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INVITED REVIEW

Dietary potassium and the renal control of salt balance and blood pressure

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Abstract Dietary potassium (K^+) intake has antihypertensive effects, prevents strokes, and improves cardiovascular outcomes. The underlying mechanism for these beneficial effects of high K^+ diets may include vasodilation, enhanced urine flow, reduced renal renin release, and negative sodium (Na^+) balance. Indeed, several studies demonstrate that dietary K^+ intake induces renal Na^+ loss despite elevated plasma aldosterone. This review briefly highlights the epidemiological and experimental evidences for the effects of dietary K^+ on arterial blood pressure. It discusses the pivotal role of the renal distal tubule for the regulation of urinary K^+ and Na^+ excretion and blood pressure and highlights that it depends on the coordinated interaction of different nephron portions, epithelial cell types, and various ion channels, transporters, and ATPases. Moreover, we discuss the relevance of aldosterone and aldosterone-independent factors in mediating the effects of an altered K^+ intake on renal K^+ and Na^+ handling. Particular focus is given to findings suggesting that an aldosterone-independent downregulation of the thiazide-sensitive NaCl cotransporter significantly contributes to the natriuretic and antihypertensive effect of a K^+-rich diet. Last but not least, we refer to the complex signaling pathways enabling the kidney to adapt its function to the homeostatic needs in response to an altered K^+ intake. Future work will have to further address the underlying cellular and molecular mechanism and to elucidate, among others, how an altered dietary K^+ intake is sensed and how this signal is transmitted to the different epithelial cells lining the distal tubule.

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Introduction

Based on observations in hypertensive patients, the Canadian physician W.L.T. Addison suggested already in 1928 that the "prevalence of arterial hypertension (…) is in large part due to potash poor diet, and an excessive use of salt" [3]. Since then, numerous epidemiological, observational, and interventional studies in humans as well as experiments in animals confirmed that not only dietary sodium (Na^+) but also potassium (K^+) intake may have profound effects on blood pressure [1, 61]. In modern societies, the average K^+ intake is usually low (70–80 mmol/day), while the average sodium (Na^+) intake is high (150–200 mmol/day). This contrasts sharply with the diet of our human ancestors who likely ate much more K^+ (230–300 mmol/day) and less Na^+ (1–10 mmol/day) [22, 106]. The change in human eating habits occurred within the last 5,000–10,000 years, when humans started to process their food, which lowered its content of K^+ due to losses during cooking. At the same time, Na^+ intake increased due to artificial salting in order to preserve food and to make it more palatable. In evolutionary terms, 5,000–10,000 years are however rather short and likely not sufficient to adapt our genetic make-up to the new conditions. Therefore, our physiological settings are more prepared for conditions when it was important to conserve Na^+ and to excrete K^+. The kidneys are the central organs that maintain Na^+ and K^+ homeostasis [106]. They are challenged with the complex task to independently match Na^+ and K^+ excretion to variable dietary intakes and control

blood pressure at the same time [124]. Healthy kidneys are usually capable to fulfill these tasks. However, the current high Na^+ and low K^+ content in our diet may have shifted the functional capacity of the kidney to its physiological limits. Small imbalances in renal function and/or in the underlying regulatory mechanism are then sufficient to deteriorate the system and thus contribute to the high prevalence of hypertension in our societies. The purpose of this review is (i) to briefly summarize the evidence for the beneficial effect of a K^+-rich diet on blood pressure and cardiovascular outcome, (ii) to briefly address the cellular and molecular mechanism by which the kidneys control Na^+ and K^+ excretion, and (iii) to highlight recent data providing possible explanations for the beneficial effect of dietary K^+ on renal salt handling and blood pressure control and on how these effects might be mediated at the molecular level.

Effect of dietary K^+ on blood pressure

An impressive body of evidence suggests that dietary K^+ intake is inversely correlated with arterial blood pressure in humans as well as in experimental animals (reviewed in [1, 2, 22, 61, 170]. Although few reports demonstrated that severe K^+ depletion in laboratory animals may decrease blood pressure under certain conditions [7, 46], it is evident from studies in humans that moderate dietary K^+ restriction, as it occurs in our diets, usually increases blood pressure [80, 83]. Conversely, dietary K^+ supplementation was shown to lower arterial blood pressure in humans with essential hypertension [97, 125, 148, 169] and in rat models with spontaneous hypertension [34, 96] or experimentally induced hypertension due to arterial stenosis [167] or dietary Na^+-loading [32, 105, 168]. While most of these interventional studies were performed with KCl supplementation, it remains controversial whether the antihypertensive effect of a K^+ diet is independent from the accompanying ion [22]. Nevertheless, He and co-workers did not find any differences between KCl and $KHCO_3$ in their antihypertensive effects [62]. Epidemiological studies have also demonstrated the beneficial effect of dietary K^+ on blood pressure and cardiovascular morbidity and mortality. A strong inverse association between arterial blood pressure and the amount of urinary K^+ excretion, used as surrogate of its dietary intake, has been observed by several investigators [1, 22, 82]. The INTERSALT study did already suggest that urinary K^+ excretion is negatively and independently associated with arterial blood pressure in the general population [71]. However, the number of participants was too small to allow robust subgrouping and a sufficient analysis of the impact of other possibly confounding factors. Very recently, the Prospective Urban Rural Epidemiology (PURE) study included blood pressure recordings, urinary ion excretion values, and other health-relevant parameters from more than 100,000 adults from 18 countries [108]. After adjustment for age, sex, geographic region, body mass index, alcohol consumption, and educational level, the data showed a dominant inverse relationship between systolic blood pressure and urinary K^+ excretion. With each gram increment of urinary K^+ excretion, the associated systolic blood pressure dropped by 1.08 mmHg. Notably, this inverse correlation was seen irrespective from the amount of the urinary Na^+ excretion and hence from the estimated sodium consumption (Fig. 1a). As

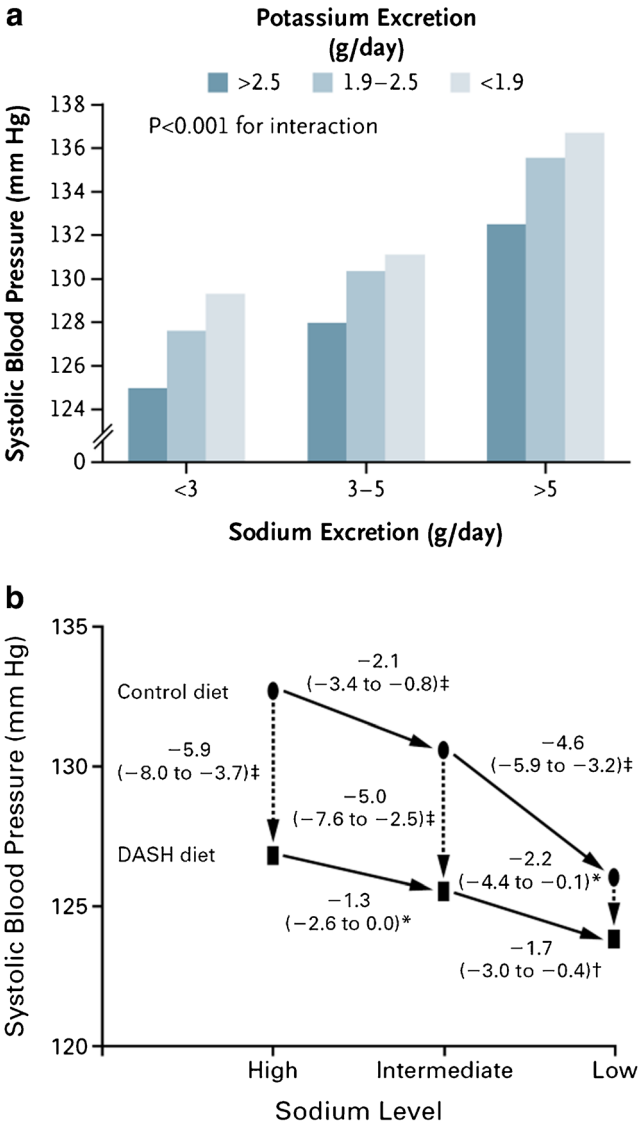

Fig. 1 Effect of dietary Na^+ and K^+ on mean systolic blood pressure in humans. **a** Correlation of 24-h urinary Na^+ and K^+ excretion (as surrogate for ion intake) with systolic blood pressure. Data were collected from 102,216 adults from 18 countries within the PURE study [108]. The *P* value is for testing the joint effect of the two electrolytes on blood pressure (from [108]). **b** Effects of Na^+ and K^+ dietary intake on the mean systolic blood pressure. The study included 412 participants which were randomly assigned to eat either a control diet or the fruit- and vegetable-rich DASH diet. Within the assigned diet, participants ate foods with either high, intermediate, or low levels of sodium for 30 consecutive days (from [148])

such, these data from an observational study are in line with data from the interventional Dietary Approach to Stop Hypertension (DASH) trial [148]. The DASH diet is rich in vegetables and fruits and part of its blood pressure-lowering effect can likely be attributed to its high K^+ content. Irrespective whether this diet was combined with a high, intermediate, or low dietary Na^+ intake, it significantly reduced blood pressure. Nevertheless, the effect was more pronounced on the high than on the low Na^+ intake (Fig. 1b). Importantly, a high K^+ diet does not only lower blood pressure but does also decrease the risk for its complications including cardiovascular events, stroke, and death [2, 116]. In general, persons especially vulnerable to these complications (e.g., obese persons, older persons, or patients with hypertension) appear to profit most from the beneficial effects of a K^+-rich diet [108]. In contrast to the pronounced effects seen in hypertensive patients, a high K^+ intake does not or only minimally decrease blood pressure of normotensive humans and animals [12, 61, 170]. These evidences suggest that dietary K^+ interferes with the regulation of blood pressure only when the balance in regulatory mechanisms is disturbed. Moreover, there might be an optimal level of K^+ intake up to which the blood pressure-lowering effect could be achieved. Indeed, experiments in Dahl salt-resistant and salt-sensitive rats on a Na^+ replete diet showed that the antihypertensive effect of K^+ supplementation occurred only with 2.6 % KCl. Treating the animals with an excessive and unphysiological high K^+ intake (4 and 8 % KCl) triggered a progressive rise in blood pressure to levels even higher than those observed in rats on low K^+ (0.7 % KCl) intake [100]. As the increase in blood pressure was paralleled by elevated plasma aldosterone levels, it was suggested that aldosterone-dependent Na^+ retention could explain the hypertension. However, the inhibition of the mineralocorticoid receptor by spironolactone was not able to prevent the hypertensive effect of an excessive K^+ intake in mice [182].

The underlying mechanisms for the beneficial effect of a physiologically relevant high K^+ diet on blood pressure and the cardiovascular system have been addressed in many research studies (reviewed in [22, 170]). They were proposed to include direct effects of altered plasma K^+ levels on endothelial cells leading to reduced endothelial stiffness and enhanced nitric oxide (NO)-mediated vasodilation [118], endothelial and vascular smooth muscle cell hyperpolarization and relaxation [22], an altered response of arterial baroreceptors [149], a lowered sympathetic activity [52], a reduced renal renin release [12], and a general negative sodium balance [70]. The latter is particularly interesting, given the fact that an enhanced dietary K^+ intake stimulates adrenal aldosterone production, which is expected to promote Na^+ retention rather than to give rise for a Na^+ loss. However, numerous experimental studies in sheep [134, 135], dog [205], rat [179], mouse [156], and human [79, 176] convincingly showed that a K^+ load is followed not only by a sustained kaliuresis but also by a pronounced natriuresis. While the first parallels the enhanced K^+ intake, the latter usually exceeds the intake of Na^+ explaining the negative Na^+ balance. The experiments in sheep [134] and mice [156] showed that the K^+-induced natriuresis starts very rapidly and in parallel to the increasing urinary K^+ excretion. The natriuresis occurs independently whether the K^+ was given with the food or administered by infusion [134, 135, 170]. Notably, the K^+-dependent inhibition of renal Na^+ reabsorption is accompanied by an enhanced chloride excretion [171, 176] suggesting a combined renal NaCl loss. Thus, there is a close interrelationship between renal K^+ and Na^+ handling that likely also impacts on renal blood pressure control.

Role of the distal tubule in the control of K^+ and Na^+ balance and blood pressure

K^+ and Na^+ are freely filtered at the glomerulus and then reabsorbed to almost 90 % along the proximal tubule (PT) and the thick ascending limb (TAL) [124, 136]. Thus, only ~10 % of the filtered Na^+ and K^+ load reach the distal tubule segments beyond the macula densa. However, these post-macula densa segments, which include the distal convoluted tubule (DCT), the connecting tubule (CNT), and the collecting duct (CD) with its cortical (CCD) and medullary (MCD) portion, are decisive for the amount of Na^+ and K^+ that gets finally excreted via the urine [92, 106, 124, 136]. The molecular identification of the major ion transporters and channels of the distal tubule enabled researchers to map these proteins along the DCT, CNT, and CD and to study their function at the molecular level as reviewed in detail recently [5, 30, 142]. Despite some subtle species differences, the cellular distribution and sequential order of the ion-transporting and regulating proteins appear to be strikingly similar in all yet investigated mammalian species (reviewed in [91]). The segmentation of the nephron and the various cell types of the distal tubule including their main Na^+ and K^+ transporting pathways are schematically depicted in Fig. 2.

