Natl Acad Sci U S A* 2017, 114:E9989–E9998., [PubMed: 29089413] * This is a first single-cell RNA-sequencing analysis of both the intercalated cells and principal cells of the collecting duct, which might be helpful for future studies of physiological regulation and pathophysiology of the collecting duct.
14. Puissant MM, Mouradian GC, Jr., Liu P, Hodges MR. Identifying Candidate Genes that Underlie Cellular pH Sensitivity in Serotonin Neurons Using Transcriptomics: A Potential Role for Kir5.1 Channels. *Front Cell Neurosci* 2017, 11:34. [PubMed: 28270749]
15. Cui Y, Yang Y, Ni Z, et al. Astroglial $K_{ir}4.1$ in the lateral habenula drives neuronal bursts in depression. *Nature* 2018, 554:323–327. [PubMed: 29446379]
16. Du M, Li J, Chen L, Yu Y, Wu Y. Astrocytic $K_{ir}4.1$ channels and gap junctions account for spontaneous epileptic seizure. *PLoS Comput Biol* 2018, 14:e1005877. [PubMed: 29590095]
17. Kelley KW, Ben Haim L, Schirmer L, et al. $K_{ir}4.1$ -Dependent Astrocyte-Fast Motor Neuron Interactions Are Required for Peak Strength. *Neuron* 2018.
18. Brasko C, Hawkins V, De La Rocha IC, Butt AM. Expression of $K_{ir}4.1$ and $K_{ir}5.1$ inwardly rectifying potassium channels in oligodendrocytes, the myelinating cells of the CNS. *Brain Struct Funct* 2017, 222:41–59. [PubMed: 26879293]
19. Pessia M, Tucker SJ, Lee K, Bond CT, Adelman JP. Subunit positional effects revealed by novel heteromeric inwardly rectifying K^+ channels. *EMBO J* 1996, 15:2980–2987. [PubMed: 8670799]
20. Mendez-Gonzalez MP, Kucheryavkh YV, Zayas-Santiago A, Velez-Carrasco W, Maldonado-Martinez G, Cubano LA, Nichols CG, Skatchkov SN, Eaton MJ. Novel KCNJ10 Gene Variations Compromise Function of Inwardly Rectifying Potassium Channel 4.1. *J Biol Chem* 2016, 291:7716–7726. [PubMed: 26867573]
21. Palygin O, Pochynyuk O, Staruschenko A. Role and mechanisms of regulation of the basolateral $K_{ir}4.1/K_{ir}5.1$ K^+ channels in the distal tubules. *Acta Physiol* 2017, 219:260–273.
22. Wang WH. Basolateral Kir4.1 activity in the distal convoluted tubule regulates K secretion by determining NaCl cotransporter activity. *Curr Opin Nephrol Hypertens* 2016, 25:429–435. [PubMed: 27306796]
23. Lachheb S, Cluzeaud F, Bens M, Genete M, Hibino H, Lourdel S, Kurachi Y, Vandewalle A, Teulon J, Paulais M. $K_{ir}4.1/K_{ir}5.1$ channel forms the major K^+ channel in the basolateral

