Beneficial Effects of High Potassium
Contribution of Renal Basolateral K^+ Channels

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The prevalence of hypertension in the United States is estimated to have reached 85.7 million adults[1] without taking into account new American College of Cardiology/American Heart Association guideline for the prevention, detection, evaluation, and management of high blood pressure,[2] which is certain to increase this estimate. Hypertension is a major risk factor for stroke, coronary heart disease, and renal failure. Additionally, high blood pressure (BP) increases cardiovascular mortality rates and progression of many other chronic diseases. Salt and water handling by the kidney directly affects BP, whereas renal ion channels and transporters maintain electrolyte homeostasis.[3,4]

Epidemiological and anthropological studies suggest that in isolated societies with diets composed primarily of fruits, vegetables, and nuts, hypertension affects only 1% of the population. In contrast, in countries consuming a modern Western diet high in processed foods and dietary sodium, the prevalence of hypertension is as high as 30%. This effect of the Western diet is not solely attributed to high sodium content but rather the dramatically decreased dietary potassium-to-sodium ratio. In industrialized countries, the daily intakes of potassium and sodium are ≈30 to 50 and 80 to 250 mmol per day, respectively. This is in sharp contrast with isolated or primitive societies, having the daily rates of 150 to 290 mmol for potassium and 20 to 40 mmol per day for sodium.[5] Therefore, estimated potassium-to-sodium intake ratios range from 0.12 to 0.63 for industrialized societies and 3.8 to 14.5 for isolated societies. According to the National Health and Nutrition Examination Survey, only about one tenth of US adults have potassium-to-sodium intake ratios consistent with the World Health Organization guidelines for reduced risk of mortality.[6]

Potassium is the most abundant intracellular ion, and its role in the regulation of BP is well established. Dietary supplementation with potassium can lower BP in normal and hypertensive patients. Potassium channels, along with Na^+-K^+-ATPase (also known as Na^+-K^+ pump), are central in determining the resting membrane potential and cell volume. Because the concentration of potassium is much higher in intracellular than extracellular medium, activation, and consecutive opening of potassium channels, results in hyperpolarization of the plasma membrane, thereby changing an electrogenic driving force for Na^+ reabsorption in the distal nephron. The critical role of inward-rectifying potassium (K_{ir}) channels in sodium and potassium homeostasis and the association of renal basolateral K_{ir} channels with BP regulation is the focus of this brief review.

Role of Potassium in the Prevention and Treatment of Hypertension

It is well recognized that higher levels of sodium intake are associated with elevated BP.[7] It was predicted more than a century ago that the effect of sodium on BP is dependent on diet composition, specifically potassium content.[8,9] Herbert Langford, who was among the first to suggest that differences in potassium consumption account for variations in the incidence of high BP among ethnic groups, described[10] "The interaction of sodium and potassium was the focus of von Bunge's studies in Germany in the mid-1870s and remains a topic of interest. Von Bunge was concerned that the natriuresis produced by potassium would lead to serious disease."[11] Studies in the 20th century followed to provide further evidence of the critical role of potassium supplementation on BP. Addison evaluated the actions of potassium and sodium chloride in humans, including himself in the study. He reported in 1928 that potassium administration could lower the elevated BP and proposed that hypertension is because of a low-potassium diet and excess sodium chloride consumption.[12]

The landmark DASH diet (Dietary Approaches to Stop Hypertension)[13,14]—a diet low in sodium and replete with potassium, calcium, and magnesium—is now being recommended as a standard lifestyle modification for patients with hypertension or other cardiovascular risk factors. The DASH diet recommends a daily intake of 4.7 g of potassium (the Table includes examples of foods rich in potassium). The standardized, worldwide epidemiological INTERSALT study (International Cooperative Study on Salt, Other Factors, and Blood Pressure) also provides evidence that potassium intake is an essential determinant of BP, independent of sodium.[15] A recent large-scale PURE study (Prospective Urban Rural Epidemiology) examined the association of urinary sodium and potassium excretion with BP in >100 000 participants and reported that higher potassium excretion is associated with a lower risk of death and major cardiovascular complications.[16] The PURE investigators also noted an inverse relation between potassium excretion and systolic BP, with each gram increment in potassium excretion per day resulting in a 1.08-mm Hg decrease in systolic BP (1 g sodium excretion produced an increment of 2.11 mm Hg). The highest BP was