In the initial 2/3 of the DCT (DCT1), the apical thiazide-sensitive NaCl cotransporter (NCC) is almost the sole apical Na^+ transport pathway. In the last 1/3 of the DCT (DCT2), NCC is co-expressed with the amiloride-sensitive epithelial sodium channel (ENaC) [6, 91, 106]. ENaC is composed of three homologous subunits (α, β, and γENaC) and is the main apical sodium-reabsorbing pathway in the CNT and CD [92]. In contrast to NCC, the activity of ENaC is electrogenic and generates a transepithelial potential difference that is crucial to drive K^+ secretion via apical K^+ channels [18, 29]. K^+ secretion is accomplished by the renal outer medullary K^+ channel in the segment-specific principal cells of the DCT, CNT, and CD [189, 192]. Interspersed between the segment-specific cells are the intercalated cells, which are abundant from

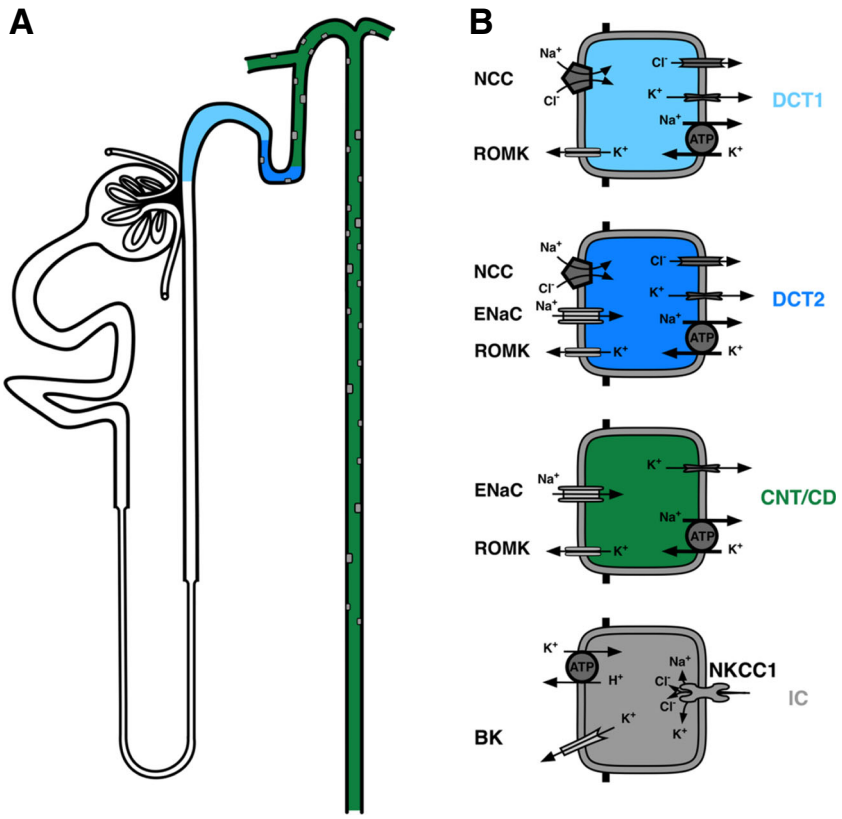

Fig. 2 **a** Schematic representation of a nephron. *Highlighted with color* is the distal nephron including the distal convoluted tubule (*DCT*) with an early and late portion (*DCT1* and *DCT2*, respectively), the connecting tubule (*CNT*), and the collecting duct (*CD*). The *gray rectangles* indicate the distribution of intercalated cells (*IC*). **b** Schematic cell models with representation of the main apical and basolateral transport pathways contributing to Na^+ reabsorption and K^+ secretion in the respective tubule segment. Abbreviations for the ion channels, transporters, and ATPases are explained in the text

DCT2 to the first portion of the MCD. Intercalated cells contribute to renal K^+ secretion via apical Ca^{2+}-dependent-maxi K channels (BK) [64, 122]. BK channels are supposed to mediate the flow-dependent K^+ secretion in the distal tubule and collecting duct [198]. BK is composed of a pore-forming α-subunit and a modulatory β-subunit, for which four distinct forms ($\beta 1-4$) with tissue-specific expression have been described [199].

The intercalated cells do also express an apical H^+-K^+-ATPase that can reabsorb K^+ from the tubular fluid in exchange for protons [31, 57]. As such, the intercalated cells are capable for both K^+ secretion and K^+ reabsorption and likely contribute to the ability of the DCT, CNT, and CD to switch from K^+ secretion during a high K^+ intake to K^+ reabsorption during dietary K^+ restriction [159]. Certain types of intercalated cells do also express an apical Cl-HCO3 exchanger (pendrin) and a Na^+-driven chloride/bicarbonate exchanger (NDCBE), which were proposed to contribute to transcellular NaCl reabsorption along the renal collecting system [37, 187]. Indeed, there is ample evidence for an important crosstalk and cooperation between the segment-specific cells and intercalated cells and their ion transport pathways in order to maintain Na^+ and K^+ homeostasis as well as a normal blood pressure [37, 64, 194]. In the segment-specific cells of the DCT, CNT, and CD, Na^+ reabsorption and K^+ secretion are driven by the activity of the Na-K-ATPase in the basolateral plasma membrane. By pumping Na^+ towards the extracellular space and K^+ in the opposite direction, it keeps the intracellular Na^+ concentration low and the intracellular K^+ concentration high, thereby providing the necessary ion gradients for the ion fluxes across the apical membrane [194]. However, the intercalated cells express very little of the Na-K-ATPase [17], and it remains unclear how these cells contribute to significant Na^+ reabsorption and K^+ secretion. It was recently postulated that intercalated cells may rely on a H^+ gradient generated by the H^+ vacuolar-ATPase as bioenergizer for secondary active transport [23]. Moreover, immunohistochemical studies revealed that the intercalated cells have a prominent abundance of the Na-K-2Cl transporter NKCC1 in their basolateral plasma membrane, which was proposed to ensure a sufficient basolateral K^+ uptake to fuel K^+ secretion via apical BK channels [89].

The functional relevance of the DCT, CNT, and CD for the control of Na^+ and K^+ homeostasis as well as blood pressure is evidenced by human monogenic diseases affecting ion transport in these three segments (reviewed in, e.g., [142, 193]). Loss-of-function mutations of NCC cause Gitelman's syndrome which is characterized by renal Na^+ loss with arterial hypotension, hypokalemic alkalosis, and hypocalciuria [76, 87, 155]. Conversely, increased NCC activity due to mutations within the regulatory network including the With-No-lysine (K) WNK kinases WNK1 or WNK4 [196] or ubiquitin-ligase co-factors cullin-3 (CUL3) [14] and kelch-like 3 protein (KLH3) [14, 95] is associated with severe salt-sensitive

hypertension, hyperkalemia, metabolic acidosis, and hypercalciuria (familial hyperkalemic hypertension (FHHt), Gordon syndrome, or pseudohypoaldosteronism type II). Likewise, loss-of-function mutations in ENaC cause severe renal salt-wasting with often life-threatening hyperkalemia and acidosis (pseudohypoaldosteronism type I) [24, 161], while gain-of-function mutations of ENaC (Liddle syndrome) are associated with salt-sensitive arterial hypertension with hypokalemic alkalosis [59, 60, 153]. Remarkably, although these diseases primarily affect Na^+ transporting pathways, they also affect renal K^+ handling and in part also renal Ca^{++}, Mg^{++}, and acid/base excretion, further emphasizing the important interrelation of these ion transport processes in the distal tubule. Transgenic mouse models for Gitelman syndrome [151], FHHt [81, 166, 203], PHA-I [11, 68, 103], and Liddle syndrome [132] have been generated and mimic to a large extent the human diseases. This review will not discuss these models but briefly highlight only those mouse models with deletion for K^+-transporting proteins for which corresponding human diseases have not been described or for which the mouse models show relevant differences from the human phenotype.

Knockout mouse models for the apical secretory potassium channels ROMK [94, 185] and BK [16, 131, 150] as well as for the gastric and colonic isoform of the H-K-ATPase [107, 157] have been developed. The phenotype of the ROMK-deficient mice is dominated by the transport defect in the thick ascending limb. Here, ROMK-dependent K^+ secretion is important to provide a sufficient intratubular K^+ concentration to ensure the activity of the apical furosemide-sensitive Na-K-2Cl cotransporter NKCC2. Consistent with a loss of NKCC2-dependent Na^+ reabsorption, the mice show a severe Bartter-like syndrome with a high perinatal lethality and poor urinary concentration ability. In contrast to patients with Bartter syndrome, the ROMK-deficient mice do not show hypokalemic alkalosis but metabolic acidosis likely resulting from the severe polyuria with subsequent hydronephrosis and renal insufficiency [94]. As such, these mice could not be used to study the role of ROMK for renal K^+ secretion in the DCT, CNT, and CD. However, the observation that infants with Bartter syndrome due to ROMK mutations are usually hyperkalemic and not hypokalemic as patients with mutations in other Bartter syndrome-related genes (i.e., NKCC2, ClC-K, barrtin, and the calcium-sensing receptor) [72] point to the relevance of ROMK for renal K^+ excretion.

The role of BK channels for renal K^+ excretion and blood pressure control has been studied using knockout mouse models for its subunits [64]. BKα-deficient mice featured an impaired flow-dependent urinary K^+ secretion and hyperaldosteronism probably to compensate for the disturbed renal K^+ secretion [138]. Likewise deletions of the ancillary BKβ1 and BKβ4 subunits results in insufficient renal K^+ excretion, hyperaldosteronism, and arterial hypertension [56, 63]. However, the effect of BKβ1 deletion on aldosterone release and blood pressure critically depends on the genetic background of the mice and the physiological role of this subunit remains elusive [147]. The experiments in ROMK-deficient and in BK-deficient mice did also reveal that both channels may compensate for each other [8, 138]. This may explain the rather mild defect in renal K^+ excretion observed in these mice.

Other putative players in the renal handling of K^+ are the gastric (HKα1) and colonic (HKα2) isoforms of the H^+-K^+-ATPase. Renal H^+-K^+-ATPases are expressed throughout the kidney, and their expression is profoundly upregulated by dietary K^+ restriction, suggesting that they may contribute to renal K^+ homeostasis [31, 57]. Besides the clear deficits in gastric and colonic functions displayed by H^+-K^+-ATPase knockout mice (including gastric achlorhydria and epithelial metaplasia (HKα1 knockout mice) [157] and insufficient colonic K^+ reabsorption under dietary K^+ restriction (HKα2 knockout mice) [107]), no overt renal phenotype has been reported so far. Further studies are warranted to elucidate their role in renal physiology as detailed in two recent review articles [31, 57].

Effect of K^+ intake on K^+ and Na^+ transport in distal tubules

The vast majority (~98 %) of the K^+ content of the body (~3,500 mmol) is stored inside the cells. Only a small amount of K^+ (70–100 mmol) is found in the extracellular space. Thus, the standard daily K^+ intake of humans (~100 mmol) just equals the amount of extracellular K^+ [55]. In smaller mammals, like the mouse, the standard daily K^+ intake may even exceed the amount of extracellular K^+ up to a factor of 40 [156]. The fact that under these conditions, a single meal does not cause a life-threatening increase of the extracellular K^+ concentration is mainly due to (i) a rapid shift of extracellular K^+ into intracellular stores (internal K^+ balance) and (ii) a rapid onset of K^+ excretion via the kidney and to less extent also via the colon (external K^+ balance) [119]. In the kidney, the increase in urinary K^+ excretion is achieved via an activation of both apical K^+ channels and Na^+ channels, as well as the basolateral Na^+-K^+-ATPase [189]. Electrophysiological data on isolated collecting ducts demonstrated that an enhanced dietary K^+ intake increases the number of active K^+ and Na^+ channels in the apical membrane rather than changes the open probability and/or conductance of single channels [120, 121]. Immunofluorescence studies and/or in vivo cell surface biotinylation assays corroborated these findings and showed that the increase in the number of active channels is due to a translocation of BK [112], ROMK [50, 173, 183], and ENaC [50, 173] from intracellular pools to the apical plasma membrane. The activation of ROMK and ENaC in response to dietary K^+ loading occurs quite rapid and was suggested to

contribute to the renal adaptation to day-to-day variations in dietary K^+ intake [121]. The K^+ diet-induced activation of BK is paralleled by an enhanced mRNA expression of the BKα and BKβ2-4 subunits [112] and BKα protein abundance [90, 138]. The latter is possibly related to a reduced ERK1/2 signaling-mediated lysosomal degradation of the channel [90]. In contrast, the activation of ROMK is not associated with an increased ROMK transcription [51] but goes along with an enhanced abundance of its fully glycosylated form suggesting an increased processing of ROMK through the Golgi apparatus [50]. ENaC does also undergo post-translational modification. The K^+ diet-induced activation of ENaC is accompanied by a proteolytic cleavage of the α- and γENaC subunits and a shift of βENaC to higher molecular weight forms consistent with an altered glycosylation pattern [50]. While the significance of the latter is unclear, the proteolytic cleavage of α- and γENaC is thought to represent the activation of otherwise silent channels [143]. It is important to note that, in contrast to ENaC [47, 102], the K^+ channels BK [40] and ROMK [120] do not get activated in response to dietary Na^+ restriction, suggesting that increased plasma aldosterone levels are per se not sufficient to bring the K^+ channels to the apical plasma membrane. The differential regulation of ENaC and ROMK in response to dietary Na^+ restriction and K^+ loading (Fig. 3) may contribute to the ability of the kidney to independently regulate Na^+ and K^+ homeostasis. Notably, the apical translocation of ROMK [183] and ENaC [106, 173] in response to dietary K^+ loading occurs mainly in the late DCT (DCT2) and early CNT. These findings are in line with early micropuncture studies suggesting that renal K^+ excretion is mainly achieved at these sites [99]. Consistent with a high K^+ transport capacity, the late DCT and early CNT are characterized by a high density of the Na-K-ATPase and of mitochondria (reviewed in [106]). The activity of ENaC in these segments is much more pronounced than in the downstream localized CD [48, 114]. The critical role of the late DCT and CNT for maintenance of K^+ and Na^+ homeostasis has been extensively discussed in several recent reviews [92, 106, 123] and is underlined by the fact that mice with targeted inactivation of ENaC in the CCD are phenotypically normal [145], while mice with targeted inactivation of ENaC in the CNT show an impaired control of K^+ and Na^+ homeostasis [29].

