Review Article

Kidney ion handling genes and their interaction in blood pressure control

Caiyan An1,2, Liuyi Yang3, Tengfei Han2, Huazhong Song2, Zichao Li2, Junjing Zhang1 and Kejin Zhang4

1Foundational and Translational Medical Research Center, Department of Allergy and General Surgery, Hohhot First Hospital, Hohhot 010030, China; 2Department of Pathophysiology, Basic Medicine College of Inner Mongolia Medical University, Hohhot 010050, China; 3Department of Medical Imaging, The First Clinical Medical College of Inner Mongolia Medical University, Hohhot 010050, China; 4Department of Biological Sciences, College of Life Science, Institute of Population and Health, Northwest University, Xi’an 710069, China

Correspondence: Junjing Zhang (zhang.jj@vip.163.com) or Kejin Zhang (zhangkj@nwu.edu.cn)

Hypertension affects 30% of adults and is the leading risk factor for cardiovascular disease. Kidney sodium reabsorption plays a vital role in the initial stage and development of essential hypertension. It has been extensively reported that the variants of kidney ion handling genes are associated to blood pressure, and clinical features of hypertension. However, the underlying mechanisms by which these variants alter protein function are rarely summarized. In addition, the variation of one single gene is often limited to induce a significant effect on blood pressure. In the past few decades, the influence by genes × genes (G × G) and/or genotype × environment (G × E) interactions on a given trait, for example, blood pressure, have been widely considered, especially in studies on polygenic genetic traits. In the present review, we discuss the progress in genetics studies on kidney ion handling genes, encoding Na+ channels (Na+-Cl− cotransporter [NCC], Na-K-2Cl cotransporter [NKCC2]), epithelial Na+ channels [ENaCs]), K+ channel (renal outer medullary potassium channel [ROMK]), and Cl− channels (Pendrin, chloride voltage-gated channel Kb [CLC-Kb]), respectively, and their upstream kinases, WNKs and SGK1. We seek to clarify how these genes are involved in kidney sodium absorption and influence blood pressure, especially emphasizing the underlying mechanisms by which genetic variants alter protein functions and interaction in blood pressure regulation. The present review aims to enhance our understanding of the important role of kidney ion handling genes/channels in blood pressure control.

Introduction

More than 1.1 billion people worldwide have hypertension [1,2], which is the main risk factor for stroke, coronary heart disease, kidney disease and other diseases, and responsible for estimated 7.8 million deaths worldwide in 2015 alone [3]. The pathogenesis of hypertension is complicated, including increased sympathetic nerve excitability, up-regulation of the renin-angiotensin-aldosterone system (RAAS) and renal sodium reabsorption, vascular damage, immune system dysfunction, and inflammation. Among those, renal sodium reabsorption plays an important role in blood pressure regulation; in fact, RAAS also involves renal sodium reabsorption through stimulating the release of aldosterone [4].

Earlier, people have realized that abnormal renal function is closely related to one’s blood pressure [5,6]. Over 4500 years ago in China, the Yellow Emperor’s Classic of Internal Medicine has suggested that ‘the kidneys pass on the diseases to the heart’ [7]. However, the mechanism by which the kidney regulates blood pressure was still not fully clarified [8], until the 1960s, Guyton’s ‘pressure natriuresis relationship’ model first explained the underlying mechanism by which renal sodium excretion is closely related to long-term blood pressure regulation [9–12]. Increased renal sodium reabsorption leads to enhanced water reabsorption in the kidneys, a subsequent increase in blood volume and the venous blood flowing back to the heart, and finally leads to an increase in blood pressure [4,12]. The evidence of blood pressure travels...
Figure 1. Renal sodium reabsorption-related genes involved in blood pressure regulation

Channels or kinases discussed in the present review were marked in red. The relative amounts of reabsorption (for sodium and potassium) and secretion (for potassium) in the different parts of kidney were shown as follows: PT (60%), TAL (30%), DCT (7%), and CCD (2%) for sodium reabsorption; PT (65%), and TAL (25%) for potassium reabsorption; and potassium secretion is accomplished mainly in the part of DCT. Abbreviations: PT, proximal tubule; TAL, thick ascending limb; DCT, distal convoluted tubule; CCD, cortical collecting duct.

with the kidney in Milan rats had indicated that the process of renal sodium reabsorption is determined by genetic background, which is sufficient to alter blood pressure in the recipients [13].