- membrane of mouse renal collecting duct principal cells. *Am J Physiol Renal Physiol* 2008, 294:F1398–1407. [PubMed: 18367659]
24. Raphemot R, Kadakia RJ, Olsen ML, Banerjee S, Days E, Smith SS, Weaver CD, Denton JS. Development and validation of fluorescence-based and automated patch clamp-based functional assays for the inward rectifier potassium channel $K_{ir}4.1$. *Assay Drug Dev Technol* 2013, 11:532–543. [PubMed: 24266659]
 25. Kinboshi M, Mukai T, Nagao Y, et al. Inhibition of Inwardly Rectifying Potassium (K_{ir}) 4.1 Channels Facilitates Brain-Derived Neurotrophic Factor (BDNF) Expression in Astrocytes. *Front Mol Neurosci* 2017, 10:408. [PubMed: 29358904]
 26. Zaika O, Palygin O, Tomilin V, Mamenko M, Staruschenko A, Pochynyuk O. Insulin and IGF-1 activate $K_{ir}4.1/5.1$ channels in cortical collecting duct principal cells to control basolateral membrane voltage. *Am J Physiol Renal Physiol* 2016, 310:F311–321. [PubMed: 26632606]
 27. Jensen BP, Roberts RL, Vyas R, Bonke G, Jardine DL, Begg EJ. Influence of ABCB1 (P-glycoprotein) haplotypes on nortriptyline pharmacokinetics and nortriptyline-induced postural hypotension in healthy volunteers. *Br J Clin Pharmacol* 2012, 73:619–628. [PubMed: 21999196]
 28. Georgotas A, McCue RE, Friedman E, Cooper TB. A placebo-controlled comparison of the effect of nortriptyline and phenelzine on orthostatic hypotension in elderly depressed patients. *J Clin Psychopharmacol* 1987, 7:413–416. [PubMed: 3323263]
 29. Scholl UI, Choi M, Liu T, Ramaekers VT, Hausler MG, Grimmer J, Tobe SW, Farhi A, Nelson-Williams C, Lifton RP. Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in *KCNJ10*. *Proc Natl Acad Sci U S A* 2009, 106:5842–5847. [PubMed: 19289823]
 30. Bockenhauer D, Feather S, Stanescu HC, et al. Epilepsy, ataxia, sensorineural deafness, tubulopathy, and *KCNJ10* mutations. *N Engl J Med* 2009, 360:1960–1970. [PubMed: 19420365]
 31. Juang JM, Lu TP, Lai LC, et al. Disease-targeted sequencing of ion channel genes identifies de novo mutations in patients with non-familial Brugada syndrome. *Sci Rep* 2014, 4:6733. [PubMed: 25339316]
 32. Paulais M, Bloch-Faure M, Picard N, et al. Renal phenotype in mice lacking the $K_{ir}5.1$ (*Kcnj16*) K⁺ channel subunit contrasts with that observed in SeSAME/EAST syndrome. *Proc Natl Acad Sci U S A* 2011, 108:10361–10366. [PubMed: 21633011]
 33. Kompatscher A, de Baaij JHF, Aboudehen K, Hoefnagels A, Igarashi P, Bindels RJM, Veenstra GJC, Hoenderop JGJ. Loss of transcriptional activation of the potassium channel $K_{ir}5.1$ by HNF1 β drives autosomal dominant tubulointerstitial kidney disease. *Kidney Int* 2017, 92:1145–1156. [PubMed: 28577853] * This research paper revealed new mechanisms of HNF1 β transcription factor in regulation of $K_{ir}5.1$ abundance and activity in the kidney and its relation to hypokalemia and hypomagnesemia in patients with autosomal dominant tubulointerstitial kidney disease.
 34. Reichold M, Zdebek AA, Lieberer E, et al. *KCNJ10* gene mutations causing EAST syndrome (epilepsy, ataxia, sensorineural deafness, and tubulopathy) disrupt channel function. *Proc Natl Acad Sci U S A* 2010, 107:14490–14495. [PubMed: 20651251]
 35. Palygin O, Levchenko V, Ilatovskaya DV, Pavlov TS, Pochynyuk OM, Jacob HJ, Geurts AM, Hodges MR, Staruschenko A. Essential role of $K_{ir}5.1$ channels in renal salt handling and blood pressure control. *JCI Insight* 2017, 2:e92331. ** This research paper utilizes new $K_{ir}5.1$ knockout in the Dahl salt-sensitive rat model and describe the contribution of $K_{ir}5.1$ in regulation of blood potassium, salt handling and hypertension.
 36. Wynne BM, Mistry AC, Al-Khalili O, Mallick R, Theilig F, Eaton DC, Hoover RS. Aldosterone Modulates the Association between NCC and ENaC. *Sci Rep* 2017, 7:4149. [PubMed: 28646163]
 37. Subramanya AR, Ellison DH: Distal convoluted tubule. *Clin J Am Soc Nephrol* 2014, 9:2147–2163. [PubMed: 24855283]
 38. McDonough AA, Veiras LC, Guevara CA, Ralph DL. Cardiovascular benefits associated with higher dietary K^{+} vs. lower dietary Na^{+} : evidence from population and mechanistic studies. *Am J Physiol Endocrinol Metab* 2017, 312:E348–E356. [PubMed: 28174181]
 39. Tomilin VN, Zaika O, Subramanya AR, Pochynyuk O. Dietary K^{+} and Cl^{-} independently regulate basolateral conductance in principal and intercalated cells of the collecting duct. *Pflügers Arch*