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Table. Examples of Common Potassium-Rich Foods

Name	Potassium Content, mg (per 100 g)	Citation
Apricots	259	USDA 09021, apricots, raw
Avocados	485	USDA 09037, avocados, raw, all commercial varieties
Bananas	358	USDA 09040, bananas, raw
Beans	454	USDA 16051, beans, white, mature seeds, canned
Coconut water	250	USDA 12119, nuts, coconut water (liquid from coconut)
Dairy milk (especially fat free or low fat)	156	USDA 01151, milk, nonfat, fluid, without added vitamin A or vitamin D
Fat-free yogurt	255	USDA 01118, yogurt, plain, skim milk
Fish	252	USDA 15117, fish, tuna, fresh, bluefin, raw
Grapefruit	135	USDA 09119, grapefruit, raw, pink and red, all areas
Lima beans	220	USDA 16073, lima beans, large, mature seeds, canned
Melon	267	USDA 09181, melons, cantaloupe, raw
Mushrooms	318	USDA 11260, mushrooms, white, raw
Oranges	181	USDA 09200, oranges, raw, all commercial varieties
Peas	200	USDA 11300, peas, edible podded, raw
Pomegranates	236	USDA 09286, pomegranates, raw
Potatoes	337	USDA 11507, sweet potato, raw, unprepared
Prunes	732	USDA 09291, plums, dried (prunes), uncooked
Raisins and dates	825	USDA 09299, raisins, seeded
Spinach	558	USDA 11457, spinach, raw
Tomatoes	237	USDA 11529, tomatoes, red, ripe, raw, year-round average
Watermelon	112	USDA 09326, watermelon, raw

USDA indicates the United States Department of Agriculture.

observed in individuals with the maximum sodium excretion combined with the lowest potassium excretion.[8] Similarly, a cluster-randomized controlled trial, in which participants increased potassium consumption and reduced sodium consumption, showed reduced cardiovascular mortality among those assigned to the higher potassium group.[17]

Animal studies using established hypertensive models further provide critical evidence of potassium in the control of BP. In the 1950s, Meneely et al[18,19] found that potassium administration modulated BP and significantly enhanced survival of rats fed high-NaCl diet. In another classical work, Dahl et al[20] found that the life expectancy of the rats, although shortened by high doses of sodium, increased back toward untreated values by concurrent supplementation with potassium. After establishing that the dietary Na/K ratio is crucial for long-term survival, Dahl et al went on to test the effect of different dietary Na/K ratios in hypertension-prone rats. All tested diets had high NaCl content (4.50%) but differed in KC1 concentration. It was concluded that the dietary Na/K molar ratio could be an important determinant of the severity, or even development, of salt-induced hypertension.[20]

Tobian et al further uncovered the benefits of potassium supplementation during the development of hypertension and renal disease. Thus, the addition of 1.36% K^+ to the diet reduced renal lesions (by 50% in the renal cortex, by 30% in the outer medulla, and by 44% in the inner medulla) in high salt-fed Dahl SS (salt sensitive) rats.[21] The added potassium also decreased BP moderately in SHR (spontaneously hypertensive) rats and modestly in Dahl SS rats. Importantly, the high-K^+ diet had a striking effect on mortality in both models. After 17 weeks on a 4% NaCl diet with no added K^+, 20 of 24 SHR rats had died. On the contrary, 49 of 50 rats on the same diet plus 1.36% K^+ were still alive. This resulted in a 98% reduction in mortality rate (Figure 1A).[22] Similarly, after 9 weeks on the high-salt (8% NaCl) diet with no K^+ supplement, 18 of 33 Dahl SS rats had died, whereas only 2 of 45 rats with 1.36% K^+ supplementation had perished (overall, 93% reduction in mortality rate; Figure 1B).[22] These changes in survival rate occurred independently from BP, and it is likely that the majority of these deaths was because of stroke. Furthermore, it was reported that the level of dietary potassium has a marked influence on NaCl sensitivity in SHR rats, which are considered NaCl resistant.[23] Another chronic study of Dahl SS rats fed 1% NaCl with increasing dietary KCl revealed that after 8 months, Dahl SS rats fed 1% NaCl supplemented with 0.7% KCl had significantly increased mean arterial pressure, plasma volume, cardiac output, and renal and cerebral vascular resistance compared with Dahl salt-resistant rats receiving the same diet. All these parameters were significantly reduced, when dietary K^+ supplement was increased to 2.6%.[24]