Following recent breakthroughs in genotyping, and sequencing numerous genes and/or their variations related to hypertension and other relative disorders have been identified. For instance, summary statistics of the NHGRI-EBI Catalog of human genome-wide association studies (GWAS Catalog, https://www.ebi.ac.uk/gwas/home) records that about 733 genetic genes/variants in 90 studies associate to persistently high systemic arterial blood pressure. Up to April 2022, in PubMed database (https://pubmed.ncbi.nlm.nih.gov/) more than 56 studies discuss the relationship between genetic variants of genes related to renal sodium reabsorption and blood pressure regulation. These identified renal sodium reabsorption-related genes involved in blood pressure regulation included: (i) Kidney ion handling genes, encoding Na+/Cl− cotransporter (NCC), Na-K-2Cl cotransporter (NKCC2), sodium channels (ENaC), renal outer medullary potassium channel (ROMK), Pendrin, chloride channels (CLC-Kb), respectively, and their upstream kinases, WNKs and SGK1, etc.; and (ii) RAAS genes, including AGT, REN, Ang I, Ang II, ACE, CYP11B2, and aldosterone etc., which participate in the kidney sodium reabsorption via the aldosterone/ENaC pathway (Figure 1 and Supplementary Table S1). Genetic variants leading to the alteration of renal sodium reabsorption are significantly associated to people’s blood pressure, and then responsible for clinical features of hypertension [14]. However, most studies usually focused on one or two kidney sodium reabsorption-related genes, which participate in blood pressure regulation, rather than provided a panel of kidney ion handling genes in blood pressure control. Meanwhile, only a few studies (i.e., Ashley et al. [15] summarized the partial mechanisms of ENaCs) elaborated detailed mechanisms by which the variants in kidney ion handling genes change the function of proteins and the interaction of G × G in blood pressure regulation.
The kidney handles a wide variety of ions including sodium, potassium, chloride, magnesium, calcium, and others to influence blood pressure. However, in the present review, we focused on the latest genetic studies of kidney sodium, potassium, and chloride handling genes, especially in the thick ascending limb of Henle's loop (TALHL), distal convoluted tubule (DCT), and cortical collecting duct (CCD), encoding Na⁺ channels (NCC, NKCC2, ENaCs), K⁺ channel (ROMK), and Cl⁻ channels (Pendrin, CLC-Kb), respectively, and their upstream kinases, WNKs and SGK1, and clarified how they were involved in kidney sodium absorption and influence blood pressure, and elaborated the underlying mechanisms of these genes variations altering protein functions and their interaction in blood pressure regulation, which may provide an opportunity to understand the relationship between genetic background of renal physiology and blood pressure regulation, and individual susceptibility to hypertension [16], and further emphasized the significance of renal sodium reabsorption in blood pressure control.

Genetic variants of ion channels in the kidney
The process of reabsorption in the kidney is, through its specialized ion channels (e.g., Sodium channels—ENaC; Potassium channels—ROMK; and Chloride channels—CLCs, etc.), the nephron removing water and solutes from the tubular fluid and returning them to the circulating blood, and ensuring appropriate electrolyte homeostasis. Given the blood volume closely influenced by renal sodium reabsorption, genetic variants, and mutations of ion channels involving the process of this reabsorption are being paid attention to by researchers and clinical doctors. Two decades of genetics studies are also indicated that these genetic backgrounds may be responsible for individuals’ blood pressure through altering the process of reabsorption on ion channel(s).

Genetic variants of Na⁺ channels
Na⁺ channels in the TAL, DCT, and CCD of kidney are mainly composed of ENaCs, NCC, and NKCC2. Human ENaCs, as the end effector of adrenocortical hormones and excitable epithelial Na⁺ channel, has four subunits: α, β, γ, and δ encoded by SCNN1A, SCNN1B, SCNN1G, and SCNN1D, respectively [17], which are mainly located in connecting tubule (CNT) and collecting ducts (CD) and responsible for the rate-limiting reabsorption of Na⁺ in the kidney, and plays an important role in maintaining homeostasis of extracellular fluid volume, blood pressure, and sodium. Gain-of-function mutations in ENaC subunits β and γ cause a rare hereditary hypertension, Liddle syndrome. Conversely, loss-of-function mutations in ENaC result in a kind of hereditary hypotension, pseudohypoaldosteronism type 1 (PHA 1) [15]. Association studies also showed that ENaC variants (e.g., p.T663A of SCNN1A [18], p.T594M of SCNN1B [19], and c.G(-173)A of SCNN1G [20]) are closely related to hypertension in the general population (Supplementary Table S3).

Functional studies showed that variants of the SCNN1A, SCNN1B, and SCNN1G genes mainly change the function of Na⁺ channels through four mechanisms: (i) Influence the surface expression of ENaC channel (e.g., p.C618F [21], p.A334T [22], p.V481M [22], p.H239R [33], and p.A663T [21,24] of SCNN1A, and c.G(-173)A [20] of SCNN1G). For instance, Tong et al. [21] found that αENaC variants p.C618F and p.A663T increased the number of apical membrane αENaC, thereby increasing the activity of αENaC above 3.3 times and 1.6 times, respectively. (ii) Modulate the open probability of channels (Po). The open probability of ion channels is positively correlated with channel activity. With the enhancement of channel open probability, the channel activity increases. Some variants (e.g., p.W493R of SCNN1A [25], p.R564 stop mutation of SCNN1B [26], and p.L511Q of SCNN1G [27]) have been reported to change the open probability of channels. Of them, SCNN1G p.L511Q [27] increased the open probability of the channel by four-fold compared with wild-type cells; (iii) Affect the proteolytic cleavage of ENaC protein. The activity of ENaC is also affected by the state of proteolytic cleavage. The channel product after proteolytic cleavage has a high-channel open probability due to the release of an inhibitory tract in ENaC protein, while the uncleavage channel is in an inactive state [28–31]. Knight et al. [28] found ENaC gene mutation not only changes surface expression of the channel but also affects the activity of the ENaC channel by changing the proteolytic cleavage state of the channel protein. Kota et al. [32] demonstrated that an alternative splicing variant of αENaC (αΔ34–82-ENaC) significantly reduces the channel activity, which is mainly due to the increase in uncleaved, near-silence ENaC; (iv) Alter the Na⁺ self-inhibition on ENaC channels, e.g., p.A334T [22], p.R476W [22], p.V481M [22], p.H239R [33], p.H239D [33], and p.H239C [33] of SCNN1A; p.H239R [33], p.yH239D [33], p.yH239C [33], p.L511Q [27] of SCNN1G. ENaC selectively allows extracellular sodium ions to enter endothelial cells, and at the same time, elevated extracellular sodium ions have a certain inhibitory effect on ENaC channels, which is referred to as Na⁺ self-inhibition [15,33–35]. Na⁺ self-inhibition enables the distal nephron to control Na⁺ reabsorption based on the urinary Na⁺ concentrations and maintains sodium homeostasis in body fluid [15]. Many studies have found that ENaC variants affect the channel function by altering Na⁺ self-inhibition [30,36–38]. For example, Rauh et al. [25] reported that compared with...
Figure 2. Variants of kidney sodium reabsorption-related genes and their effects on SBP (red), DBP (blue), and hypertension (black)