Although recent experiments in rats suggested that part of the K^+ secretion in response to a dietary K^+ load occurs independent from ENaC [49], the upregulation of this electrogenic Na^+ reabsorption certainly supports renal K^+ secretion. As mentioned earlier in this review, the activity of ENaC is necessary to generate a transepithelial potential difference that drives K^+ apical secretion [18, 29]. However, the increased Na^+ reabsorption in the distal tubule is at odds with the described natriuretic and antihypertensive effect of a K^+-rich diet. A possible explanation for this apparent paradox comes from recent observations on the effect of dietary K^+ intake on the activity of NCC in the DCT [156]. An oral K^+ load by gastric gavage or feeding rapidly (<15 min) dephosphorylates and hence inactivates the thiazide-sensitive NaCl cotransporter NCC. This response parallels the K^+-induced kaliuresis and natriuresis (Fig. 4) and precedes a detectable activation of ENaC by proteolytic cleavage [156]. The K^+ diet-induced NCC downregulation is also seen under chronic

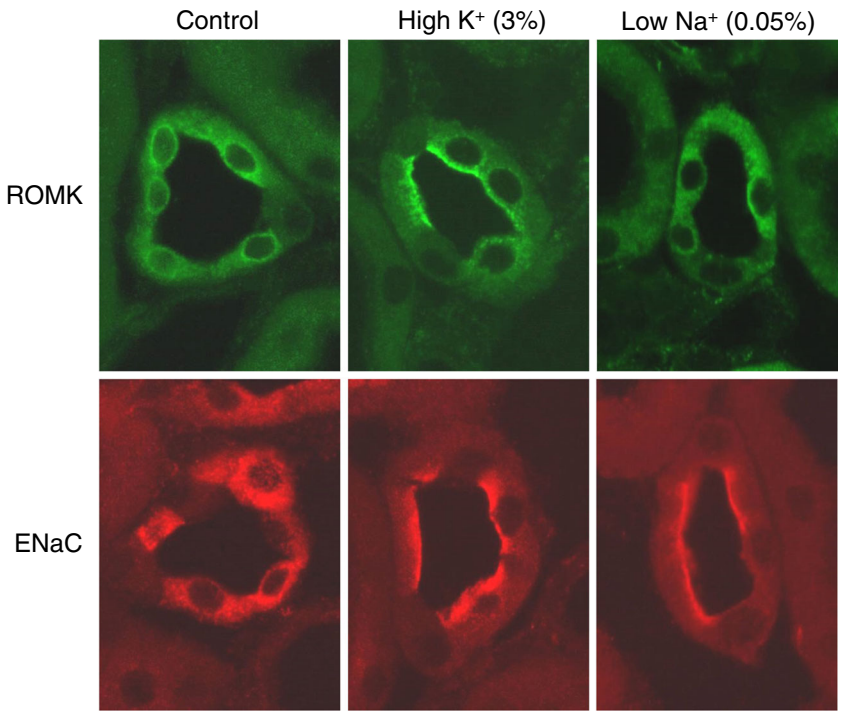

Fig. 3 Effect of dietary K^+ loading and dietary Na^+ restriction on the subcellular localization of ROMK and γENaC in mouse CNTs. Mice were kept either for 1 week on a control diet (0.8 % K^+, 0.3 % Na^+), for 2 days on a high K^+ diet (3 % K^+, 0.3 % Na^+), or for 10 days on a low Na^+ (0.8 % K^+, 0.01 % Na^+). Immunohistochemical detection of ROMK (*in green*) and γENaC (*in red*)

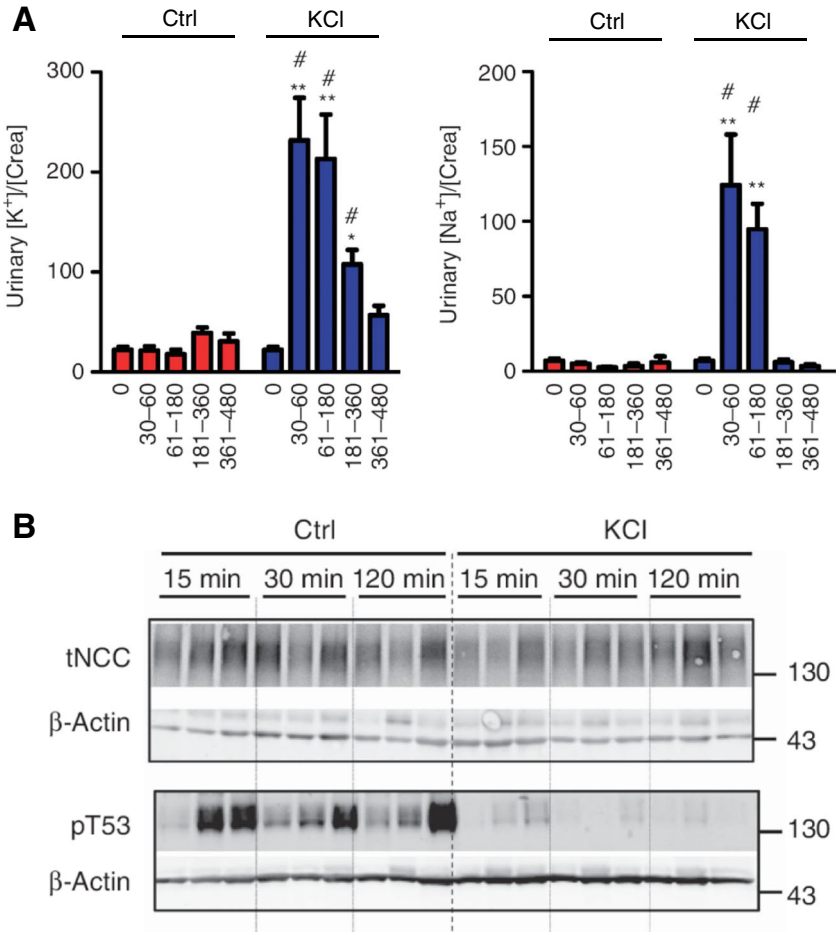

Fig. 4 Rapid effects of an oral K^+ load on urinary ion excretion and NCC phosphorylation. **a** Urine K^+ and Na^+ concentrations normalized to creatinine concentrations from mice after receiving a gastric gavage of control (*Ctrl*; *red*; 0 % KCl) or KCl (*blue*; 2 % KCl) solutions. Spot urines were collected for the indicated time intervals after gavage. **P*<0.05 and ***P*<0.01 between Ctrl and experimental groups. #*P*<0.05 between the "zero" and the time intervals within the same experimental group. **b** Male mice received control (*Ctrl*) and 2 % KCl solutions through gavage, and kidneys were collected after 15, 30, and 120 min. Total NCC (*tNCC*) and phosphorylation of NCC at position 53 (*pT53*) were assessed by immunoblotting with specific antibodies. *Error bars* indicate standard error of the mean. (Graphs and immunoblots from [156])

conditions (i.e., days to weeks of a high K^+ diet) but concerns mainly the total and cell surface-expressed NCC rather than its phosphorylation [50, 73, 179, 182, 200]. Moreover, while the acute effect on NCC appears to be independent from the co-administered anion [156], the chronic effect on NCC abundance and phosphorylation was reported to occur only when the K^+ is accompanied by chloride and not by citrate [20]. Notably, the downregulatory effect of a high K^+ diet is independent from dietary Na^+ intake and is seen on standard Na^+ [50, 175], high Na^+ [182], and low Na^+ intake [179]. These findings are in agreement with early renal tubule micropuncture studies on rats showing a diminished natriuretic response to thiazides after dietary K^+ loading [154]. Previous morphological studies had already revealed a reduced density of mitochondria and basolateral membrane infoldings in DCTs of rabbits on a low Na^+/high K^+ intake [75].

The downregulation of NCC in response to a high K^+ diet was proposed to improve the secretion of K^+ in DCT2, CNT, and CD due to the increased apical Na^+ and fluid delivery [5, 104]. Na^+ can be then reabsorbed in exchange for K^+ while the enhanced urinary flow may activate flow-dependent K^+ secretion and lower intratubular K^+, keeping the driving force for K^+ secretion high [192]. Nevertheless, it is unlikely that a reduced activity of NCC is sufficient to increase urinary K^+ excretion unless a sufficient number of active K^+ and Na^+ channels is present at the apical plasma membrane [26, 69]. However, given that thiazide diuretics [39] significantly lower blood pressure, it is reasonable to assume that the observed NCC downregulation in K^+-repleted animals is sufficient to contribute to the antihypertensive effect of a high K^+ diet. On the other hand, an upregulation of NCC may increase blood pressure on a low K^+ intake. In fact, studies in rats and mice demonstrated that dietary K^+ restriction increases the abundance and phosphorylation of NCC [38] leading to renal Na^+ retention and an elevated blood pressure [182]. However, it is unlikely that the effects of an altered dietary K^+ intake on renal Na^+ excretion and blood pressure control can be solely attributed to an altered NCC activity. In fact, although the K^+-induced natriuresis in NCC-deficient mice is diminished, they still excrete more Na^+ than NCC-deficient mice without any K^+ loading [156]. The nature of the remaining K^+-induced natriuresis in NCC-deficient mice is unclear but might be related to inhibitory effects of K^+ loading on Na^+ transport in the proximal tubule [15] and in the TAL [26, 78, 160, 164]. Consistently, an altered K^+ intake may modulate also the expression of ion transporters in the proximal tubule and the

TAL including NHE3 and NKCC2 as shown in some [38, 47, 73] but not all studies [115].

The role of aldosterone

Aldosterone is regarded as the main hormone mediating the effects of K^+ intake on the kidney while also regulating Na^+ balance and contributing to blood pressure control. A high dietary K^+ intake increases plasma [K^+], which promotes aldosterone production and release from the zona glomerulosa of the adrenal cortex [10]. The elevated plasma aldosterone levels are then thought to stimulate renal K^+ secretion until the excess of K^+ is excreted [55]. Indeed, aldosterone is known to stimulate K^+ secretion in the renal collecting system, and several evidences suggest that it may interfere with the regulation of most of the molecular players involved in distal tubule K^+ transport including ENaC [92], ROMK [186], BK [195], and NCC [77, 177, 178]. However, the effects of physiological elevations of plasma aldosterone on renal K^+ excretion are rather minor and a dietary K^+ load induces a kaliuresis often already before plasma aldosterone levels get elevated [133]. Moreover, adrenalectomized animals are able to adapt their urinary K^+ excretion and to increase apical Na^+ and K^+ conductances in the CD in response to a dietary K^+ load [120, 158, 197]. Likewise, mice with a genetic inactivation of the aldosterone synthase maintain an adequate renal adaptation to a physiological K^+ load (2 % K^+ diet). Only when challenged with an unphysiological high (5 %) K^+ diet, the aldosterone synthase-deficient mice decompensate and become severely hyperkalemic likely due to an insufficient upregulation of ENaC rather than of ROMK [173]. The independence of ROMK and BK activity from aldosterone could be also deduced from the fact that these channels do not get activated upon Na^+ dietary restriction, despite the elevated plasma aldosterone levels [40, 120, 121]. Moreover, aldosterone does not increase K^+ channel activity in a mouse CCD cell line [45]. It was also shown that the K^+ diet-induced downregulation of NCC is aldosterone-independent [156].

Thus, there is ample evidence that in addition to aldosterone, aldosterone-independent factors contribute to the renal control of K^+ homeostasis. A variety of additional hormones were implicated in the regulation of renal K^+ secretion, and many of them do also control Na^+ balance and blood pressure. Indeed, glucocorticoids [43] and vasopressin [19, 44] stimulate renal K^+ secretion. Part of their effect might be related to their known activating effects on ENaC. Moreover, glucocorticoids increase urinary flow and thereby may activate flow-dependent K^+ secretion [43], while vasopressin was reported to directly activate ROMK [19]. Conversely, progesterone gets increased during hypokalemia and was shown to stimulate renal K^+ reabsorption via an increased H^+-K^+-ATPase activity in the kidney [31, 36]. Angiotensin II suppresses the activity of BK [211] and ROMK [191, 207] but stimulates ENaC [165, 188] and NCC [21, 85, 177] and hence might be critical to limit renal K^+ secretion and to maximize renal Na^+ reabsorption during hypovolemia [5]. Nevertheless, although all of the abovementioned hormones likely contribute to the modulation of the K^+ response of the kidney, their described physiological effects on renal K^+ handling are comparably small and unlikely account for the marked aldosterone-independent regulations of, for example, ROMK and NCC in response to a high K^+ diet.

The existence of additional humoral kaliuretic factors has been proposed since more than 25 years [146]. Although there are evidences for the presence of such factors in blood [33] and urine [98] of K^+-loaded animals, their molecular identity remains unclear. It has been proposed that the amount of dietary K^+ is already sensed in the gut and/or the portal vein even before plasma K^+ levels rise [55]. This would trigger the release of kaliuretic peptides and/or modulate the activity of the autonomous nervous system ultimately increasing renal K^+ excretion [55]. Similar feed-forward control systems involving gut-derived peptides have been implicated in the control of glucose and Na^+ homeostasis [109]. Although previous data suggested a gut-kidney crosstalk for the control of K^+ homeostasis [86], additional work is needed to further substantiate this concept.

Changes in extracellular K^+ concentrations may also directly affect renal ion transport. There is strong evidence that increases in plasma K^+ are already sufficient to stimulate renal K^+ and Na^+ excretion [180], to increase the apical K^+ conductance in distal tubules [43, 197], and to downregulate NCC in the DCT [137]. K^+ infusions into one renal artery of dogs induce a prominent kaliuresis and natriuresis in the ipsilateral kidney, while the contralateral kidney shows only mild kaliuresis and no natriuresis [180]. One possible intrarenal mediator could be tissue kallikrein (TK), which is a serine protease synthesized in large quantities in the late DCT and CNT [181]. TK synthesis and excretion into the urine is increased by dietary K^+ intake [181], and it activates ENaC by proteolytic cleavage [126]. Nevertheless, the defect in renal adaptation to a K^+ load displayed by TK-deficient mice is rather subtle [35], and the proteolytic cleavage of ENaC in TK-deficient mice is only marginally changed [129].