2018, 470:339–353., [PubMed: 29134279] * This research paper uses precise electrophysiological analyses of kidney collecting duct cells and describing fine-tuning mechanisms of urinary excretion of electrolytes dependence on dietary potassium and chloride intake.

40. Wang MX, Cuevas CA, Su XT, Wu P, Gao ZX, Lin DH, McCormick JA, Yang CL, Wang WH, Ellison DH. Potassium intake modulates the thiazide-sensitive sodium-chloride cotransporter (NCC) activity via the $K_{ir}4.1$ potassium channel. *Kidney Int* 2018, 93:893–902., [PubMed: 29310825] * This research paper uses recently generated kidney-specific $K_{ir}4.1$ knockout to reveal the role of $K_{ir}4.1/K_{ir}5.1$ distal tubule channels in mediating the effect of potassium intake on NCC activity and potassium homeostasis.
41. Lachheb S, Cluzeaud F6, Bens M, Genete M, Hibino H, Lourdel Sp, Kurachi Y, Vandewalle A, Teulon J, Paulais M. $K_{ir}4.1/K_{ir}5.1$ channel forms the major K^+ channel in the basolateral membrane of mouse renal collecting duct principal cells. *Am J Physiol Renal Physiol* 2008, 294:F1398–F1407. [PubMed: 18367659]
42. Sepulveda FV, Pablo Cid L, Teulon J, Niemeyer MI. Molecular aspects of structure, gating, and physiology of pH-sensitive background K2P and Kir K^+ -transport channels. *Physiol Rev* 2015, 95:179–217. [PubMed: 25540142]
43. Cuevas CA, Su XT, Wang MX, Terker AS, Lin DH, McCormick JA, Yang CL, Ellison DH, Wang WH. Potassium sensing by renal distal tubules requires $K_{ir}4.1$. *J Am Soc Nephrol* 2017, 28:1814–1825., [PubMed: 28052988] ** This research paper described the role of $K_{ir}4.1$ protein and corresponding $K_{ir}4.1/K_{ir}5.1$ channels in dynamic process of potassium sensing and coupling this signal to the apical transport processes in renal distal tubule.
44. Hansen SB, Tao X, MacKinnon R. Structural basis of PIP2 activation of the classical inward rectifier K^+ channel Kir2.2. *Nature* 2011, 477:495–498. [PubMed: 21874019]
45. Cadet JL, Jayanthi S, McCoy MT, Beauvais G, Cai NS. Dopamine D1 receptors, regulation of gene expression in the brain, and neurodegeneration. *CNS Neurol Disord Drug Targets* 2010, 9:526–538. [PubMed: 20632973]
46. Zaika OL, Mamenko M, Palygin O, Boukelmoune N, Staruschenko A, Pochynyuk O. Direct inhibition of basolateral $K_{ir}4.1/5.1$ and $K_{ir}4.1$ channels in the cortical collecting duct by dopamine. *Am J Physiol Renal Physiol* 2013, 305:F1277–1287. [PubMed: 23986512]
47. Pochynyuk O, Tong Q, Medina J, Vandewalle A, Staruschenko A, Bugaj V, Stockand JD. Molecular determinants of $PI(4,5)P_2$ and $PI(3,4,5)P_3$ regulation of the epithelial Na^+ channel. *J Gen Physiol* 2007, 130:399–413. [PubMed: 17893193]
48. Pochynyuk O, Tong Q, Staruschenko A, Ma HP, Stockand JD. Regulation of the epithelial Na^+ channel (ENaC) by phosphatidylinositides. *Am J Physiol Renal Physiol* 2006, 290:F949–F957. [PubMed: 16601296]
49. Zeng WZ, Li XJ, Hilgemann DW, Huang CL. Protein kinase C inhibits ROMK1 channel activity via a phosphatidylinositol 4,5-bisphosphate-dependent mechanism. *J Biol Chem* 2003, 278:16852–16856. [PubMed: 12615924]
50. An SW, Cha SK, Yoon J, Chang S, Ross EM, Huang CL. WNK1 promotes PIP_2 synthesis to coordinate growth factor and GPCR-Gq signaling. *Curr Biol* 2011, 21:1979–1987. [PubMed: 22119528]
51. Wang WH, Giebisch G. Regulation of potassium (K) handling in the renal collecting duct. *Pflügers Arch* 2009, 458:157–168. [PubMed: 18839206]
52. McDonough AA, Youn JH. Potassium Homeostasis: The Knowns, the Unknowns, and the Health Benefits. *Physiology* 2017, 32:100–111. [PubMed: 28202621]
53. Sorensen MV, Grossmann S, Roesinger M, Gresko N, Todkar AP, Barmettler G, Ziegler U, Odermatt A, Löffing-Cueni D, Löffing J. Rapid dephosphorylation of the renal sodium chloride cotransporter in response to oral potassium intake in mice. *Kidney Int* 2013, 83:811–824. [PubMed: 23447069]
54. Ellison DH, Terker AS, Gamba G. Potassium and its discontents: new insight, new treatments. *J Am Soc Nephrol* 2016, 27:981–989. [PubMed: 26510885]
55. Terker AS, Zhang C, McCormick JA, et al. Potassium modulates electrolyte balance and blood pressure through effects on distal cell voltage and chloride. *Cell Metab* 2015, 21:39–50. [PubMed: 25565204]