(A) SLC12A3 gene; (B) SGK1 gene; (C) WNK1 gene; (D) KCNJ1 gene. The detailed information are shown in Supplementary Table S3.

wild-type cells, αENaC W493R mutant cell increased the amiloride-sensitive whole-cell current by about four-fold, partially by reducing the inhibitory effect of extracellular sodium ions on ENaC, thereby increasing the activity of ENaC channels.

Besides ENaC, two cotransporters including NCC and NKCC2 are also involved in kidney sodium reabsorption, and exert vital roles in blood pressure regulation. For NCC, its encoding gene SLC12A3 is specifically expressed in the apical membrane of the DCT cells of kidney, whose genetic variants and mutations (Figure 2A and Supplementary Table S3) show closely relationship to individual’s blood pressure and/or hypertension [39–41]. SLC12A3 gene mutations cause the functional changes of NCC protein through modifying NCC’s expression (e.g., SLC12A3 p.S186F [42]), localization (e.g., NCC1/2 variants [43]), and activity (e.g., SLC12A3 p.Arg919Cys [44]) in membrane of cells. Moreover, several studies have also found that NCC transporters carrying different mutants have a different affinity for thiazide diuretics. For instance, in 2006, Moreno et al. [45] defined NCC transporter TM (transmembrane domain) 8–12 as a residue domain with high thiazide affinity; in 2007, Vormfelde et al. [46] found that subjects with NCC G264A mutants had greater diuretic response to diuretics; in 2010, an in-vitro validation study with Xenopus oocytes found that mutations in specific amino acids located within TM8-12 were the main cause of thiazide affinity differences between NCC transporters containing different mutants [47].

For NKCC2 encoding gene SLC12A1, it is specifically mainly expressed in the apical membrane of the TALH and responsible for nearly 24% of kidney sodium reabsorption [48]. Therefore, NKCC2 is one transporter with the strongest renal sodium reabsorption capacity and even subtle changes in the activity of NKCC2 can significantly
change kidney sodium reabsorption [48]. As listed in Supplementary Table S3, mutations of SLC12A1 were observed having strong association to blood pressure and hypertension in the general population [49,50]. Functional verification showed that variants of SLC12A1 change the protein function through effecting the surface expression (e.g., p.R302W and p.L505V [51]), location (e.g., p.R302W and p.L505V [51]), and activation (e.g., p.R298W, p.P344L, p.L501V, p.N395S, p.P565H, and p.Y1066C [42]) of NKCC2. Some studies have also found that the current targeted medicines to NKCC2 have differential action depending on the underlying mutation in NKCC2. For example, NKCC2 with different mutants have different affinities for a loop diuretic (bumetanil) [46].

Genetic variants of K+ channel

The ROMK (Kir1.1) is a kind of K+ channel, encoded by the KCNJ1 gene. ROMK is mainly expressed in two areas of kidney: CCD and TALH/L. ROMK strictly regulates the secretion of potassium in CCD and at the same time controls the potassium cycle in TALH/L. Potassium plays an important role in the regulation of blood pressure. Diet potassium intake, serum potassium, and urinary potassium are all negatively associated with blood pressure [52,53], and for example, low potassium diets could lead to salt-sensitive hypertension [54]. Potassium regulates blood pressure mainly via affecting kidney sodium reabsorption, vasodilation, baroreflex sensitivity to catecholamine and angiotensin II, and other mechanisms [52]. Specifically, how does potassium channel affect renal sodium reabsorption? Taking ROMK as an example, (i) in CCD cells, ROMK is the driving force for ENaC; (ii) in TAL, ROMK is the driving force for NKCC2 as well [55]. The activity of ROMK channel decreases the concentration of intracellular K+ (that is a decrease in intracellular cation concentration). Therefore, maintenance of intracellular charge homeostasis requires ENaC and NKCC2 reabsorb more cation (Na+, etc.) into the cells [55], ultimately causing the increase in kidney sodium reabsorption and subsequent hypertension. ROMK inhibitors have been used as novel diuretic targets for the treatment of hypertension and heart failure [56].

The KCNJ1 gene was previously reported to associate with blood pressure. For instance, loss-of-function mutations of the KCNJ1 gene cause Barter syndrome type II characterized by kidney salt wasting, hypotension, and mild hypokalemia. And Ji et al. [49] determined that multiple variants in the KCNJ1 gene caused a decrease in blood pressure in 3125 individuals and 292 Gitelman or Bartter syndrome patients in the Framingham Heart Study in the United States. Additionally, p.E151K [57], p.Y314C [58], p.T191N [58], p.E284Q [58], rs675759 [59], rs675388 [59], rs2846679 [59], rs2855800 [59], and rs2186832 [59] in the KCNJ1 gene are observed to associate with blood pressure or hypertension (Figure 2D and Supplementary Table S3). Researchers have previously verified that the KCNJ1 gene variation affect the function of ROMK channel through affecting the surface expression and the activity (e.g., p.R193P, p.H251Y, and p.T313FS), and conferring a gain in regulated-inhibitory gating (p.P166S and p.R169H) of ROMK [60].