Providing further evidence supporting the importance of dietary potassium in renal disease and hypertension, it has been reported that potassium depletion and hypokalemia induce renal injury, salt sensitivity, and hypertension in rats.[25,26] For example, Sprague Dawley rats have significant growth retardation, increased renin–angiotensin system activity, tubulointerstitial injury, macrophage infiltration, and early fibrosis when fed a potassium-deficient (<0.05% K^+) diet. Furthermore, these rats had elevated BP and increased salt sensitivity.[25]

In summary, dietary supplementation of potassium can lower BP in human and animal models, especially if they are prone to have salt sensitivity. However, despite the clinical relevance and translational magnitude of these studies, the specific molecular mechanisms underlying the beneficial effects of a high-potassium diet are still not fully understood.

Mechanisms of Regulation of BP by Potassium

There are multiple mechanisms by which potassium may control BP. Here, we will focus on mechanisms mediated by renal tubular K^+ channels in the distal tubules. However, it should be taken into account that other tubular segments

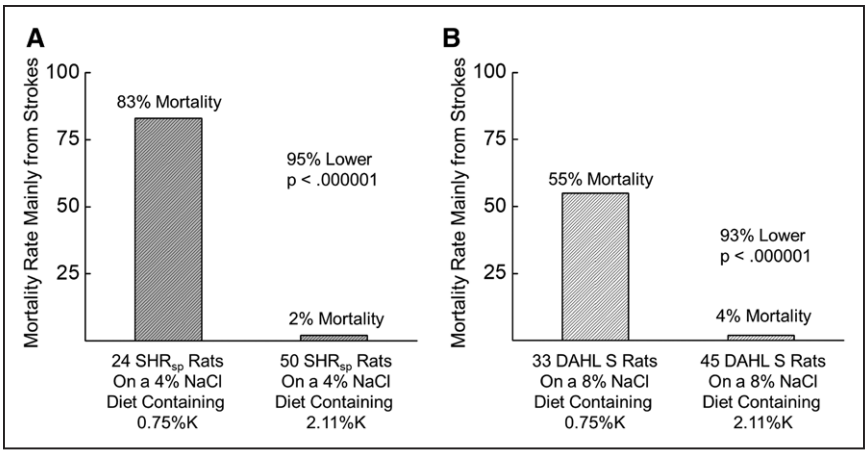

Figure 1. Mortality rate of SHR (spontaneously hypertensive; **A**) and Dahl SS (salt sensitive; **B**) rats challenged with the high-salt diet supplemented with either normal or high dietary K^+ intake. The actual final concentration of K^+ in each diet is listed. For these experiments, SHR rats were fed a 4% NaCl diet for 17 wk, and Dahl SS rats were fed an 8% NaCl diet for 9 wk. Redrawn and adapted from Tobian et al[22] with permission. Copyright © 1985, the American Heart Association, Inc.

also contribute to potassium excretion. For example, recent studies by Wang et al[27] revealed that the activities of NKCC2 (Na^+-K^+-Cl^- cotransporter) and $K_{ir}1.1$ (also known as ROMK [renal outer medullary K^+ channel]) are elevated in mice on a low-Na^+, high-K^+ diet.[28]

Furthermore, renal vascular potassium channels could be involved in the regulation of BP.[29] For instance, small changes in serum potassium can cause endothelium-dependent vasodilation by hyperpolarizing the endothelial and vascular smooth muscle cells. The high-K^+ diet might also improve the vascular integrity on increased tension, as a result of hypertension. In studies of the kidneys of Dahl SS rats on normal and high-K^+ diets, K^+ supplementation prevented the usual thickening of the arteriolar walls of the kidneys in hypertensive rats. Similarly, even during the development of severe hypertension, the high-K^+ diet promoted a substantial reduction of wall thickening in either very large or small arteries of SHR rats.[30]