Thus, there is a large body of experimental evidence suggesting that aldosterone-dependent and aldosterone-independent mechanisms contribute to the renal response to a high K^+ intake. Aldosterone is certainly not an absolute prerequisite [192], but it is important to achieve a maximal K^+ secretion [101, 173]. Moreover, aldosterone may have an important additional role. The aldosterone-dependent upregulation of ENaC in the late DCT, CNT, and CD may not only improve K^+ secretion but may also limit the renal Na^+ loss caused by the inactivation of upstream Na^+ transport systems. As such, the increase of plasma aldosterone would contribute

to maintain Na^+ balance and hence finally blood pressure on high K^+ diet. The relevance of an intact aldosterone system in this context is highlighted by experiments performed by Young and co-workers in dogs [205]. While intact dogs showed only a limited natriuresis and no significant change in blood pressure in response to a K^+ load, adrenalectomized dogs with a fixed corticosteroid and aldosterone replacement revealed a profound K^+ intake-induced renal Na^+ loss with a marked drop in arterial blood pressure (Fig. 5). Thus, the K^+ sensitivity of blood pressure may become overt only when underlying feedback mechanisms of blood pressure control are disturbed. This may also explain the observation that a high K^+ diet has a marked blood pressure-lowering effect only in hypertensive but not in normotensive individuals (see above).

The role of SGK1 and the WNK/SPAK pathway

In recent years, tremendous progress has been made in the identification and characterization of molecular mechanisms that regulate the ion transporters and channels involved in renal Na^+ and K^+ handling in the DCT, CNT, and CD. This research was summarized in several recent reviews [4, 54, 127, 162, 174, 192]. In brief, the current evidence suggests that the regulation of Na^+ and K^+ transport in the post-macula densa segments depends on an intricate regulatory network that includes the interaction of several kinases (e.g., WNK1, 3, and 4, SPAK/OSR1, SGK1) [4, 54, 65], phosphatases, and their regulators (e.g., PP1, PP4, I-1) [53, 88, 130] as well as ubiquitin ligases (e.g., Nedd4-2, KLHL-3, cullin-3) [141, 174]. In the context of the renal adaptation to an altered dietary K^+ intake, the kinases SGK1, WNK1, and WNK4 receive particular attention. SGK1 was proposed to mediate the aldosterone-dependent effects of a high K^+ diet [192]. In fact, aldosterone [27, 113] and a high K^+ intake [204] induce the expression of SGK1. Moreover, SGK1 increases the cell surface abundance and/or activity of apical and basolateral players contributing to K^+ secretion including ROMK [204, 207], BK [208], ENaC [93], and the Na-K-ATPase [209]. Consistent with the idea that SGK1 takes part in the renal adaptation to a high K^+ intake, SGK1-deficient mice show an

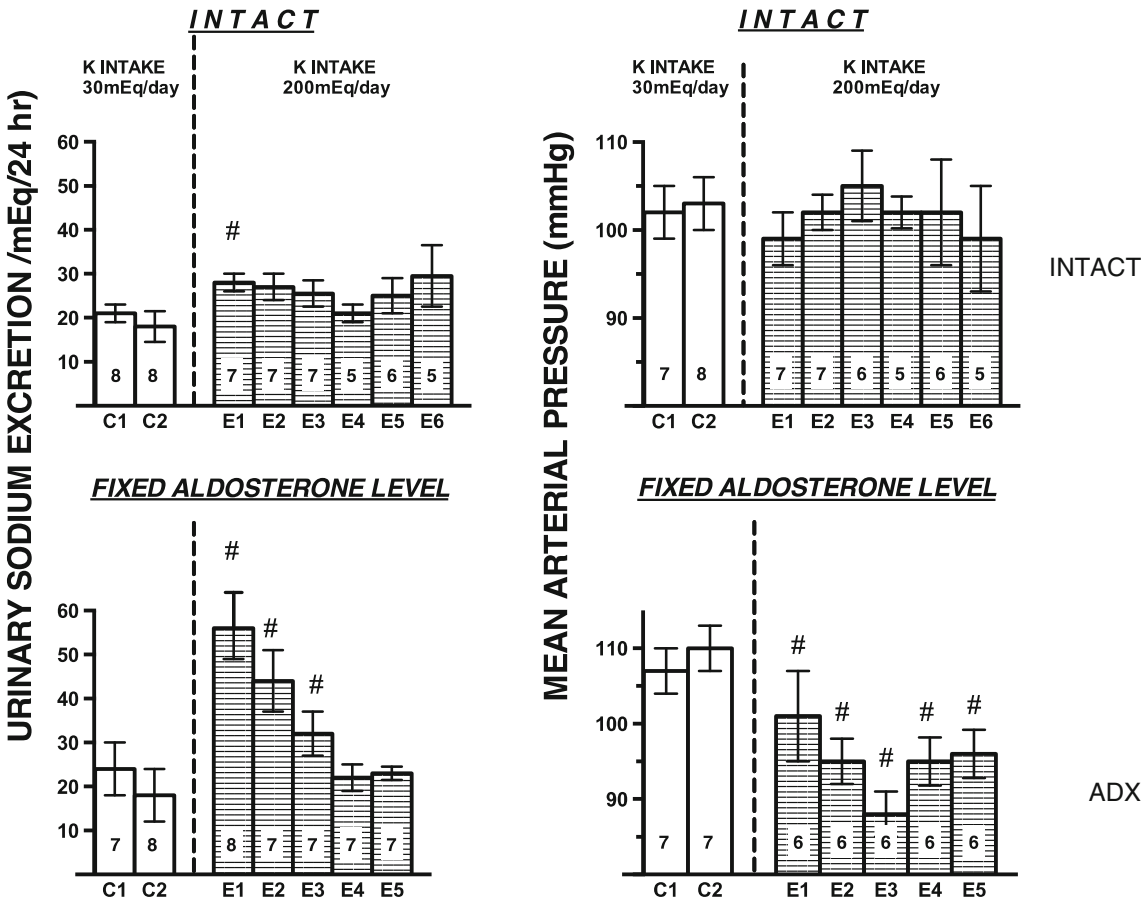

Fig. 5 Intact dogs (*n* indicated in the *bars*) were kept for 2 days (*C1–C2*) in metabolic cages with a control diet in which the K^+ intake was fixed to 30 mEq/day. After the second control day, additional 170 mEq/ KCl (total 200 mEq/day) was administered by a venous catheter connected to a pump for the next 6 days (*E1–E6*). After this set of experiments, the dogs were adrenalectomized (*ADX*) and supplemented with 50 μg/day of aldosterone, and the experiment was repeated. In both experimental setups, urinary Na^+ and mean arterial pressure were measured. *Hashtags* indicate statistical significance between the given measurement and C2. *Error bars* indicate standard error of the mean. (Redrawn from [205])

impaired renal K^+ excretion and become hyperkalemic when placed on a high K^+ diet [67]. However, the underlying molecular mechanisms are likely complex. In contrast to what was expected, SGK1-deficient mice do not show a reduced but rather an increased apical localization of ROMK [67]. Moreover, the effect of the loss of SGK1 on apical ENaC activity is inconsistent. While an early study [200] reported a reduced activity of ENaC in kidneys of SGK1 knockout mice, a later study in a different mouse model [42] reported unchanged apical ENaC activity. Interestingly, SGK1-deficient mice reveal a reduced NCC abundance and phosphorylation that drops even more during dietary K^+ loading [175] and Na^+ restriction [41]. The downregulation of NCC under standard conditions could be explained by the loss of the stimulatory action of SGK1 on NCC [144], but the further decrease of NCC on high K^+ or low Na^+ diet is apparently SGK1-independent and perhaps secondary to the developing hyperkalemia in these mice [41, 175]. Thus, SGK1 likely contributes to the renal control of K^+ balance, but there is certainly a high degree of redundancy in the underlying signaling pathways.

In these, WNK1 and WNK4 kinases may play a particular role. The WNK kinases are serine/threonine kinases that were implicated in a variety of functions in the body [4, 54]. The relevance of these kinases for the renal control of Na^+ and K^+ balance and blood pressure is evidenced by the fact that mutations in WNK1 and WNK4 cause familial hyperkalemic hypertension (FHHt) (e.g., [54, 127] and see above). A great body of experimental evidence suggests that the kidney-specific short isoform of WNK1 (KS-WNK1) and the ubiquitously expressed long isoform of WNK1 (L-WNK1) act together with WNK4 in a complex cascade. KS-WNK1 antagonizes the inhibitory effect of L-WNK1 on WNK4 [5, 54, 110]. In this concept, the balance between KS-WNK1 and L-WNK1 and the activity mode of WNK4 are decisive for the control of ion-transporting proteins in the distal tubule including NCC, ROMK, and ENaC and hence for the physiological adaptation of the DCT, CNT, and CD to altered dietary K^+ and Na^+ intake [5, 54, 192]. The balance between KS-WNK1 and L-WNK1 appears to be central for the adaptation of the kidney to either a low K^+ or a high K^+ diet. On a low dietary K^+ intake, the ratio of L-WNK1/KS-WNK1 increases [84] and the excess of L-WNK1 is thought to cause an endocytotic retrieval of ROMK [84] and an activation of both NCC [25, 163] and possibly ENaC [201]. The downregulation of ROMK would directly limit K^+ secretion in the distal tubule. The upregulation of NCC would help to minimize K^+ secretion, by reducing the Na^+ and fluid delivery to the downstream localized segments. At the same time, the stimulatory effect of L-WNK1 on ENaC partially counteracts the downregulation of ENaC caused by the suppressed aldosterone levels due to the low K^+ intake. This may promote an inadequately high Na^+ reabsorption in the ENaC-positive distal tubules contributing to the hypertensive effect of a low K^+ diet [66]. In contrast, a high K^+ diet lowers the ratio of L-WNK1/KS-WNK1 [184] and the increased level of KS-WNK1 should ultimately lead to a stimulation of ROMK [184] and inhibition of NCC [58, 163]. Together with the aldosterone-dependent activation of ENaC, this profoundly favors renal K^+ secretion. L-WNK1 and KS-WNK1 may also contribute to the control of BK activity. Hadchouel et al. observed an enhanced BKα protein abundance in KS-WNK1 knockout mice suggesting a possible regulatory role of KS-WNK1 [58]. However, Cheng et al. did not find any evidence for an altered BK channel activity in collecting ducts of K^+-loaded KS-WNK1-deficient mice [28]. L-WNK1 was reported to activate BK, which may alleviate L-WNK-1-dependent inhibition of ROMK [90].

At the same time, the WNK kinases may also allow to independently adapt renal K^+ and Na^+ excretion and to account for the so-called aldosterone paradox [5]. Both a low Na^+ diet and a high K^+ diet increase plasma aldosterone levels. However, the primary physiological response elicited by aldosterone during dietary Na^+ restriction is renal Na^+ retention, whereas during dietary K^+ loading, the response is kaliuresis [5]. WNK4 was proposed to act as an essential molecular switch between these two states [74, 81]. Under standard conditions, WNK4 inhibits NCC [74, 81, 202], ENaC [139, 206], ROMK [74, 84, 140], and BK [190, 208, 212] activity. During dietary Na^+ restriction, the elevated plasma aldosterone and angiotensin II levels stimulate ENaC activity [92]. The elevated angiotensin II (Ang II) levels do also convert WNK4 to a profound stimulator of NCC [21], which together with the activation of ENaC maximizes renal Na^+ retention. At the same time, angiotensin II seems to stabilize the inhibitory activity of WNK4 on ROMK and thereby to minimize renal K^+ secretion [207]. During dietary K^+ loading, ENaC is also activated via aldosterone, but due to the unchanged angiotensin II levels, WNK4 does not switch from inhibition to activation of NCC [5]. Support for these hypotheses comes from numerous experiments in vitro and in vivo (reviewed in [4, 5, 54, 127, 162, 174, 192]) and the observation that dietary Na^+ and K^+ intake indeed differentially modulate the renal mRNA expression of KS-WNK1, L-WNK1, and/or WNK4 in the expected directions [84, 117, 184]. Likewise, dietary Na^+ and K^+ intake were reported to modulate the protein abundance of WNK4 as well as the abundance and phosphorylation of the downstream-acting kinase SPAK [137, 179, 182]. However, the results were not always consistent, and their interpretation is complicated by the fact that WNK4 and SPAK are expressed in several nephron portions, making analyses on the whole organ level difficult. Moreover, altered dietary K^+ intake may not only change the abundance and phosphorylation but also the subcellular localization of these kinases [179], which may further contribute to the complexity of this signaling pathway. Interestingly, a recent study using

WNK4 knockout and SPAK knock-in mouse models suggested that the regulation of NCC by ANG II but not by dietary K^+ depends on the integrity of the WNK4/SPAK pathway [20], suggesting that the K^+-induced effects on NCC may involve additional molecular regulators.

The mechanism, by which an altered dietary K^+ intake interferes with the WNK pathway, begins to be unraveled. There is evidence that changes in extracellular K^+ concentration directly affect WNK1 expression and activity [111]. A possible hypothesis for the explanation of such direct effects comes from recent observations in a mouse model for the human EAST/SeSAME syndrome [210]. The EAST/SeSAME syndrome is caused by mutations in the KCNJ10 K^+ channel that is expressed in certain neurons and in the basolateral plasma membrane of the DCT. The patients suffer from epilepsy, ataxia, sensorineural deafness, and a salt-wasting renal tubulopathy that is similar to that seen in patients with Gitelman syndrome [9]. Consistently, KCNJ10-deficient mice reveal a drastically reduced NCC abundance in the kidney [210]. The authors proposed that the loss of the KCNJ10-mediated K^+ conductance depolarizes the cells and decreases the electrochemical driving force for Cl^- to exit across the basolateral ClC-K Cl^- channels. The subsequent increase in intracellular Cl^- concentration would ultimately suppress SPAK and hence NCC activity [210]. Interestingly, recent crystallographic data and mutational analysis suggested that the WNK1 kinase domain comprises a Cl^--binding pocket. The binding of Cl^- to this site would inhibit the autophosphorylation of WNK1 and thereby its kinase activity [128]. Likewise, Cl^--binding to a homologous binding pocket in WNK4 may switch this kinase from an activator to an inhibitor of NCC phosphorylation and activity [13]. Thus, WNK1 and WNK4 may act as intracellular Cl^- sensors that indirectly sense changes in extracellular K^+ concentrations. Support for this model comes from recent experimental studies in HEK293 cells which suggested that lowered extracellular plasma K^+ concentrations cause a KCNJ10-dependent hyperpolarization of the plasma membrane. Such depolarization increases Cl^- efflux through ClC-Kb Cl^- channels and finally activates the WNK/SPAK pathway through the lowered intracellular Cl^- concentration [172]. Interestingly, WNK4 knockout mice and a knock-in mouse model expressing a mutant form of SPAK that cannot be activated via WNK4 still respond to a dietary K^+ load with reduced NCC phosphorylation [25]. These evidences suggest some redundancy in the signaling mediating the effect of altered dietary K^+ on NCC.