Genetic variants of Cl− channels

Extracellular fluid volume is determined by NaCl, but not by Na+ only; therefore, Cl− transporter/channels, such as Pendrin and CLC-Kb, also play important roles in blood pressure control [61]. Pendrin protein encoded by the SLC26A4 gene (also PDS) is a transmembrane chloride/anion transporter and mediates the secretion of bicarbonate and the reabsorption of chloride, and mainly expressed in the thyroid [62], inner ear [63,64], and kidney [65]. The expression of pendrin in the kidney is regional, and mainly distributed on the apical membrane of the intercalated cells in the posterior segment of DCT, CCD, and CNT [66]. Wall et al. [67] reported that pendrin disruption not only impairs the secretion of HCO3− but also totally abolished Cl− reabsorption, and pointed out that the Cl− transport regulated by pendrin is the most important Cl− reabsorption pathway in the collection system. Pendrin gene ablation (SLC26A4−/−) has been reported to associate with reduced renal sodium reabsorption and blood pressure and resistant to hypertension caused by aldosterone in vivo [68,69].

Association analyses have also confirmed that SLC26A4 gene variants are related to SBP and DBP [70]. In functional studies, pendrin P70L, P301L, F667C [71], E29Q, V881/R409H, G424D, T485R [72], V239D, G334V/X335, I487Y/FSX39 [73], and V510D [74] are found to be the reduction or loss of function variants, whereas pendrin V881 and G740S exhibit a gain of function [71]. To date pendrin variants identified by functional studies have been well summarized in the review of Dossena et al. [75], which pointed out that the involvement of a charged amino acid of pendrin is not always sufficient to induce a detrimental effect on the ion transport such as D266N and K369E.

Another important chloride channel is CLC-Kb encoded by the CLCNKB gene. The CLC-Kb channel and its accessory subunit barttin (encoded by the BSND gene) are expressed in Henle’s loop, DCT and CCD of the kidney, and their function is to help the reabsorption of chloride, and the maintenance of urine concentration [76]. Loss-of-function mutations in CLCNKB cause Bartter syndrome type III, while gain-of-function mutations in CLCNKA and CLCNK cause rare salt-sensitive hypertension [77]. Accumulating evidences demonstrated that the CLCNKB gene...
variants, such as p.S12A, p.E192Ter [78], p.T481S [79,80], p.R27L [81], rs5253, and rs2275166 [82], are significantly associated with hypertension or blood pressure levels. Functional verification confirm that CLCNKB gene mutations affect the function of CLC-Kb channel through increasing the activity (e.g., p.T481S [79,83]), or reducing the activity of CLC-Kb channel (e.g., p.G167V [84], p.A242E [84], p.R351W [85], p.R30X [85], and p.A210V [85]).

Two important kinases regulating kidney ion channels

With-no-lysine (WNK) and SGK1 are two important kinases regulating kidney ion channels, and hence involved in kidney sodium reabsorption and hypertension. WNK is a serine/threonine protein kinase, and four members of the WNKs family (WNK1–4) have been identified in mammals (Supplementary Table S2). WNKs are widely expressed in human organs and tissues. Except for WNK2, all the other WNKs are expressed in kidney [86]. Alternatively spliced transcript variants encoding different isoforms of WNK1–4 have been reported. The existence of these variants greatly enriched the functions of WNKs [87]. The best-studied variant of WNKs for hypertension is the kidney-specific WNK1 (KS-WNK1), a variant of full-length WNK1 (L-WNK1). KS-WNK1 is very specifically expressed in kidney, and antagonizes the function of L-WNK1 in blood pressure regulation [87].

There are interactions between WNKs as follows. (i) WNK1 and WNK3 exist compensation effects. In mice lacking WNK3, no obvious salt consumption phenotype was observed for compensatory up-regulation of WNK1/SPAK axis [88]; (ii) WNK1/WNK3 and WNK4 inhibit each other. In addition to act alone, WNK1 can regulate renal sodium handling genes by inhibiting WNK4 [89]. WNK3 carboxy-terminal domain reduced the WNK4 kinase domain affinity for chloride, which is important for WNK4 to regulate kidney ion channels [90]. Meanwhile, WNK4 antagonizes effects of WNK1 and WNK3 on NCC [91]; (iii) KS-WNK1 inhibits the activity of L-WNK1/WNK3. Based on observations in genetically inactivated mice of two WNK1 isoforms, the effect of activating L-WNK1 exceeds that of KS-WNK1 [92].

WNKs are extremely important kinases that connect angiotensin II, aldosterone, and renal sodium and potassium transporters. Mutations of WNK1 and WNK4 cause Gordon syndrome (pseudohypoaldosteronism type 2, PHA 2) accompanied by hypertension, elevated serum potassium, and acidosis [93]. Laliotie et al. [94] found that mice carrying PHA2 WNK4 mutant transgene have higher blood pressure than wild-type mice. In 2007, yang et al. [95] carried out a functional study in vivo and generated Wnk4D561A/+ knockin mice. They found this knockin mice increased apical expression of phosphorylated NCC protein in DCTs through activation of the OSR1/SPAK-NCC phosphorylation cascade, and showed the phenotypes of hyperkalemia and hypertension.