Potassium Homeostasis in the Kidney and Its Transport in the Distal Tubules

In the kidney, discretionary Na^+ reabsorption and K^+ secretion in the distal nephron and collecting duct is a critical determinant of the pressure–natriuresis relationship, which is of fundamental importance in the long-term control of arterial pressure. The distal convoluted tubule (DCT), connecting tubule, and cortical collecting duct (CCD) have been established as major targets for multiple hormones, also responding to sympathetic nerve stimulation and changes in ion concentrations.[31–33] Figure 2 shows a simplified diagram illustrating water and electrolyte transport in the early (DCT1) and late (DCT2) DCT segments, as well as in the CCD. Although the NCC (Na^+-Cl^- transporter) contributes to sodium reabsorption in both DCT1 and DCT2, DCT2 differs in that the ENaC (epithelial Na^+ channel) also involved in sodium absorption. Additionally, ENaC is the primary channel responsible for sodium transport in the CCD.

The ROMK and the large conductance BK (calcium-activated K^+) are the K^+ channels in the apical membrane serving as the principal pathways for controlled K^+ secretion in the distal nephron (Figure 2). Mutations in the *KCNJ1* gene, encoding $K_{ir}1.1$, cause type II Barter syndrome.[34] Most of these mutations are loss-of-function mutations. Interestingly, screening of subjects of the Framingham Heart Study also identified that variations in *KCNJ1* produce clinically significant BP reductions and protect against the development of hypertension.[35] Zhou et al addressed the role of ROMK by creating a *Kcnj1* knock out in Dahl SS rats ($SS^{ROMK-/-}$).[36,37] The authors demonstrated that the disruption of ROMK channels led to attenuation of salt-sensitive hypertension. It was reported that the survival rate of $SS^{ROMK-/-}$ pups dramatically declined after postnatal day 14, body weight was significantly reduced, volume was severely depleted, whole-blood electrolyte concentration (Na^+, K^+, and Cl^-) was increased, metabolic acidosis was observed, and blood urea nitrogen level was elevated. The heterozygous $SS^{ROMK+/-}$ rats, when challenged with a 4% salt diet, exhibited a reduced BP compared with their wild-type littermates and when fed with an 8% salt diet, the $SS^{ROMK+/-}$ rats showed increased protection from salt-induced BP elevation and signs of protection from renal injury.[38] Subsequent pharmacological studies revealed that chronic inhibition of ROMK not only prevented but also reversed the development of hypertension and end-organ damage in Dahl SS rats.[39]

The role of BK channels in renal K^+ excretion and BP control has also been suggested.[40–42] BK channels are essential for flow-induced K^+ secretion triggered by loop diuretics and high-K^+ diet.[43] BKα-deficient mice exhibited an impaired flow-dependent urinary K^+ secretion and hyperaldosteronism, and it was proposed that upregulation of ROMK may compensate for the absence of functional BK channels.[40] Similarly, deletions of the ancillary $BK\beta_1$ and $BK\beta_4$ subunits also result in deficient renal K^+ excretion, hyperkalemia, primary hyperaldosteronism, and hypertension.[42,44] Further studies revealed that increased tubular flow in the distal nephron activates mechanosensitive Ca^{2+}-permeable TRPV4 (transient receptor potential vanilloid type 4) channel to increase $[Ca^{2+}]_i$ levels and activate BK channels. TRPV4 deletion results in hyperkalemia in response to dietary K^+ load because of renal K^+ retention.[45] Several recent excellent reviews have covered the role of ROMK and BK channels in potassium homeostasis in the kidney in great details.[28,46,47]

Basolateral Potassium Channels in the Distal Tubules

Inward-rectifier potassium channels, $K_{ir}4.1$ and $K_{ir}5.1$ (encoded by *Kcnj10* and *Kcnj16*, respectively), play a dominant role in the control of the resting membrane potential of the basolateral