Conclusion

As outlined in this review, there are numerous complex interactions between dietary K^+ intake and the renal control of Na^+ balance and blood pressure. Since the initial suggestion by W.L.T. Addison, an impressive body of evidence confirmed the beneficial effect of a high K^+ diet on arterial blood pressure and cardiovascular outcome. Studies in animal models linked part of these effects to the inhibition of renal Na^+ reabsorption, which may involve a rapid inactivation of the thiazide-sensitive NCC in the DCT. This thiazide-like effect of K^+ may not only lower arterial blood pressure but may also improve renal K^+ excretion by increasing Na^+ and fluid delivery to downstream localized tubular segments. In addition to the pronounced effect of dietary K^+ on NCC, the downregulation of other ion transport processes in the nephron also contributes to the natriuretic and antihypertensive effect of a K^+-rich diet. This may not only include the inhibition of Na^+ transport in the proximal tubule and thick ascending limb but also effects on intercalated cells in the renal collecting system. The role of the latter in blood pressure control is receiving increasing attention, which is further boosted by the recent demonstration that a high K^+ diet modulates the phosphorylation and hence the activity of the mineralocorticoid receptor specifically in intercalated cells [152]. Although the precise physiological impact of this effect remains to be established, the findings further underline the intricate interplay of different renal epithelial cell types in the maintenance of ion homeostasis.

We just started to get insights into the molecular mechanism by which an altered dietary K^+ intake modulates the activity of ion transporting pathways along the renal tubular system. Particular roles appear to play the WNK kinases, which are thought to act as molecular switches, allowing the kidney to independently adapt urinary K^+ and Na^+ excretion to functional needs. Nevertheless, important questions regarding the interaction of these kinases with other signaling pathways in the context of an altered dietary K^+ intake are still unresolved. Moreover, although direct K^+ sensing in adrenal zona glomerulosa has been demonstrated, it remains elusive if and how direct K^+ sensing occurs in the kidney and perhaps in other organs including the gut and by which mechanisms the sensed information is transmitted to the renal epithelia and their various membrane proteins involved in transepithelial Na^+ and K^+ transport. The identification of aldosterone-dependent and independent effects and the characterization of their crosstalk are needed to better understand the complex regulation of K^+ and Na^+ homeostasis and blood pressure control. Eventually, this may help to develop novel strategies to take advantage of the beneficial effects of a K^+-rich diet that does not only include the antihypertensive effects but also reduced risks for urolithiasis and osteoporosis and an improved glucose tolerance [61].

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References

1. Aaron KJ, Sanders PW (2013) Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence. Mayo Clin Proc 88(9):987–995
2. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP (2013) Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ 346:f1378
3. Addison WL (1988) The Canadian Medical Association Journal, vol. XVIII (1928) The use of sodium chloride, potassium chloride, sodium bromide, and potassium bromide in cases of arterial hypertension which are amenable to potassium chloride. Nutr Rev 46(8): 295–296
4. Alessi DR, Zhang J, Khanna A, Hochdorfer T, Shang Y, Kahle KT (2014) The WNK-SPAK/OSR1 pathway: master regulator of cation-chloride cotransporters. Science signaling 7 (334):re3
5. Arroyo JP, Ronzaud C, Lagnaz D, Staub O, Gamba G (2011) Aldosterone paradox: differential regulation of ion transport in distal nephron. Physiology 26(2):115–123
6. Bachmann S, Bostanjoglo M, Schmitt R, Ellison DH (1999) Sodium transport-related proteins in the mammalian distal nephron—distribution, ontogeny and functional aspects. Anat Embryol (Berl) 200(5):447–468
7. Bahler RC, Rakita L (1971) Cardiovascular function in potassium-depleted dogs. Am Heart J 81(5):650–657
8. Bailey MA, Cantone A, Yan Q, MacGregor GG, Leng Q, Amorim JB, Wang T, Hebert SC, Giebisch G, Malnic G (2006) Maxi-K channels contribute to urinary potassium excretion in the ROMK-deficient mouse model of type II Bartter's syndrome and in adaptation to a high-K diet. Kidney Int 70(1):51–59
9. Bandulik S, Schmidt K, Bockenhauer D, Zdebik AA, Humberg E, Kleta R, Warth R, Reichold M (2011) The salt-wasting phenotype of EAST syndrome, a disease with multifaceted symptoms linked to the KCNJ10 K+ channel. Pflugers Arch 461(4):423–435
10. Bandulik S, Tauber P, Lalli E, Barhanin J, Warth R (2014) Two-pore domain potassium channels in the adrenal cortex. Pflugers Arch
11. Barker PM, Nguyen MS, Gatzy JT, Grubb B, Norman H, Hummler E, Rossier B, Boucher RC, Koller B (1998) Role of gammaENaC subunit in lung liquid clearance and electrolyte balance in newborn mice. Insights into perinatal adaptation and pseudohypoaldosteronism. J Clin Invest 102(8):1634–1640
12. Barri YM, Wingo CS (1997) The effects of potassium depletion and supplementation on blood pressure: a clinical review. Am J Med Sci 314(1):37–40
13. Bazua-Valenti S, Chavez-Canales M, Rojas LL, Vázquez NH, Rodriguez-Gama A, Melo Z, Plata C, Ellison DH, Hadchouel J, Gamba G (2014) The effect of WNK4 on the NaCl cotransporter is modulated by intracellular chloride. J Am Soc Nephrol 25:375A
14. Boyden LM, Choi M, Choate KA, Nelson-Williams CJ, Farhi A, Toka HR, Tikhonova IR, Bjornson R, Mane SM, Colussi G, Lebel M, Gordon RD, Semmekrot BA, Poujol A, Valimaki MJ, De Ferrari ME, Sanjad SA, Gutkin M, Karet FE, Tucci JR, Stockigt JR, Keppler-Noreuil KM, Porter CC, Anand SK, Whiteford ML, Davis ID, Dewar SB, Bettinelli A, Fadrowski JJ, Belsha CW, Hunley TE, Nelson RD, Trachtman H, Cole TR, Pinsk M, Bockenhauer D, Shenoy M, Vaidyanathan P, Foreman JW, Rasoulpour M, Thameem F, Al-Shahrouri HZ, Radhakrishnan J, Gharavi AG, Goilav B, Lifton RP (2012) Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. Nature 482(7383):98–102
15. Brandis M, Keyes J, Windhager EE (1972) Potassium-induced inhibition of proximal tubular fluid reabsorption in rats. Am J Physiol 222(2):421–427
16. Brenner R, Chen QH, Vilaythong A, Toney GM, Noebels JL, Aldrich RW (2005) BK channel beta4 subunit reduces dentate gyrus excitability and protects against temporal lobe seizures. Nat Neurosci 8(12):1752–1759
17. Brown D, Lydon J, McLaughlin M, Stuart-Tilley A, Tyszkowski R, Alper S (1996) Antigen retrieval in cryostat tissue sections and cultured cells by treatment with sodium dodecyl sulfate (SDS). Histochem Cell Biol 105(4):261–267
18. Cao XR, Shi PP, Sigmund RD, Husted RF, Sigmund CD, Williamson RA, Stokes JB, Yang B (2006) Mice heterozygous for beta-ENaC deletion have defective potassium excretion. Am J Physiol Renal Physiol 291(1):F107–F115
19. Cassola AC, Giebisch G, Wang W (1993) Vasopressin increases density of apical low-conductance K+ channels in rat CCD. Am J Physiol 264(3 Pt 2):F502–F509
20. Castaneda-Bueno M, Cervantes-Perez LG, Rojas-Vega L, Arroyo-Garza I, Vazquez N, Moreno E, Gamba G (2014) Modulation of NCC activity by low and high K(+) intake: insights into the signaling pathways involved. Am J Physiol Renal Physiol 306(12): F1507–F1519
21. Castaneda-Bueno M, Cervantes-Perez LG, Vazquez N, Uribe N, Kantesaria S, Morla L, Bobadilla NA, Doucet A, Alessi DR, Gamba G (2012) Activation of the renal Na+:Cl- cotransporter by angiotensin II is a WNK4-dependent process. Proc Natl Acad Sci U S A 109(20):7929–7934
22. Castro H, Raij L (2013) Potassium in hypertension and cardiovascular disease. Semin Nephrol 33(3):277–289
23. Chambrey R, Kurth I, Peti-Peterdi J, Houillier P, Purkerson JM, Leviel F, Hentschke M, Zdebik AA, Schwartz GJ, Hubner CA, Eladari D (2013) Renal intercalated cells are rather energized by a proton than a sodium pump. Proc Natl Acad Sci U S A 110(19): 7928–7933
24. Chang SS, Grunder S, Hanukoglu A, Rosler A, Mathew PM, Hanukoglu I, Schild L, Lu Y, Shimkets RA, Nelson-Williams C, Rossier BC, Lifton RP (1996) Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. Nat Genet 12(3):248–253
25. Chavez-Canales M, Zhang C, Soukaseum C, Moreno E, Pacheco-Alvarez D, Vidal-Petiot E, Castaneda-Bueno M, Vazquez N, Rojas-Vega L, Meermeier NP, Rogers S, Jeunemaitre X, Yang CL, Ellison DH, Gamba G, Hadchouel J (2014) WNK-SPAK-NCC cascade revisited: WNK1 stimulates the activity of the Na-Cl cotransporter via SPAK, an effect antagonized by WNK4. Hypertension 64(5): 1047–1053
26. Cheema-Dhadli S, Lin SH, Keong-Chong C, Kamel KS, Halperin ML (2006) Requirements for a high rate of potassium excretion in rats consuming a low electrolyte diet. J Physiol 572(Pt 2):493–501
27. Chen SY, Bhargava A, Mastroberardino L, Meijer OC, Wang J, Buse P, Firestone GL, Verrey F, Pearce D (1999) Epithelial sodium channel regulated by aldosterone-induced protein sgk. Proc Natl Acad Sci U S A 96(5):2514–2519
28. Cheng CJ, Baum M, Huang CL (2013) Kidney-specific WNK1 regulates sodium reabsorption and potassium secretion in mouse cortical collecting duct. Am J Physiol Renal Physiol 304(4):F397–F402
29. Christensen BM, Perrier R, Wang Q, Zuber AM, Maillard M, Mordasini D, Malsure S, Ronzaud C, Stehle JC, Rossier BC, Hummler E (2010) Sodium and potassium balance depends on alphaENaC expression in connecting tubule. J Am Soc Nephrol 21(11):1942–1951