Except for WNK2, the other members of WNKs family have been reported to be associated with blood pressure or hypertension. A lot of blood pressure-associated polymorphisms of WNKs have been identified, including rs1468326 [96], rs765250 [97], rs880054 [98,99], rs956868 [98], and rs12828016 [98,99] of the WNK1 gene (Figure 2C and Supplementary Table S3); and p.Ala589Ser [100] of the WNK4 gene.

The other important kinase in blood pressure control is a serum- and glucocorticoid-regulated kinase 1 (SGK1), which has at least three isoforms: SGK1 (iso-1), and its two N-terminal variant subtypes Sgk1i2 (iso-2) and Sgk1i3 (iso-3). Iso-2 and iso-3 are more stable than iso-1; Therefore, they are considered to be the main players for the role of SGK1 in hypertension [101–103]. SGK1 is highly expressed in renal tubules and plays an important role in sodium and potassium homeostasis and blood pressure regulation via activating ENaC [104–107]. In addition, SGK1 regulates the expression of NKCCs, NCC and NHE3 [108–113]. Evidences from experiments in vivo certified that high sodium intake up-regulates SGK1/ENaC pathway, leading to salt-sensitive hypertension [114]. In contrary, SGK1 deficiency prevents the occurrence of hypertension caused by a high-fat/high-fructose diet [104].

Some SNPs in the SGK1 gene have been demonstrated to relate to blood pressure or hypertension, including rs1057293, rs1743966 [115–117], rs2758151 [118,119], rs9402571 [118], rs9376026, rs9389154, rs1763509, rs9376026, rs3813344 [120], rs1763498, rs114414980, rs229133, and rs6924468 [121] (Figure 2B and Supplementary Table S3). Zhang’s gene-based analyses declared that SGK1 gene was associated with risk of hypertension (P=7.4 × 10−3) in the Chinese Han population [121].

SGK1 participates in the regulation of hypertension mainly through ENaC. In-vitro study demonstrate that iso-2 is preferentially localized to the plasma membrane, and can better stimulate ENaC compared with wild-type SGK1 [103]. In addition, iso-3 also dramatically enhanced ENaC activity through increasing the number of cleaved ENaC protein [102].

Taken together, accumulating evidences clarified that kidney sodium reabsorption-related genes did exert a vital role in blood pressure control. However, one gene’s function is limited to induce a significant effect on blood pressure. In the past few decades, the influence from the interactions of genes × genes (G × G) and/or genotype × environment
Interaction of genes × genes (G × G) related-renal sodium reabsorption in blood pressure regulation

Compensation between NCC and other ion channels (Pendrin/ENaC)

Pendrin is a Cl⁻/HCO₃⁻ transporter, and NCC is a Na⁺-Cl⁻ cotransporter, both of which play an important role in renal sodium reabsorption. When pendrin and NCC were mutated separately, the renal function of mice including sodium chloride excretion, urine output, and blood urea nitrogen were comparable with wild-type mice. However, when pendrin and NCC were double knocked out in mice, and they showed volume depletion or hypotension under salt restriction conditions [123]. Therefore, compensation exists between NCC and Pendrin in regulating renal function and blood pressure. For instance, NCC gene knockout mice do not have a significant salt loss for up-regulated Pendrin and ENaCs making up for NCC deletion [124]. Similarly, down-regulation of Pendrin in Carbonic Anhydrase II (CAII) knockout mice did not cause significant salt wasting because of compensatory up-regulation of NCC, but they showed severe salt wasting after NCC was inactivated or inhibited [125]. In future, targeted inhibition of both NCC and pendrin will provide a strong diuretic regimen for the treatment of hypertension.

Similar to NCC and Pendrin, compensation also exists between NCC and ENaCs, and their interaction maintains the homeostasis of systemic blood pressure. For example, it is generally believed that NCC activation causes hypertension. However, the result observed in KS-WNK1-KO mice is that NCC activity is significantly enhanced, but systemic blood pressure only showed a slight increase, and failed to cause hypertension, which is related to decreased expression of ENaC [126]. Conversely, genetic inactivation of NCC in mice indeed enhances the expression of ENaC and the absent effect of NCC phosphorylation in SPAK-KO mice is compensated by enhanced expression and function of ENaC [127,128]. In addition, NCC and ENaCs are coexpressed in DCT2 cells and a study confirmed that NCC interacts with ENaCα and ENaCγ subunits probably through directly binding [129].

Taken together, there are strong compensatory effects between NCC and Pendrin/ENaCs. When NCC or Pendrin/ENaCs is knocked out or malfunction, the expression or activity of another protein will compensatively increase to maintain the homeostasis of individual's salt wasting, urine output maintains, and blood pressure. However, NCC and ENaCs, or NCC and pendrin were both knocked out or inactivated, exceeding the compensatory ability between genes, which will lead to serious salt wasting or blood pressure variation.

Pendrin working in tandem with ENaCs

Pendrin and ENaCs are expressed in aldosterone-sensitive kidney areas, mainly including DCT, CNT, and CCD. Previous studies showed that Pendrin works in tandem with ENaC, while NCC works alone [124]. In animal models, the up- or down-regulations of ENaCs and Pendrin showed to be highly consistent. For example, the abundances of ENaC and pendrin both increase with aldosterone and aldosterone analogs [130,131], dietary NaCl restriction [67,130], and Cl⁻ restriction alone [132–135]. Meanwhile, the abundance and activity of ENaC are reduced in pendrin-null mice, ultimately leading to a decrease in natriuresis and chloriuresis and blood pressure [68].