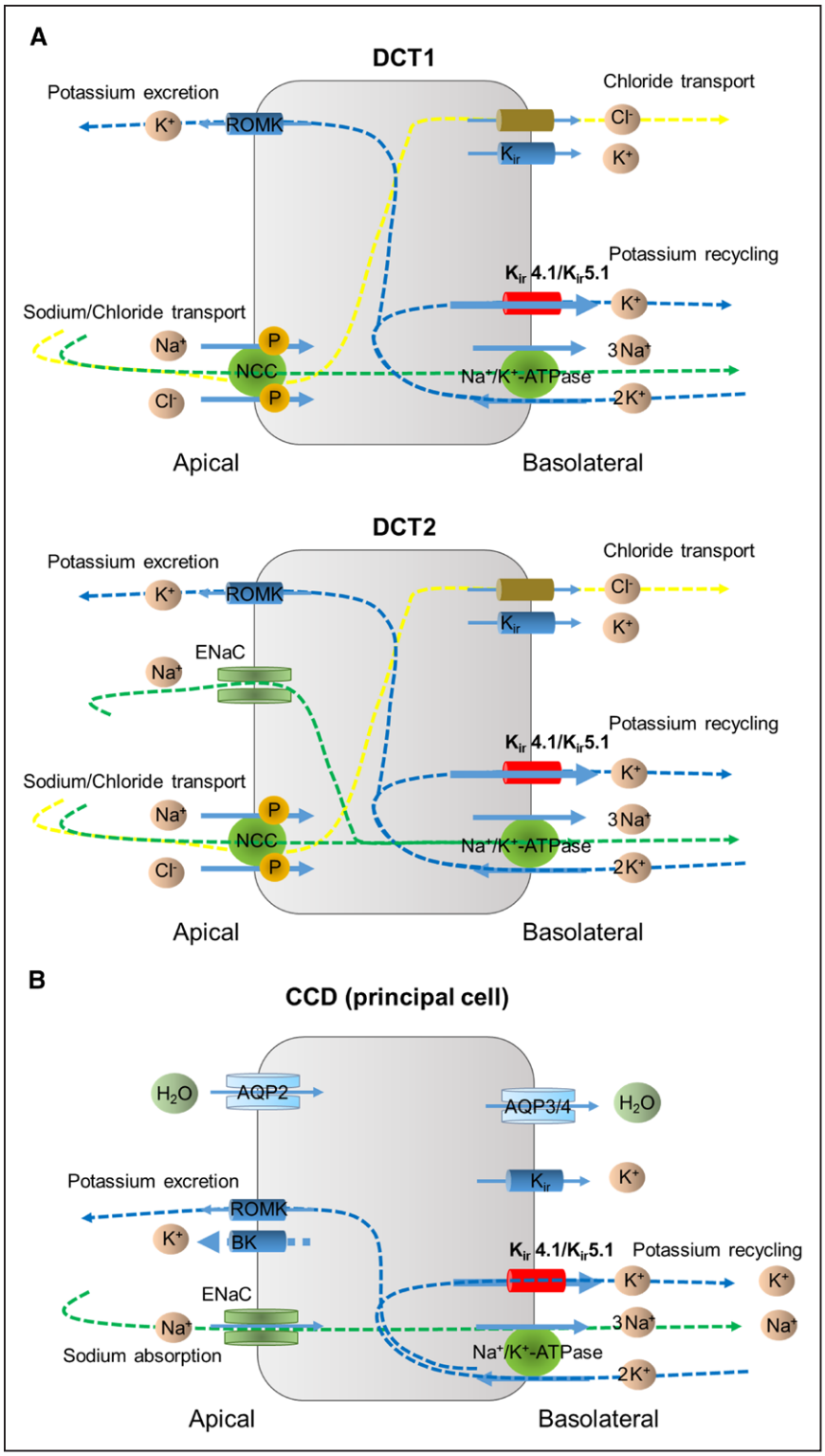

Figure 2. Model of electrolyte transport in the early and late distal convoluted tubules (DCT1 and DCT2, respectively; **A**) and the principal cells of cortical collecting duct (CCD; **B**). BK indicates calcium-activated K^+; ENaC, epithelial Na^+ channel; and ROMK, renal outer medullary K^+ channel.