30. Christensen EI, Wagner CA, Kaissling B (2012) Uriniferous tubule: structural and functional organization. Compre Physiol 2(2):805–861
31. Crambert G (2014) H-K-ATPase type 2: relevance for renal physiology and beyond. Am J Physiol Renal Physiol 306(7):F693–F700
32. Dahl LK, Leitl G, Heine M (1972) Influence of dietary potassium and sodium/potassium molar ratios on the development of salt hypertension. J Exp Med 136(2):318–330
33. Dekel B, Nakhoul F, Abassi Z, Aviv R, Winaver J, Szylman P (1997) Complete adaptation to chronic potassium loading after adrenalectomy: possible humoral mechanisms. J Lab Clin Med 129(4):453–461
34. Dietz R, Schomig A, Rascher W, Strasser R, Ganten U, Kubler W (1981) Partial replacement of sodium by potassium in the diet restores impaired noradrenaline inactivation and lowers blood pressure in stroke-prone spontaneously hypertensive rats. Clin Sci (Lond) 61(Suppl 7):69s–71s
35. El Moghrabi S, Houillier P, Picard N, Sohet F, Wootla B, Bloch-Faure M, Leviel F, Cheval L, Frische S, Meneton P, Eladari D, Chambrey R (2010) Tissue kallikrein permits early renal adaptation to potassium load. Proc Natl Acad Sci U S A 107(30):13526–13531
36. Elabida B, Edwards A, Salhi A, Azroyan A, Fodstad H, Meneton P, Doucet A, Bloch-Faure M, Crambert G (2011) Chronic potassium depletion increases adrenal progesterone production that is necessary for efficient renal retention of potassium. Kidney Int 80(3): 256–262
37. Eladari D, Chambrey R, Picard N, Hadchouel J (2014) Electroneutral absorption of NaCl by the aldosterone-sensitive distal nephron: implication for normal electrolytes homeostasis and blood pressure regulation. Cellular and molecular life sciences : CMLS
38. Elkjaer ML, Kwon TH, Wang W, Nielsen J, Knepper MA, Frokiaer J, Nielsen S (2002) Altered expression of renal NHE3, TSC, BSC-1, and ENaC subunits in potassium-depleted rats. Am J Physiol Renal Physiol 283(6):F1376–F1388
39. Ellison DH, Loffing J (2009) Thiazide effects and adverse effects: insights from molecular genetics. Hypertension 54(2):196–202
40. Estilo G, Liu W, Pastor-Soler N, Mitchell P, Carattino MD, Kleyman TR, Satlin LM (2008) Effect of aldosterone on BK channel expression in mammalian cortical collecting duct. Am J Physiol Renal Physiol 295(3):F780–F788
41. Faresse N, Lagnaz D, Debonneville A, Ismailji A, Maillard M, Fejes-Toth G, Naray-Fejes-Toth A, Staub O (2012) Inducible kidney-specific Sgk1 knockout mice show a salt-losing phenotype. Am J Physiol Renal Physiol 302(8):F977–F985
42. Fejes-Toth G, Frindt G, Naray-Fejes-Toth A, Palmer LG (2008) Epithelial Na+ channel activation and processing in mice lacking SGK1. Am J Physiol Renal Physiol 294(6):F1298–F1305
43. Field MJ, Stanton BA, Giebisch GH (1984) Differential acute effects of aldosterone, dexamethasone, and hyperkalemia on distal tubular potassium secretion in the rat kidney. J Clin Invest 74(5): 1792–1802
44. Field MJ, Stanton BA, Giebisch GH (1984) Influence of ADH on renal potassium handling: a micropuncture and microperfusion study. Kidney Int 25(3):502–511
45. Fodstad H, Gonzalez-Rodriguez E, Bron S, Gaeggeler H, Guisan B, Rossier BC, Horisberger JD (2009) Effects of mineralocorticoid and K+ concentration on K+ secretion and ROMK channel expression in a mouse cortical collecting duct cell line. Am J Physiol Renal Physiol 296(5):F966–F975
46. Freed SC, Friedman M (1950) Hypotension in the rat following limitation of potassium intake. Science 112(2922):788–789
47. Frindt G, Houde V, Palmer LG (2011) Conservation of Na+ vs. K+ by the rat cortical collecting duct. Am J Physiol Renal Physiol 301(1):F14–F20
48. Frindt G, Palmer LG (2004) Na channels in the rat connecting tubule. Am J Physiol Renal Physiol 286(4):F669–F674
49. Frindt G, Palmer LG (2009) K+ secretion in the rat kidney: Na+ channel-dependent and -independent mechanisms. Am J Physiol Renal Physiol 297(2):F389–F396
50. Frindt G, Palmer LG (2010) Effects of dietary K on cell-surface expression of renal ion channels and transporters. Am J Physiol Renal Physiol 299(4):F890–F897
51. Frindt G, Zhou H, Sackin H, Palmer LG (1998) Dissociation of K channel density and ROMK mRNA in rat cortical collecting tubule during K adaptation. Am J Physiol 274(3 Pt 2):F525–F531
52. Fujita T, Sato Y (1984) Changes in renal and central noradrenergic activity with potassium in DOCA-salt rats. Am J Physiol 246(5 Pt 2):F670–F675
53. Glover M, Mercier Zuber A, Figg N, O'Shaughnessy KM (2010) The activity of the thiazide-sensitive Na(+)-Cl(−) cotransporter is regulated by protein phosphatase PP4. Can J Physiol Pharmacol 88(10):986–995
54. Glover M, O'Shaughnessy KM (2013) Molecular insights from dysregulation of the thiazide-sensitive WNK/SPAK/NCC pathway in the kidney: Gordon syndrome and thiazide-induced hyponatraemia. Clin Experiment Pharmacol Physiol 40(12):876–884
55. Greenlee M, Wingo CS, McDonough AA, Youn JH, Kone BC (2009) Narrative review: evolving concepts in potassium homeostasis and hypokalemia. Ann Intern Med 150(9):619–625
56. Grimm PR, Irsik DL, Liu L, Holtzclaw JD, Sansom SC (2009) Role of BKbeta1 in Na+ reabsorption by cortical collecting ducts of Na +-deprived mice. Am J Physiol Renal Physiol 297(2):F420–F428
57. Gumz ML, Lynch IJ, Greenlee MM, Cain BD, Wingo CS (2010) The renal H+-K+-ATPases: physiology, regulation, and structure. Am J Physiol Renal Physiol 298(1):F12–F21
58. Hadchouel J, Soukaseum C, Busst C, Zhou XO, Baudrie V, Zurrer T, Cambillau M, Elghozi JL, Lifton RP, Loffing J, Jeunemaitre X (2010) Decreased ENaC expression compensates the increased NCC activity following inactivation of the kidney-specific isoform of WNK1 and prevents hypertension. Proc Natl Acad Sci U S A 107(42):18109–18114
59. Hansson JH, Nelson-Williams C, Suzuki H, Schild L, Shimkets R, Lu Y, Canessa C, Iwasaki T, Rossier B, Lifton RP (1995) Hypertension caused by a truncated epithelial sodium channel gamma subunit: genetic heterogeneity of Liddle syndrome. Nat Genet 11(1):76–82
60. Hansson JH, Schild L, Lu Y, Wilson TA, Gautschi I, Shimkets R, Nelson-Williams C, Rossier BC, Lifton RP (1995) A de novo missense mutation of the beta subunit of the epithelial sodium channel causes hypertension and Liddle syndrome, identifying a proline-rich segment critical for regulation of channel activity. Proc Natl Acad Sci U S A 92(25):11495–11499
61. He FJ, MacGregor GA (2008) Beneficial effects of potassium on human health. Physiol Plant 133(4):725–735
62. He FJ, Markandu ND, Coltart R, Barron J, MacGregor GA (2005) Effect of short-term supplementation of potassium chloride and potassium citrate on blood pressure in hypertensives. Hypertension 45(4):571–574
63. Holtzclaw JD, Cornelius RJ, Hatcher LI, Sansom SC (2011) Coupled ATP and potassium efflux from intercalated cells. Am J Physiol Renal Physiol 300(6):F1319–F1326
64. Holtzclaw JD, Grimm PR, Sansom SC (2011) Role of BK channels in hypertension and potassium secretion. Curr Opin Nephrol Hypertens 20(5):512–517
65. Hoorn EJ, Nelson JH, McCormick JA, Ellison DH (2011) The WNK kinase network regulating sodium, potassium, and blood pressure. J Am Soc Nephrol 22(4):605–614
66. Huang CL, Kuo E, Toto RD (2008) WNK kinases and essential hypertension. Curr Opin Nephrol Hypertens 17(2):133–137

67. Huang DY, Wulff P, Volkl H, Loffing J, Richter K, Kuhl D, Lang F, Vallon V (2004) Impaired regulation of renal K+ elimination in the sgk1-knockout mouse. J Am Soc Nephrol 15(4):885–891
68. Hummler E, Barker P, Gatzy J, Beermann F, Verdumo C, Schmidt A, Boucher R, Rossier BC (1996) Early death due to defective neonatal lung liquid clearance in alpha-ENaC-deficient mice. Nat Genet 12(3):325–328
69. Hunter RW, Craigie E, Homer NZ, Mullins JJ, Bailey MA (2014) Acute inhibition of NCC does not activate distal electrogenic Na+ reabsorption or kaliuresis. Am J Physiol Renal Physiol 306(4): F457–F467
70. Iimura O, Kijima T, Kikuchi K, Miyama A, Ando T, Nakao T, Takigami Y (1981) Studies on the hypotensive effect of high potassium intake in patients with essential hypertension. Clin Sci (Lond) 61(Suppl 7):77s–80s
71. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group (1988). Bmj 297 (6644): 319–328
72. Jain G, Ong S, Warnock DG (2013) Genetic disorders of potassium homeostasis. Semin Nephrol 33(3):300–309
73. Jung JY, Kim S, Lee JW, Jung ES, Heo NJ, Son MJ, Oh YK, Na KY, Han JS, Joo KW (2011) Effects of potassium on expression of renal sodium transporters in salt-sensitive hypertensive rats induced by uninephrectomy. Am J Physiol Renal Physiol 300(6):F1422–F1430
74. Kahle KT, Wilson FH, Leng Q, Lalioti MD, O'Connell AD, Dong K, Rapson AK, MacGregor GG, Giebisch G, Hebert SC, Lifton RP (2003) WNK4 regulates the balance between renal NaCl reabsorption and K+ secretion. Nat Genet 35(4):372–376
75. Kaissling B, Le Hir M (1982) Distal tubular segments of the rabbit kidney after adaptation to altered Na- and K-intake. I Struct Chang Cell Tissue Res 224(3):469–492
76. Karolyi L, Ziegler A, Pollak M, Fischbach M, Grzeschik KH, Koch MC, Seyberth HW (1996) Gitelman's syndrome is genetically distinct from other forms of Bartter's syndrome. Pediatr Nephrol 10(5):551–554
77. Kim GH, Masilamani S, Turner R, Mitchell C, Wade JB, Knepper MA (1998) The thiazide-sensitive Na-Cl cotransporter is an aldosterone-induced protein. Proc Natl Acad Sci U S A 95(24): 14552–14557
78. Kirchner KA (1983) Effect of acute potassium infusion on loop segment chloride reabsorption in the rat. Am J Physiol 244(6): F599–F605
79. Krishna GG, Kapoor SC (1991) Potassium depletion exacerbates essential hypertension. Ann Intern Med 115(2):77–83
80. Krishna GG, Miller E, Kapoor S (1989) Increased blood pressure during potassium depletion in normotensive men. N Engl J Med 320(18):1177–1182
81. Lalioti MD, Zhang J, Volkman HM, Kahle KT, Hoffmann KE, Toka HR, Nelson-Williams C, Ellison DH, Flavell R, Booth CJ, Lu Y, Geller DS, Lifton RP (2006) Wnk4 controls blood pressure and potassium homeostasis via regulation of mass and activity of the distal convoluted tubule. Nat Genet 38(10):1124–1132
82. Langford HG (1983) Dietary potassium and hypertension: epidemiologic data. Ann Intern Med 98(5 Pt 2):770–772
83. Lawton WJ, Fitz AE, Anderson EA, Sinkey CA, Coleman RA (1990) Effect of dietary potassium on blood pressure, renal function, muscle sympathetic nerve activity, and forearm vascular resistance and flow in normotensive and borderline hypertensive humans. Circulation 81(1):173–184
84. Lazrak A, Liu Z, Huang CL (2006) Antagonistic regulation of ROMK by long and kidney-specific WNK1 isoforms. Proc Natl Acad Sci U S A 103(5):1615–1620
85. Lee DH, Maunsbach AB, Riquier-Brison AD, Nguyen MT, Fenton RA, Bachmann S, Yu AS, McDonough AA (2013) Effects of ACE inhibition and ANG II stimulation on renal Na-Cl cotransporter distribution, phosphorylation, and membrane complex properties. Am J Physiol Cell Physiol 304(2):C147–C163
86. Lee FN, Oh G, McDonough AA, Youn JH (2007) Evidence for gut factor in K+ homeostasis. Am J Physiol Renal Physiol 293(2): F541–F547
87. Lemmink HH, van den Heuvel LP, van Dijk HA, Merkx GF, Smilde TJ, Taschner PE, Monnens LA, Hebert SC, Knoers NV (1996) Linkage of Gitelman syndrome to the thiazide-sensitive sodium-chloride cotransporter gene with identification of mutations in Dutch families. Pediatr Nephrol 10(4):403–407
88. Lin DH, Yue P, Rinehart J, Sun P, Wang Z, Lifton R, Wang WH (2012) Protein phosphatase 1 modulates the inhibitory effect of With-no-Lysine kinase 4 on ROMK channels. Am J Physiol Renal Physiol 303(1):F110–F119
89. Liu W, Schreck C, Coleman RA, Wade JB, Hernandez Y, Zavilowitz B, Warth R, Kleyman TR, Satlin LM (2011) Role of NKCC in BK channel-mediated net K(+) secretion in the CCD. Am J Physiol Renal Physiol 301(5):F1088–F1097
90. Liu Y, Song X, Shi Y, Shi Z, Niu W, Feng X, Gu D, Bao HF, Ma HP, Eaton DC, Zhuang J, Cai H (2014) WNK1 activates large-conductance Ca2+-activated K+ channels through modulation of ERK1/2 signaling. J Am Soc Nephrol
91. Loffing J, Kaissling B (2003) Sodium and calcium transport pathways along the mammalian distal nephron: from rabbit to human. Am J Physiol Renal Physiol 284(4):F628–F643
92. Loffing J, Korbmacher C (2009) Regulated sodium transport in the renal connecting tubule (CNT) via the epithelial sodium channel (ENaC). Pflugers Arch 458(1):111–135
93. Loffing J, Zecevic M, Feraille E, Kaissling B, Asher C, Rossier BC, Firestone GL, Pearce D, Verrey F (2001) Aldosterone induces rapid apical translocation of ENaC in early portion of renal collecting system: possible role of SGK. Am J Physiol Renal Physiol 280(4): F675–F682
94. Lorenz JN, Baird NR, Judd LM, Noonan WT, Andringa A, Doetschman T, Manning PA, Liu LH, Miller ML, Shull GE (2002) Impaired renal NaCl absorption in mice lacking the ROMK potassium channel, a model for type II Bartter's syndrome. J Biol Chem 277(40):37871–37880
95. International Consortium for Blood P, Louis-Dit-Picard H, Barc J, Trujillano D, Miserey-Lenkei S, Bouatia-Naji N, Pylypenko O, Beaurain G, Bonnefond A, Sand O, Simian C, Vidal-Petiot E, Soukaseum C, Mandet C, Broux F, Chabre O, Delahousse M, Esnault V, Fiquet B, Houillier P, Bagnis CI, Koenig J, Konrad M, Landais P, Mourani C, Niaudet P, Probst V, Thauvin C, Unwin RJ, Soroka SD, Ehret G, Ossowski S, Caulfield M, Bruneval P, Estivill X, Froguel P, Hadchouel J, Schott JJ, Jeunemaitre X (2012) KLHL3 mutations cause familial hyperkalemic hypertension by impairing ion transport in the distal nephron. Nat Genet 44(4):456–460, S451-453
96. Louis WJ, Tabei R, Spector S (1971) Effects of sodium intake on inherited hypertension in the rat. Lancet 2(7737):1283–1286
97. MacGregor GA, Smith SJ, Markandu ND, Banks RA, Sagnella GA (1982) Moderate potassium supplementation in essential hypertension. Lancet 2(8298):567–570
98. Malnic G, Berliner RW, Giebisch G (1990) Distal perfusion studies: transport stimulation by native tubule fluid. Am J Physiol 258(6 Pt 2):F1523–F1527
99. Malnic G, Klose RM, Giebisch G (1966) Microperfusion study of distal tubular potassium and sodium transfer in rat kidney. Am J Physiol 211(3):548–559
100. Manger WM, Simchon S, Stier CT Jr, Loscalzo J, Jan KM, Jan R, Haddy F (2003) Protective effects of dietary potassium chloride on hemodynamics of Dahl salt-sensitive rats in response to chronic administration of sodium chloride. J Hypertens 21(12):2305–2313
101. Martin RS, Hayslett JP (1986) Role of aldosterone in the mechanism of renal potassium adaptation. Pflugers Arch 407(1):76–81