Pech et al. [136] showed that Pendrin gene ablation reduces ENaC-regulated renal sodium reabsorption by altering subunit abundance, subcellular distribution, and channel open probability of ENaCs in wild-type mice. However, how do Pendrin and ENaCs interact with each other? This has become the focus of attention of scientists, because ENaC and Pendrin are expressed in different types of cells in the kidney though their abundances show consistency in many animal models. ENaC is mainly expressed in the apical plasma membrane of epithelia of CNT and CD [137]. Nevertheless, Pendrin is mainly expressed on the apical membrane of intercalated cells in renal CCD, CNT, and DCT. Therefore, it is impossible for them to influence each other through direct protein–protein interaction. How they interact with each other remains to be studied in future.

WNKs regulate Na⁺ and K⁺ channels in the kidney

WNKs protein and isoforms are composed of WNK1–4, and KS-WNK1 etc. Except for WNK2, all of the others are expressed in the kidney. As the difference of WNKs in structure, their regulatory functions for renal ion channels also vary.

Regulation of NCC and NKCC2 by WNKs

There are many regulatory mechanisms whereby WNKs regulate the function of NCC and NKCC2 (Figure 3A,B). First, both NCC and NKCC2 belong to the solute carrier family 12 (SLC 12), and WNK1 and WNK4
Figure 3. WNKs regulate Na+ and K+ channels in the kidney

WNKs regulate NCC (A), NKCC2 (B), ENaC (C), and ROMK (D).

up-regulates NCC and NKCC2 in the same way and mainly via two mechanisms: (i) kinase activity-dependent (WNKs-SPAK/OSR1-NCC/NKCC2 pathway) and (ii) kinase activity-independent manners [138,139]. WNKs change activities of NCC and NKCC2 mainly in a kinase activity-dependent manner. SPAK/OSR1 are direct substrates of WNK1 and WNK4 [140,141]. For instance, Richardson et al. [139] reported that WNK1 phosphorylates and activates SPAK/OSR1, which further phosphorylates and activates NCC in HEK cells. And Castaneda-Bueno et al. [142,143] reported that WNK4-deficient mice showed decreased NCC phosphorylation and manifested hypotension. Differently, WNKs change surface expression of NCC and NKCC2 mainly through a kinase activity-independent manner (Figure 3A,B; pathways 1 and 2) [144,145]. Some reports showed that WNK1 up-regulates NCC via abolishing the inhibitory role of WNK4 on NCC [89].

Second, WNK3 increases NCC and NKCC2 through SPAK pathway (Figure 3A,B; pathway 1). WNK3 is expressed in DCT of the kidney, and its carboxyl-terminal can activate NCC and is one of the important members of up-regulating NCC [146]. Studies showed that wild-type WNK3 enhances membrane surface expression of NCC, mainly through phosphorylation of SPAK [146]; however, WNK3 with no kinase activity inhibits the expression of NCC [147]. Similar to NCC, WNK3 promotes the phosphorylation of NKCC2 by activating the SPAK pathway and mediates the chloride induction of TAL cells [146]. Although there is conclusive evidence that WNK3 is a stimulator of NKCC2 activity in vitro, the overall effect of this kinase on NKCC2 in vivo seems to be limited.

Third, the regulation of WNK4 on NCC is complicated, and besides the above positive regulation, WNK4 also plays an inhibitory role on NCC (Figure 3A; pathway 3). WNK4 has been reported to directly inhibit NCC and is a strong inhibitor of NCC, which deletion causes overactivity of NCC and thus hypertension [89,148]. Moreover, WNK4 inhibits the function of NCC by decreasing cellular surface expression of NCC, but not by reducing the transport capacity of NCC transporter. Gamba et al. [138] found that the concentration of Cl− plays a vital role in the conversion of positive and negative regulations of WNK4 on NCC. They confirmed that WNK4 is a chloride-sensitive kinase, and its effect on the SPAK-NCC pathway is regulated by Cl− concentration. Under low-chlorine conditions, WNK4 is
automatically phosphorylated through a SPAK-dependent mechanism to activate NCC and play a positive regulatory role; Under high-chlorine conditions, WNK4 cannot be automatically phosphorylated due to its significant negative effects on WNK1 and WNK3, and inhibits NCC, plays as a negative regulator. NKCC2 is regulated by WNK4 via SPAK/OSR1 in a kinase activity-dependent manner [144].

Fourth, previous studies showed KS-WNK1 antagonizes the ability of L-WNK1 to inhibit NCC and NKCC2 (Figure 3A; pathway 4) [126, 149]. KS-WNK1 and WNK1 form a dynamic balance and fine regulate NCC. However, recent studies certified that the KS-WNK1 isoform is a powerful activator of NCC as well, in which KS-WNK1 may activate an endogenous SPAK-dependent pathway that is not affected by L-WNK1 (Figure 3A; pathway 5) [150].