membrane and transepithelial voltage, thereby modulating water and electrolyte transport in the distal nephron.[48] Shown on Figure 3 are immunostaining images demonstrating $K_{ir}5.1$ (encoded by *Kcnj16*) expression in DCT and CCD and representative single-channel recordings, as well as summarized current–voltage relationships for both homomeric $K_{ir}4.1$ (*Kcnj10*) and heteromeric $K_{ir}4.1/K_{ir}5.1$ (*Kcnj10*/*Kcnj16*) channels. $K_{ir}4.1$ channel subunits can form homomeric channels or instead may polymerize with $K_{ir}5.1$ subunits to form $K_{ir}4.1/K_{ir}5.1$ heteromers.[49] It is established that the $K_{ir}4.1/K_{ir}5.1$ heteromer is the main basolateral K^+ channel in the DCT and CDs.[50–52] This heteromeric conformation has unique properties, including high sensitivity to pH changes within the physiological range.[53–55] Potassium recycling mediated by these channels is necessary to maintain a stable source of extracellular K^+ to perform transcellular Na^+ reabsorption driven by the Na^+/

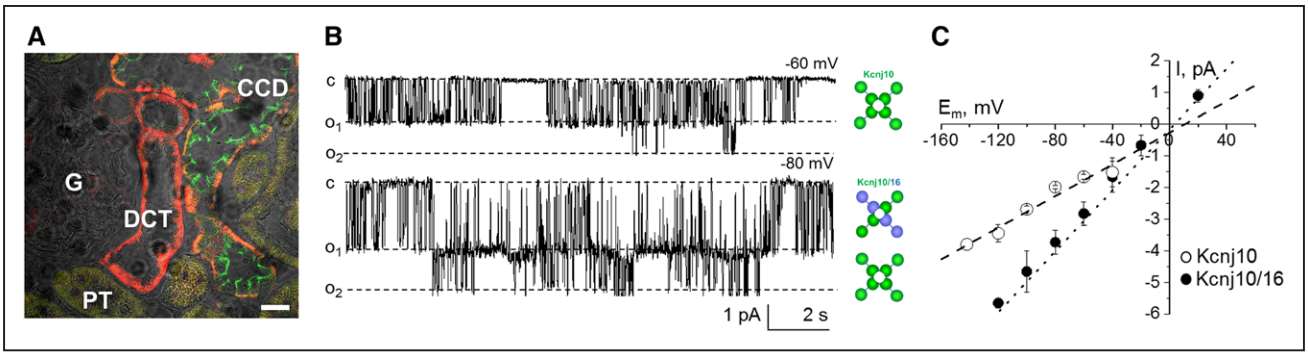

Figure 3. Expression and electrophysiological analysis of $K_{ir}4.1$ homotetrameric and $K_{ir}4.1/K_{ir}5.1$ heterotetrameric channels. **A**, Double immunostaining images show $K_{ir}5.1$ expression (red) in the distal convoluted tubule (DCT) and cortical collecting duct (CCD) cells. Aqp2 (aquaporin 2; green) was used as a marker of CD principal cells. Proximal tubules (PT) and glomerulus (G) are also shown (scale bar=20 µm). **B**, Representative current traces and (**C**) current–voltage relationships of the unitary current amplitude of $K_{ir}4.1$ and $K_{ir}4.1/K_{ir}5.1$ channels measured in Dahl SS (salt sensitive) rats. Shown at –80 mV is the activity of both heteromeric $K_{ir}4.1/K_{ir}5.1$ and homomeric $K_{ir}4.1$ channels in the same patch. Adapted from Palygin et al[71] with permission. Copyright © 2017, American Society for Clinical Investigation.

K^+-ATPase. Recently, it was also shown that basolateral $K_{ir}4.1/K_{ir}5.1$ channels in DCT are stimulated by low K^+ intake and inhibited by high K^+.[56] In another study, it was reported that Cl^- intake also contributes to basolateral potassium and chloride conductance in principal and intercalated cells of CCD. Treatment of mice with high-K^+ diet without concomitant elevations in dietary Cl^- elicited a comparable increase in basolateral K^+-selective current and single-channel $K_{ir}4.1/K_{ir}5.1$ activity in CCD principal cells. Furthermore, stimulation of aldosterone signaling by deoxycorticosterone acetate recapitulated the stimulatory actions of high K^+ intake on $K_{ir}4.1/K_{ir}5.1$ channels.[57] This opposite regulation of $K_{ir}4.1/K_{ir}5.1$ by high-K^+ diet in DCT and CCD segments might suggest that they play discrete roles at the corresponding segments.