56. Castaneda-Bueno M, Cervantes-Perez LG, Rojas-Vega L, Arroyo-Garza I, Vazquez N, Moreno E, Gamba G. Modulation of NCC activity by low and high K^+ intake: insights into the signaling pathways involved. *Am J Physiol Renal Physiol* 2014, 306:F1507–1519. [PubMed: 24761002]
57. Wu P, Gao ZX, Duan XP, Su XT, Wang MX, Lin DH, Gu R, Wang WH. AT2R (Angiotensin II Type 2 Receptor)-Mediated Regulation of NCC (Na-Cl Cotransporter) and Renal K Excretion Depends on the K Channel, $K_{ir}4.1$. *Hypertension* 2018, 71:622–630. [PubMed: 29483225]
58. Patel S, Hussain T. Role of AT2R (Angiotensin Type 2 Receptor) in Maintaining Sodium-Potassium Balance. *Hypertension* 2018, 71:563–565. [PubMed: 29483226]

KEY POINTS

- Renal basolateral K_{ir} channels are critical in the control of electrolyte homeostasis in the kidney and blood pressure
- $K_{ir}4.1$ and $K_{ir}5.1$ (encoded by *Kcnj10* and *Kcnj16*, respectively) form heteromeric channel ($K_{ir}4.1/K_{ir}5.1$) in the distal convoluted tubules and principal cells of collecting duct
- $K_{ir}4.1$ and $K_{ir}4.1/K_{ir}5.1$ are regulated by dietary potassium content as well as various hormonal and metabolic factors

FIGURE 1.A schematic of phylogenetic groups of K⁺ channels.

Table 1.

Scheme of regulation of $K_{ir}4.1/K_{ir}5.1$ channels in DCT and CCD by high K^+ diet based on recent studies by Wang et al. [40] and Tomilin et al. [39].

High K^+ diet	
DCT	CCD
$K_{ir}4.1/K_{ir}5.1 \downarrow$	$K_{ir}4.1/K_{ir}5.1 \uparrow$
$NCC \downarrow$ ENaC ?	ENaC $\uparrow$
ROMK $\uparrow$	ROMK $\uparrow$
CLC-K2/b $\downarrow$	CLC-K2/b $\downarrow$