**Regulation of ENaC by WNKs**

WNK1 activates ENaC via two pathways: (i) WNK1-Nedd4-ENaC pathway (Figure 3C; pathway 1); and (ii) WNK1-SGK1-ENaC pathway (Figure 3C; pathway 2) [151, 152]. WNK4 up-regulates or down-regulates the protein level of ENaC, respectively, by two different pathways: (i) WNK4 increases the expression of ENaC protein on the plasma membrane via phosphorylating SGK1 (Figure 3C; pathway 2) [86]; and (ii) WNK4 down-regulates ENaC level in a kinase-dependent manner probably involved in the regulation of Nedd4 (Figure 3C; pathway 3) [153]. However, WNK3 has almost no effect on the activity of ENaC (Figure 3C; pathway 4) [154].

**Regulation of ROMK by WNKs**

First, WNK1 and WNK4 inhibit ROMK via enhancing clathrin-dependent endocytosis, and the C terminus of ROMK plays an important role in the inhibitory effect (Figure 3D; pathway 1) [155]. Second, WNK3 inhibits the activity of ROMK by varying the membrane surface expression of ROMK instead of varying the conductance or opening probability of ROMK1 channel (Figure 3D; pathway 2). Third, KS-WNK1 has no kinase activity and cannot block ROMK directly. It indirectly activates ROMK by antagonizing the inhibition of L-WNK1 on ROMK [156]. Cheng et al. [157] found that ROMK-regulated K secretion significantly decreased in KS-WNK1 knockout mice, confirming that KS-WNK1 does indirectly activate ROMK in vivo.

**SGK1 up-regulates Na\(^+\), K\(^+\), and Cl\(^-\) channels in the kidney**

SGK1 exerts a vital role in regulating Na\(^+\), K\(^+\), and Cl\(^-\) channels in the kidney. Among them, the regulation of SGK1 on ENaC, ROMK, and CLC-Kb has been well summarized in the review of Valinsky et al. [158]. In addition, SGK1 can also up-regulate NKCC [112] and NCC [111], and enhance the sodium reabsorption in the renal tubules, resulting in an increase in extracellular fluid volume and blood pressure.

**Conclusions and perspectives**

Hypertension affects 30% of adults and is the leading risk factor for major cardiovascular events such as heart attack and stroke, chronic kidney disease, and heart failure [159]. Kidney ion handling genes participate in kidney sodium reabsorption and play a vital role in the initial stage and development of essential hypertension. The past few decades have seen remarkable progress in the studies on kidney ion handling genes and blood pressure control, and consequently antihypertensive medicines targeting kidney ion handling genes (such as thiazide diuretics for NCC) have been developed and available for clinical treatment. Nevertheless, in clinical practice hypertensive patients caused by up-regulation of kidney sodium reabsorption have yet to be identified and separated from patients with hypertension due to other causes, such as increased sympathetic nerve excitation and immune activity, up-regulation of RAAS, and vascular damage. The following two key points are especially worthy of noting. The first is that the clinical translation of molecular genetic findings is relatively lagging. Most hypertensive patients have not been tested for susceptibility genes or drug sensitivity before treatment and their treatments are consequently largely empiric though there are many evidences that the current medicines (e.g., thiazides, and loop diuretics) have differential action depending on the different mutation in the transporter [45–47]. In the future, promoting clinical translation and developing test kits based on molecular genetic findings should be the top priority of our work. Also, the research progress in the genetics and molecular mechanisms of hypertension has been inadequate in enabling precise diagnosis and tailored medicines for individual patients with hypertension. The genetic factors of hypertension are complicated and hypertension susceptibility gene identified so far can only explain the genetic etiology of a small number of hypertensive patients. The genetic causes of most hypertension patients are unknown. Therefore, there is a long way for us to go in elucidating the genetic basis of hypertension thoroughly.

Over the past decades, there has been a rapid increase in our understanding that the immune system plays a vital role in the regulation of renal ion channels [160]. For example, CD8\(^+\) T cells [161], IL-17A [162], TNF-α [163], and
interferon-γ [164] have been known to be important regulators of NCC, and IL-1 receptor activates salt reabsorption in Ang II-induced hypertension via the NKCC2 in the nephron [165], which provided new insights into the targeting antihypertension therapies according to the immune mechanism of hypertension. Therefore, the immune regulation on renal ion channels might become an attractive direction for hypertension research in future.

In the present review, we discuss the progress of genetics studies on kidney ion handling genes and their interaction in blood pressure regulation, and provide a panel of genes effecting kidney sodium reabsorption. Since hypertension is a polygenic disease and there are G × G interactions between kidney sodium reabsorption-related genes, it may be more effective to detect a gene panel than to detect a single susceptibility gene for patients with hypertension. Taking into account the key role of kidney sodium reabsorption in blood pressure control, in future studies, combining all the mutations of renal sodium reabsorption-related genes for a comprehensive analysis is more helpful and powerful for clarifying the mechanisms of essential hypertension.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

Funding
This study was supported by the (National Natural Science Foundation of China) [grant numbers 81760080, 31960149], (Inner Mongolia Youth Science and Technology Innovation Talent Project) [grant number NJYT-20-A12], (the Natural Science Foundation of Inner Mongolia) [grant number 2019MS08163], (‘Zhiyuan Talent Program’ of Inner Mongolia Medical University) [grant number ZY0120024], (2021 undergraduate science and technology innovation ‘Cultivation of Talents’ project of Inner Mongolia Medical University) [grant number YCPY2021082].

CRediT Author Contribution
Caiyan An: Supervision, Funding acquisition, Writing—original draft. Liuyi Yang: Investigation. Tengfei Han: Investigation. Huazhong Song: Resources, Investigation. Zichao Li: Resources, Investigation. Junjing Zhang: Supervision, Writing—review & editing. Kejin Zhang: Supervision, Writing—review & editing.