In humans, loss-of-function mutations in the *Kcnj10* gene have been shown to cause SeSAME (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance)/EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy) syndrome.[58–60] The renal phenotype of these mutations includes salt wasting, hypomagnesemia, metabolic alkalosis, and hypokalemia. It is thought that these mutations in *Kcnj10* impair the function of heteromeric $K_{ir}4.1/K_{ir}5.1$ channels. Targeted disruption of the *Kcnj16* gene in mice resulted in hypokalemic and hyperchloremic metabolic acidosis with hypercalciuria.[61] Mutations in the *Kcnj16* gene may also cause nonfamilial Brugada syndrome associated with sudden cardiac death.[62] Furthermore, loss of transcriptional activation of $K_{ir}5.1$ by HNF1β (hepatocyte nuclear factor 1 homeobox β) drives autosomal dominant tubulointerstitial kidney disease characterized by renal cysts and several hereditary forms of diabetes mellitus.[63] Moreover, it was recently reported that the lack of *Kcnj10* resulted in decreased expression of NCC in DCT[64] and activation of ENaC.[65]

K_{ir} channels are named inward-rectifier channels because they carry larger inward (at negative potentials) than outward currents. These channels are sensitive to extracellular K^+ concentrations. According to the Nernst equation, reduction in plasma K^+ concentration shifts the equilibrium potential for K^+ to hyperpolarization, which alters channel gating and suppresses the overall conductance of K_{ir}.[66] Therefore, it was hypothesized that $K_{ir}4.1$ (likely as a heteromer with $K_{ir}5.1$) acts as the K^+ sensor in the distal tubules.[67] Special emphasis is paid to the key role NCC plays in mediating the effect of dietary K^+ intake on K^+ excretion by the kidney. Compelling evidence is provided that high K intake inhibits, whereas low K intake stimulates, NCC activity.[56,67–69]

Homozygous $Kcnj10^{-/-}$ mice do not live >1 to 2 weeks.[59,64,70] Therefore, recent studies utilized techniques to conditionally delete $K_{ir}4.1$ in the kidney after the completion of development using a Pax8 promoter paired with the administration of doxycycline.[67] Deletion of $K_{ir}4.1$ in these mice

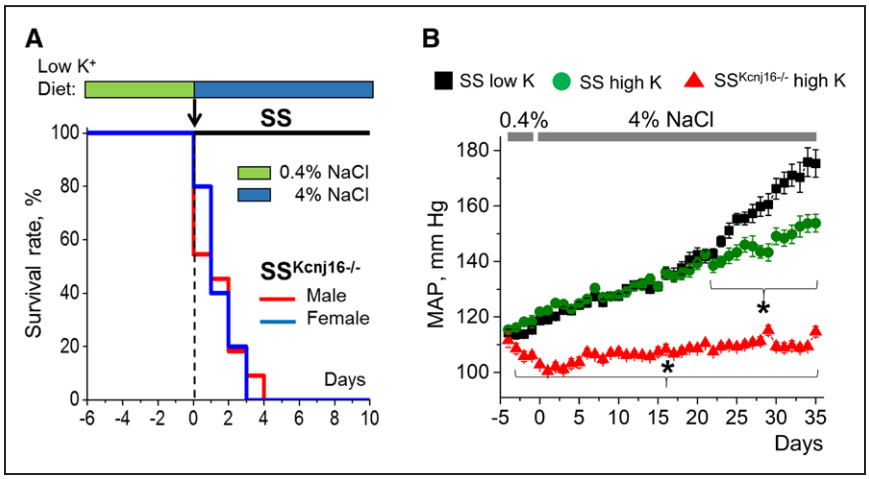

Figure 4. High salt intake triggers rapid mortality of SS (salt sensitive)$^{Kcnj16-/-}$ rats, which is rescued by supplementation of high potassium. **A**, Survival rate of SS and $SS^{Kcnj16-/-}$ rats on a low-potassium (0.36% K^+) and 4% NaCl diet. **B**, Mean arterial pressure (MAP) in SS and $SS^{Kcnj16-/-}$ rats. Animals were switched from a 0.4% to a 4% NaCl diet at day 0. Then, SS rats were fed either a standard 4% NaCl diet (black) or a 4% NaCl diet supplemented with high K^+ (1.41% K^+; green). $SS^{Kcnj16-/-}$ rats were fed a 4% diet supplemented with high K^+ (red). Adapted from Palygin et al[71] with permission. Copyright © 2017, American Society for Clinical Investigation.