102. Masilamani S, Kim GH, Mitchell C, Wade JB, Knepper MA (1999) Aldosterone-mediated regulation of ENaC alpha, beta, and gamma subunit proteins in rat kidney. J Clin Invest 104(7):R19–R23
103. McDonald FJ, Yang B, Hrstka RF, Drummond HA, Tarr DE, McCray PB Jr, Stokes JB, Welsh MJ, Williamson RA (1999) Disruption of the beta subunit of the epithelial Na+ channel in mice: hyperkalemia and neonatal death associated with a pseudohypoaldosteronism phenotype. Proc Natl Acad Sci U S A 96(4):1727–1731
104. McDonough AA, Youn JH (2013) Need to quickly excrete K(+)? Turn off NCC. Kidney Int 83(5):779–782
105. Meneely GR, Lemley-Stone J, Darby WJ (1961) Changes in blood pressure and body sodium of rats fed sodium and potassium chloride. Am J Cardiol 8:527–532
106. Meneton P, Loffing J, Warnock DG (2004) Sodium and potassium handling by the aldosterone-sensitive distal nephron: the pivotal role of the distal and connecting tubule. Am J Physiol Renal Physiol 287(4):F593–F601
107. Meneton P, Schultheis PJ, Greeb J, Nieman ML, Liu LH, Clarke LL, Duffy JJ, Doetschman T, Lorenz JN, Shull GE (1998) Increased sensitivity to K+ deprivation in colonic H, K-ATPase-deficient mice. J Clin Invest 101(3):536–542
108. Mente A, O'Donnell MJ, Rangarajan S, McQueen MJ, Poirier P, Wielgosz A, Morrison H, Li W, Wang X, Di C, Mony P, Devanath A, Rosengren A, Oguz A, Zatonska K, Yusufali AH, Lopez-Jaramillo P, Avezum A, Ismail N, Lanas F, Puoane T, Diaz R, Kelishadi R, Iqbal R, Yusuf R, Chifamba J, Khatib R, Teo K, Yusuf S, Investigators P (2014) Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med 371(7): 601–611
109. Michell AR, Debnam ES, Unwin RJ (2008) Regulation of renal function by the gastrointestinal tract: potential role of gut-derived peptides and hormones. Annu Rev Physiol 70:379–403
110. Moes AD, van der Lubbe N, Zietse R, Loffing J, Hoorn EJ (2014) The sodium chloride cotransporter SLC12A3: new roles in sodium, potassium, and blood pressure regulation. Pflugers Arch 466(1): 107–118
111. Naito S, Ohta A, Sohara E, Ohta E, Rai T, Sasaki S, Uchida S (2011) Regulation of WNK1 kinase by extracellular potassium. Clin Exp Nephrol 15(2):195–202
112. Najjar F, Zhou H, Morimoto T, Bruns JB, Li HS, Liu W, Kleyman TR, Satlin LM (2005) Dietary K+ regulates apical membrane expression of maxi-K channels in rabbit cortical collecting duct. Am J Physiol Renal Physiol 289(4):F922–F932
113. Naray-Fejes-Toth A, Canessa C, Cleaveland ES, Aldrich G, Fejes-Toth G (1999) sgk is an aldosterone-induced kinase in the renal collecting duct. Effects on epithelial Na+ channels. J Biol Chem 274(24):16973–16978
114. Nesterov V, Dahlmann A, Krueger B, Bertog M, Loffing J, Korbmacher C (2012) Aldosterone-dependent and -independent regulation of the epithelial sodium channel (ENaC) in mouse distal nephron. Am J Physiol Renal Physiol 303(9):F1289–F1299
115. Nguyen MT, Yang LE, Fletcher NK, Lee DH, Kocinsky H, Bachmann S, Delpire E, McDonough AA (2012) Effects of K+-deficient diets with and without NaCl supplementation on Na+, K+, and H2O transporters' abundance along the nephron. Am J Physiol Renal Physiol 303(1):F92–F104
116. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, Rosengren A, Lopez-Jaramillo P, Diaz R, Avezum A, Lanas F, Yusoff K, Iqbal R, Ilow R, Mohammadifard N, Gulec S, Yusufali AH, Kruger L, Yusuf R, Chifamba J, Kabali C, Dagenais G, Lear SA, Teo K, Yusuf S, Investigators P (2014) Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 371(7):612–623
117. O'Reilly M, Marshall E, Macgillivray T, Mittal M, Xue W, Kenyon CJ, Brown RW (2006) Dietary electrolyte-driven responses in the renal WNK kinase pathway in vivo. J Am Soc Nephrol 17(9):2402–2413
118. Oberleithner H, Callies C, Kusche-Vihrog K, Schillers H, Shahin V, Riethmuller C, Macgregor GA, de Wardener HE (2009) Potassium softens vascular endothelium and increases nitric oxide release. Proc Natl Acad Sci U S A 106(8):2829–2834
119. Palmer BF (2014) Regulation of potassium homeostasis. Clinical Journal of the American Society of Nephrology, CJASN
120. Palmer LG, Antonian L, Frindt G (1994) Regulation of apical K and Na channels and Na/K pumps in rat cortical collecting tubule by dietary K. J Gen Physiol 104(4):693–710
121. Palmer LG, Frindt G (1999) Regulation of apical K channels in rat cortical collecting tubule during changes in dietary K intake. Am J Physiol 277(5 Pt 2):F805–F812
122. Palmer LG, Frindt G (2007) High-conductance K channels in intercalated cells of the rat distal nephron. Am J Physiol Renal Physiol 292(3):F966–F973
123. Palmer LG, Frindt G (2007) Na+ and K+ transport by the renal connecting tubule. Curr Opin Nephrol Hypertens 16(5):477–483
124. Palmer LG, Schnermann J (2014) Integrated control of Na transport along the nephron. Clinical Journal of the American Society of Nephrology: CJASN
125. Parfrey PS, Condon K, Wright P, Vandenburg MJ, Holly JM, Goodwin FJ, Evans SJ, Ledingham JM (1981) Blood pressure and hormonal changes following alteration in dietary sodium and potassium in young men with and without a familial predisposition to hypertension. Lancet 1(8212):113–117
126. Patel AB, Chao J, Palmer LG (2012) Tissue kallikrein activation of the epithelial Na channel. Am J Physiol Renal Physiol 303(4): F540–F550
127. Pathare G, Hoenderop JG, Bindels RJ, San-Cristobal P (2013) A molecular update on pseudohypoaldosteronism type II. Am J Physiol Renal Physiol 305(11):F1513–F1520
128. Piala AT, Moon TM, Akella R, He H, Cobb MH, Goldsmith EJ (2014) Chloride sensing by WNK1 involves inhibition of autophosphorylation. Sci Signal 7(324):ra41
129. Picard N, Eladari D, El Moghrabi S, Planes C, Bourgeois S, Houillier P, Wang Q, Burnier M, Deschenes G, Knepper MA, Meneton P, Chambrey R (2008) Defective ENaC processing and function in tissue kallikrein-deficient mice. J Biol Chem 283(8): 4602–4611
130. Picard N, Trompf K, Yang CL, Miller RL, Carrel M, Loffing-Cueni D, Fenton RA, Ellison DH, Loffing J (2014) Protein phosphatase 1 inhibitor-1 deficiency reduces phosphorylation of renal NaCl cotransporter and causes arterial hypotension. J Am Soc Nephrol 25(3):511–522
131. Pluger S, Faulhaber J, Furstenau M, Lohn M, Waldschutz R, Gollasch M, Haller H, Luft FC, Ehmke H, Pongs O (2000) Mice with disrupted BK channel beta1 subunit gene feature abnormal Ca(2+) spark/STOC coupling and elevated blood pressure. Circ Res 87(11):E53–E60
132. Pradervand S, Vandewalle A, Bens M, Gautschi I, Loffing J, Hummler E, Schild L, Rossier BC (2003) Dysfunction of the epithelial sodium channel expressed in the kidney of a mouse model for Liddle syndrome. J Am Soc Nephrol 14(9):2219–2228
133. Rabinowitz L (1996) Aldosterone and potassium homeostasis. Kidney Int 49(6):1738–1742
134. Rabinowitz L, Green DM, Sarason RL, Yamauchi H (1988) Homeostatic potassium excretion in fed and fasted sheep. Am J Physiol 254(2 Pt 2):R357–R380
135. Rabinowitz L, Sarason RL, Yamauchi H (1985) Effects of KCl infusion on potassium excretion in sheep. Am J Physiol 249(2 Pt 2):F263–F271
136. Reilly RF, Ellison DH (2000) Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. Physiol Rev 80(1):277–313

137. Rengarajan S, Lee DH, Oh YT, Delpire E, Youn JH, McDonough AA (2014) Increasing plasma [K+] by intravenous potassium infusion reduces NCC phosphorylation and drives kaliuresis and natriuresis. Am J Physiol Renal Physiol 306(9):F1059–F1068
138. Rieg T, Vallon V, Sausbier M, Sausbier U, Kaissling B, Ruth P, Osswald H (2007) The role of the BK channel in potassium homeostasis and flow-induced renal potassium excretion. Kidney Int 72(5):566–573
139. Ring AM, Cheng SX, Leng Q, Kahle KT, Rinehart J, Lalioti MD, Volkman HM, Wilson FH, Hebert SC, Lifton RP (2007) WNK4 regulates activity of the epithelial Na+ channel in vitro and in vivo. Proc Natl Acad Sci U S A 104(10):4020–4024
140. Ring AM, Leng Q, Rinehart J, Wilson FH, Kahle KT, Hebert SC, Lifton RP (2007) An SGK1 site in WNK4 regulates Na+ channel and K+ channel activity and has implications for aldosterone signaling and K+ homeostasis. Proc Natl Acad Sci U S A 104(10): 4025–4029
141. Ronzaud C, Staub O (2014) Ubiquitylation and control of renal Na+ balance and blood pressure. Physiology 29(1):16–26
142. Rossier BC, Staub O, Hummler E (2013) Genetic dissection of sodium and potassium transport along the aldosterone-sensitive distal nephron: importance in the control of blood pressure and hypertension. FEBS Lett 587(13):1929–1941
143. Rossier BC, Stutts MJ (2009) Activation of the epithelial sodium channel (ENaC) by serine proteases. Annu Rev Physiol 71:361–379
144. Rozansky DJ, Cornwall T, Subramanya AR, Rogers S, Yang YF, David LL, Zhu X, Yang CL, Ellison DH (2009) Aldosterone mediates activation of the thiazide-sensitive Na-Cl cotransporter through an SGK1 and WNK4 signaling pathway. J Clin Invest 119(9):2601–2612
145. Rubera I, Loffing J, Palmer LG, Frindt G, Fowler-Jaeger N, Sauter D, Carroll T, McMahon A, Hummler E, Rossier BC (2003) Collecting duct-specific gene inactivation of alphaENaC in the mouse kidney does not impair sodium and potassium balance. J Clin Invest 112(4):554–565
146. Rutledge JC, Rabinowitz L (1987) Kaliuretic regulatory factors in the rat. Am J Physiol 253(6 Pt 2):F1182–F1196
147. Sachse G, Faulhaber J, Seniuk A, Ehmke H, Pongs O (2014) Smooth muscle BK channel activity influences blood pressure independent of vascular tone in mice. J Physiol 592(Pt 12):2563–2574
148. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH, Group DA-SCR (2001) Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. DASH-sodium collaborative research group. N Engl J Med 344(1):3–10
149. Saum WR, Ayachi S, Brown AM (1977) Actions of sodium and potassium ions on baroreceptors of normotensive and spontaneously hypertensive rats. Circ Res 41(6):768–774
150. Sausbier M, Arntz C, Bucurenciu I, Zhao H, Zhou XB, Sausbier U, Feil S, Kamm S, Essin K, Sailer CA, Abdullah U, Krippeit-Drews P, Feil R, Hofmann F, Knaus HG, Kenyon C, Shipston MJ, Storm JF, Neuhuber W, Korth M, Schubert R, Gollasch M, Ruth P (2005) Elevated blood pressure linked to primary hyperaldosteronism and impaired vasodilation in BK channel-deficient mice. Circulation 112(1):60–68
151. Schultheis PJ, Lorenz JN, Meneton P, Nieman ML, Riddle TM, Flagella M, Duffy JJ, Doetschman T, Miller ML, Shull GE (1998) Phenotype resembling Gitelman's syndrome in mice lacking the apical Na+-Cl- cotransporter of the distal convoluted tubule. J Biol Chem 273(44):29150–29155
152. Shibata S, Rinehart J, Zhang J, Moeckel G, Castaneda-Bueno M, Stiegler AL, Boggon TJ, Gamba G, Lifton RP (2013) Mineralocorticoid receptor phosphorylation regulates ligand binding and renal response to volume depletion and hyperkalemia. Cell Metab 18(5):660–671
153. Shimkets RA, Warnock DG, Bositis CM, Nelson-Williams C, Hansson JH, Schambelan M, Gill JR Jr, Ulick S, Milora RV, Findling JW et al (1994) Liddle's syndrome: heritable human hypertension caused by mutations in the beta subunit of the epithelial sodium channel. Cell 79(3):407–414
154. Shirley DG, Skinner J, Walter SJ (1987) The influence of dietary potassium on the renal tubular effect of hydrochlorothiazide in the rat. Br J Pharmacol 91(3):693–699
155. Simon DB, Nelson-Williams C, Bia MJ, Ellison D, Karet FE, Molina AM, Vaara I, Iwata F, Cushner HM, Koolen M, Gainza FJ, Gitleman HJ, Lifton RP (1996) Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na-Cl cotransporter. Nat Genet 12(1):24–30
156. Sorensen MV, Grossmann S, Roesinger M, Gresko N, Todkar AP, Barmettler G, Ziegler U, Odermatt A, Loffing-Cueni D, Loffing J (2013) Rapid dephosphorylation of the renal sodium chloride cotransporter in response to oral potassium intake in mice. Kidney Int 83(5):811–824
157. Spicer Z, Miller ML, Andringa A, Riddle TM, Duffy JJ, Doetschman T, Shull GE (2000) Stomachs of mice lacking the gastric H, K-ATPase alpha-subunit have achlorhydria, abnormal parietal cells, and ciliated metaplasia. J Biol Chem 275(28): 21555–21565
158. Stanton B, Pan L, Deetjen H, Guckian V, Giebisch G (1987) Independent effects of aldosterone and potassium on induction of potassium adaptation in rat kidney. J Clin Invest 79(1):198–206
159. Stanton BA (1989) Renal potassium transport: morphological and functional adaptations. Am J Physiol 257(5 Pt 2):R989–R997
160. Stokes JB (1982) Consequences of potassium recycling in the renal medulla. Effects of ion transport by the medullary thick ascending limb of Henle's loop. J Clin Invest 70(2):219–229
161. Strautnieks SS, Thompson RJ, Gardiner RM, Chung E (1996) A novel splice-site mutation in the gamma subunit of the epithelial sodium channel gene in three pseudohypoaldosteronism type 1 families. Nat Genet 13(2):248–250
162. Subramanya AR, Ellison DH (2014) Distal convoluted tubule. Clinical journal of the American Society of Nephrology: CJASN
163. Subramanya AR, Yang CL, Zhu X, Ellison DH (2006) Dominant-negative regulation of WNK1 by its kidney-specific kinase-defective isoform. Am J Physiol Renal Physiol 290(3):F619–F624
164. Sufit CR, Jamison RL (1983) Effect of acute potassium load on reabsorption in Henle's loop in the rat. Am J Physiol 245(5 Pt 1): F569–F576
165. Sun P, Yue P, Wang WH (2012) Angiotensin II stimulates epithelial sodium channels in the cortical collecting duct of the rat kidney. Am J Physiol Renal Physiol 302(6):F679–F687
166. Susa K, Sohara E, Rai T, Zeniya M, Mori Y, Mori T, Chiga M, Nomura N, Nishida H, Takahashi D, Isobe K, Inoue Y, Takeishi K, Takeda N, Sasaki S, Uchida S (2014) Impaired degradation of WNK1 and WNK4 kinases causes PHAII in mutant KLHL3 knock-in mice. Hum Mol Genet 23(19):5052–5060
167. Suzuki H, Kondo K, Saruta T (1981) Effect of potassium chloride on the blood pressure in two-kidney, one clip Goldblatt hypertensive rats. Hypertension 3(5):566–573
168. Suzuki H, Kondo K, Saruta T (1981) Inhibitory effect of potassium on blood pressure in DOCA salt hypertension in rats. Acta Endocrinol (Copenh) 97(4):525–532
169. Svetkey LP, Yarger WE, Feussner JR, DeLong E, Klotman PE (1987) Double-blind, placebo-controlled trial of potassium chloride in the treatment of mild hypertension. Hypertension 9(5):444–450
170. Tannen RL (1983) Effects of potassium on blood pressure control. Ann Intern Med 98(5 Pt 2):773–780
171. Tannen RL, Wedell E, Moore R (1973) Renal adaptation to a high potassium intake. the role of hydrogen ion. J Clin Invest 52(9): 2089–2101