led to moderate salt wasting, low BP, and profound potassium wasting.[67] Notably, effects of dietary potassium on the basolateral potassium conductance and membrane potential in DCT were completely absent in these kidney-specific $K_{ir}4.1$ KO mice. However, the same study also noted that dietary K^+ intake affects Cl^- conductance in DCT.[56]

To define the importance of $K_{ir}4.1/K_{ir}5.1$ in BP control under conditions of salt-induced hypertension, we recently generated a *Kcnj16* knockout in Dahl SS rats ($SS^{Kcnj16-/-}$).[71] $SS^{Kcnj16-/-}$ rats exhibited hypokalemia and reduced BP. Single-channel patch-clamp analysis of the basolateral K^+ conductance in isolated CCDs of SS and $SS^{Kcnj16-/-}$ rats revealed activity of only homomeric $K_{ir}4.1$ channels. Expression of $K_{ir}4.1$ was significantly increased in $SS^{Kcnj16-/-}$ rats. However, an immunohistochemical analysis revealed that $K_{ir}4.1$ channels were predominantly expressed in the cytosol of $SS^{Kcnj16-/-}$ rats, in contrast to strong basolateral localization of this channel in SS rats. These data suggest that $K_{ir}5.1$ is required for proper trafficking and localization of both $K_{ir}4.1$ homomeric and $K_{ir}4.1/K_{ir}5.1$ heteromeric channels to the basolateral membrane of both DCT and CCD segments. The most striking phenotype was observed when $SS^{Kcnj16-/-}$ rats were fed a high-salt diet. In contrast to wild-type Dahl SS rats, $SS^{Kcnj16-/-}$ rats experienced 100% mortality within a few days of switching to the high-salt diet, triggered by salt wasting and severe hypokalemia (Figure 4A). Importantly, administration of benzamil—an ENaC inhibitor—was able to rescue $SS^{Kcnj16-/-}$ rats from mortality induced by a high-salt diet. In contrast, supplementation of drinking water with hydrochlorothiazide (an inhibitor of NCC in DCT) only slightly delayed the animals' death, whereas furosemide (targeting NKCC2 in thick ascending limb) had no effect.[71] Further studies revealed that $SS^{Kcnj16-/-}$ rats survived when their high-salt diet was supplemented with high K^+ (Figure 4B). Figure 4B also shows that BP was reduced in SS rats fed a high-salt diet when chow was supplemented with high potassium. Crucially, BP did not change in $SS^{Kcnj16-/-}$ fed a high-K^+ diet, which demonstrates the critical role of this channel in the development of salt-induced hypertension.[71]

Summary and Conclusions

It is well recognized that higher levels of sodium intake are associated with elevated BP. Importantly, the effect of high sodium on BP is dependent on diet composition, specifically on the potassium content. It is clear that high dietary potassium is associated with a decrease in BP, particularly in the presence of a high-sodium diet. The studies summarized in this brief review emphasize the essential role of basolateral K_{ir} channels, specifically $K_{ir}4.1/K_{ir}5.1$, in the control of potassium homeostasis and BP, respectively. Moreover, there are several other K_{ir} channels identified in the renal tubular cells, such as $K_{ir}7.1$ and $K_{ir}2.3$ (encoded by *Kcnj13* and *Kcnj4*, respectively),[48,72–74] having largely unexplored roles. Further efforts are required to examine the relevance of these channels in BP and renal disease, especially under conditions of salt-induced hypertension and dietary supplementation with high potassium. Understanding of renal K_{ir} channelopathies is essential for the development of new antihypertensive therapies. Some of these studies are underway.[39,75,76] Therefore, there is hope that novel small-molecule inhibitors selectively targeting K_{ir} channels would be beneficial for the treatment of BP and kidney diseases.

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Disclosures

None.

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