172. Terker A, McCormick JA, Weinstein AM, Wang WH, Yang C-L, Ellison DH (2014) Chloride-sensing by WNK kinases mediates effects of dietary potassium on systemic ion balance. J Am Soc Nephrol 25:375A
173. Todkar A, Picard N, Loffing-Cueni D, Sorensen MV, Mihailova M, Nesterov V, Makhanova N, Korbmacher C, Wagner CA, Loffing J (2014) Mechanisms of renal control of potassium homeostasis in complete aldosterone deficiency. J Am Soc Nephrol
174. Uchida S (2014) Regulation of blood pressure and renal electrolyte balance by Cullin-RING ligases. Curr Opin Nephrol Hypertens 23(5):487–493
175. Vallon V, Schroth J, Lang F, Kuhl D, Uchida S (2009) Expression and phosphorylation of the Na+-Cl- cotransporter NCC in vivo is regulated by dietary salt, potassium, and SGK1. Am J Physiol Renal Physiol 297(3):F704–F712
176. van Buren M, Rabelink TJ, van Rijn HJ, Koomans HA (1992) Effects of acute NaCl, KCl and KHCO3 loads on renal electrolyte excretion in humans. Clin Sci (Lond) 83(5):567–574
177. van der Lubbe N, Lim CH, Fenton RA, Meima ME, Jan Danser AH, Zietse R, Hoorn EJ (2011) Angiotensin II induces phosphorylation of the thiazide-sensitive sodium chloride cotransporter independent of aldosterone. Kidney Int 79(1):66–76
178. van der Lubbe N, Lim CH, Meima ME, van Veghel R, Rosenbaek LL, Mutig K, Danser AH, Fenton RA, Zietse R, Hoorn EJ (2012) Aldosterone does not require angiotensin II to activate NCC through a WNK4-SPAK-dependent pathway. Pflugers Arch 463(6):853–863
179. van der Lubbe N, Moes AD, Rosenbaek LL, Schoep S, Meima ME, Danser AH, Fenton RA, Zietse R, Hoorn EJ (2013) K+-induced natriuresis is preserved during Na+ depletion and accompanied by inhibition of the Na+-Cl- cotransporter. Am J Physiol Renal Physiol 305(8):F1177–F1188
180. Vander AJ (1970) Direct effects of potassium on renin secretion and renal function. Am J Physiol 219(2):455–459
181. Vio CP, Figueroa CD (1987) Evidence for a stimulatory effect of high potassium diet on renal kallikrein. Kidney Int 31(6):1327–1334
182. Vitzthum H, Seniuk A, Schulte LH, Muller ML, Hetz H, Ehmke H (2014) Functional coupling of renal K+ and Na+ handling causes high blood pressure in Na+ replete mice. J Physiol 592(Pt 5):1139–1157
183. Wade JB, Fang L, Coleman RA, Liu J, Grimm PR, Wang T, Welling PA (2011) Differential regulation of ROMK (Kir1.1) in distal nephron segments by dietary potassium. Am J Physiol Renal Physiol 300(6):F1385–F1393
184. Wade JB, Fang L, Liu J, Li D, Yang CL, Subramanya AR, Maouyo D, Mason A, Ellison DH, Welling PA (2006) WNK1 kinase isoform switch regulates renal potassium excretion. Proc Natl Acad Sci U S A 103(22):8558–8563
185. Wagner CA, Loffing-Cueni D, Yan Q, Schulz N, Fakitsas P, Carrel M, Wang T, Verrey F, Geibel JP, Giebisch G, Hebert SC, Loffing J (2008) Mouse model of type II Bartter's syndrome. II. Altered expression of renal sodium- and water-transporting proteins. Am J Physiol Renal Physiol 294(6):F1373–F1380
186. Wald H, Garty H, Palmer LG, Popovtzer MM (1998) Differential regulation of ROMK expression in kidney cortex and medulla by aldosterone and potassium. Am J Physiol 275(2 Pt 2):F239–F245
187. Wall SM, Pech V (2010) Pendrin and sodium channels: relevance to hypertension. J Nephrol 23(Suppl 16):S118–S123
188. Wang T, Giebisch G (1996) Effects of angiotensin II on electrolyte transport in the early and late distal tubule in rat kidney. Am J Physiol 271(1 Pt 2):F143–F149
189. Wang WH, Giebisch G (2009) Regulation of potassium (K) handling in the renal collecting duct. Pflugers Arch 458(1):157–168
190. Wang Z, Subramanya AR, Satlin LM, Pastor-Soler NM, Carattino MD, Kleyman TR (2013) Regulation of large-conductance Ca2+-activated K+ channels by WNK4 kinase. Am J Physiol Cell Physiol 305(8):C846–C853
191. Wei Y, Liao Y, Zavilowitz B, Ren J, Liu W, Chan P, Rohatgi R, Estilo G, Jackson EK, Wang WH, Satlin LM (2014) Angiotensin II type 2 receptor regulates ROMK-like K+ channel activity in the renal cortical collecting duct during high dietary K+ adaptation. Am J Physiol Renal Physiol 307(7):F833–F843
192. Welling PA (2013) Regulation of renal potassium secretion: molecular mechanisms. Semin Nephrol 33(3):215–228
193. Welling PA (2014) Rare mutations in renal sodium and potassium transporter genes exhibit impaired transport function. Curr Opin Nephrol Hypertens 23(1):1–8
194. Wen D, Cornelius RJ, Rivero-Hernandez D, Yuan Y, Li H, Weinstein AM, Sansom SC (2014) Relation between BK-alpha/beta4-mediated potassium secretion and ENaC-mediated sodium reabsorption. Kidney Int 86(1):139–145
195. Wen D, Cornelius RJ, Yuan Y, Sansom SC (2013) Regulation of BK-alpha expression in the distal nephron by aldosterone and urine pH. Am J Physiol Renal Physiol 305(4):F463–F476
196. Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Achard JM, Feely MP, Dussol B, Berland Y, Unwin RJ, Mayan H, Simon DB, Farfel Z, Jeunemaitre X, Lifton RP (2001) Human hypertension caused by mutations in WNK kinases. Science 293(5532):1107–1112
197. Wingo CS, Seldin DW, Kokko JP, Jacobson HR (1982) Dietary modulation of active potassium secretion in the cortical collecting tubule of adrenalectomized rabbits. J Clin Invest 70(3):579–586
198. Woda CB, Bragin A, Kleyman TR, Satlin LM (2001) Flow-dependent K+ secretion in the cortical collecting duct is mediated by a maxi-K channel. Am J Physiol Renal Physiol 280(5):F786–F793
199. Wu RS, Marx SO (2010) The BK potassium channel in the vascular smooth muscle and kidney: alpha- and beta-subunits. Kidney Int 78(10):963–974
200. Wulff P, Vallon V, Huang DY, Volkl H, Yu F, Richter K, Jansen M, Schlunz M, Klingel K, Loffing J, Kauselmann G, Bosl MR, Lang F, Kuhl D (2002) Impaired renal Na(+) retention in the sgk1-knockout mouse. J Clin Invest 110(9):1263–1268
201. Xu BE, Stippec S, Chu PY, Lazrak A, Li XJ, Lee BH, English JM, Ortega B, Huang CL, Cobb MH (2005) WNK1 activates SGK1 to regulate the epithelial sodium channel. Proc Natl Acad Sci U S A 102(29):10315–10320
202. Yang CL, Angell J, Mitchell R, Ellison DH (2003) WNK kinases regulate thiazide-sensitive Na-Cl cotransport. J Clin Invest 111(7):1039–1045
203. Yang SS, Morimoto T, Rai T, Chiga M, Sohara E, Ohno M, Uchida K, Lin SH, Moriguchi T, Shibuya H, Kondo Y, Sasaki S, Uchida S (2007) Molecular pathogenesis of pseudohypoaldosteronism type II: generation and analysis of a Wnk4(D561A/+) knockin mouse model. Cell Metab 5(5):331–344
204. Yoo D, Kim BY, Campo C, Nance L, King A, Maouyo D, Welling PA (2003) Cell surface expression of the ROMK (Kir 1.1) channel is regulated by the aldosterone-induced kinase, SGK-1, and protein kinase A. J Biol Chem 278(25):23066–23075
205. Young DB, McCaa RE, Pan YJ, Guyton AC (1976) The natriuretic and hypotensive effects of potassium. Circ Res 38(6 Suppl 2):84–89
206. Yu L, Cai H, Yue Q, Alli AA, Wang D, Al-Khalili O, Bao HF, Eaton DC (2013) WNK4 inhibition of ENaC is independent of Nedd4-2-mediated ENaC ubiquitination. Am J Physiol Renal Physiol 305(1):F31–F41
207. Yue P, Sun P, Lin DH, Pan C, Xing W, Wang W (2011) Angiotensin II diminishes the effect of SGK1 on the WNK4-mediated inhibition of ROMK1 channels. Kidney Int 79(4):423–431
208. Yue P, Zhang C, Lin DH, Sun P, Wang WH (2013) WNK4 inhibits Ca(2+)-activated big-conductance potassium channels (BK) via mitogen-activated protein kinase-dependent pathway. Biochim Biophys Acta 1833(10):2101–2110

209. Zecevic M, Heitzmann D, Camargo SM, Verrey F (2004) SGK1 increases Na, K-ATP cell-surface expression and function in Xenopus laevis oocytes. Pflugers Arch 448(1): 29–35
210. Zhang C, Wang L, Zhang J, Su XT, Lin DH, Scholl UI, Giebisch G, Lifton RP, Wang WH (2014) KCNJ10 determines the expression of the apical Na-Cl cotransporter (NCC) in the early distal convoluted tubule (DCT1). Proc Natl Acad Sci U S A 111(32):11864–11869
211. Zhang Z, Li M, Lu R, Alioua A, Stefani E, Toro L (2014) The angiotensin II type 1 receptor (AT1R) closely interacts with large conductance voltage- and Ca2+-activated K+ (BK) channels and inhibits their activity independent of G-protein activation. J Biol Chem 289(37):25678–25689
212. Zhuang J, Zhang X, Wang D, Li J, Zhou B, Shi Z, Gu D, Denson DD, Eaton DC, Cai H (2011) WNK4 kinase inhibits Maxi K channel activity by a kinase-dependent mechanism. Am J Physiol Renal Physiol 301(2):F410–F419