Abbreviations
BP, blood pressure; CCD, cortical collecting duct; CD, collecting duct; CHO, Chinese hamster ovary; CLC, chloride channel; CLC-Kb, chloride voltage-gated channel Kb; CNT, connecting tubule; DBP, diastolic blood pressure; DCT, distal convoluted tubule; EH, essential hypertension; ENaC, epithelial Na⁺ channel; KO, knockout; KS-WNK1, kidney-specific WNK1; L-WNK1, full-length WNK1; MAP, mean arterial pressure; NCC, Na⁺2Cl⁻ cotransporter; NKCC2, Na-K-2Cl cotransporter; PCT, proximal convoluted tubule; PHA 1, pseudohypoaldosteronism type 1; PHA 2, pseudohypoaldosteronism type 2; RAAS, renin-angiotensin-aldosterone system; ROMK, renal outer medullary potassium channel; SBP, systolic blood pressure; SGK1, serum- and glucocorticoid-regulated kinase 1; TAL, thick ascending limb; TALHL, thick ascending limb of Henle’s loop; TM, transmembrane; WNK, with no lysis (K) kinase.

References
1. Lawes, C.M., Vander Hoorn, S. and Rodgers, A. (2008) Global burden of blood-pressure-related disease. Lancet 371, 1513–1518, https://doi.org/10.1016/S0140-6736(08)60655-8
2. NCD Risk Factor Collaboration (NCD-RisC) (2017) Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet 389, 37–55, https://doi.org/10.1016/S0140-6736(16)31919-5
3. Forouzanfar, M.H., Liu, P., Roth, G.A., Ng, M., Biryukov, S., Marczak, L. et al. (2017) Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. JAMA 317, 165–182, https://doi.org/10.1001/jama.2016.19043
4. Lifton, R.P., Gharavi, A.G. and Geller, D.S. (2001) Molecular mechanisms of human hypertension. Cell 104, 545–556, https://doi.org/10.1016/S0092-8674(01)00241-0
5. Traube, L. (1871) Über den Zusammenhang von Herz und Nieren-krankheiten. Gesammet Beitrage Zur Pathologie Und Physiologie 2, 290–353
6. Bright, R. (1836) Tabular view of the morbid appearances in 100 cases connected with albuminuous urine. With observations. Guy’s Hosp. Rep. 1, 380
7. Ruskin, A. (1956) Classics in Arterial Hypertension, Charles C Thomas, Springfield, Ill
8. Hall, J.E. (2003) The kidney, hypertension, and obesity. Hypertension 41, 625–633, https://doi.org/10.1161/01.HYP.0000052314.95497.78
9. Guyton, A.C. (1961) Physiologic regulation of arterial pressure. Am. J. Cardiol. 8, 401–407, https://doi.org/10.1016/0002-9149(61)90515-0
10. Borst, J.G. and Borst-De Geus, A. (1963) Hypertension explained by Starling’s theory of circulatory homeoestasis. Lancet 1, 677–682, https://doi.org/10.1016/S0140-6736(63)91443-0
11. Guyton, A.C. and Coleman, T.G. (1969) Quantitative analysis of the pathophysiology of hypertension. Circ. Res. 24, 1–19
12. Guyton, A.C. and Coleman, T.G. (1999) Quantitative analysis of the pathophysiology of hypertension. 1969. J. Am. Soc. Nephrol. 10, 2248–2258
Matsuo, A., Katsuya, T., Ishikawa, K., Sugimoto, K., Iwashima, Y., Yamamoto, K. et al. (2004) G2736A polymorphism of thiazide-sensitive Na-Cl cotransporter gene predisposes to hypertension in young women. J. Hypertens. 22, 2123–2127, https://doi.org/10.1097/00004872-200411000-00014

Acuna, R., Martinez-de-la-Maza, L., Ponce-Coría, J., Vazquez, N., Ortai-Vite, P., Pacheco-Alvarez, D. et al. (2011) Rare mutations in SLC12A1 and SLC12A3 protect against hypertension by reducing the activity of renal salt cotransporters. J. Hypertens. 29, 475–483, https://doi.org/10.1097/JHJ.0b013e328341dfdf

Tutakhel, O.A., Jelen, S., Valdez-Flores, M., Dimke, H., Piersma, S.R., Jimenez, C.R. et al. (2016) Alternative splice variant of the thiazide-sensitive NaCl cotransporter: a novel player in renal salt handling. Am. J. Physiol. Renal. Physiol. 310, F204–F216, https://doi.org/10.1152/ajprenal.00429.2015

Keszei, A.P., Tisler, A., Backx, P.H., Andrilis, I.L., Bull, S.B. and Logan, A.G. (2007) Molecular variants of the thiazide-sensitive Na+-Cl− cotransporter in hypertensive families. J. Hypertens. 25, 2074–2081, https://doi.org/10.1097/01.hij.0000266540.36877.3f

Moreno, E., Cristobal, P.S., Rivera, M., Vazquez, N., Bobadilla, N.A. and Gamba, G. (2006) Affinity-defining domains in the Na-CI cotransporter: a different location for Cl- and thiazide binding. J. Biol. Chem. 281, 17266–17275, https://doi.org/10.1074/jbc.M606261200

Vormfelde, S.V., Sehrt, D., Toliat, M.R., Schirmer, M., Meineke, I., Tzvetkov, M. et al. (2007) Genetic variation in the renal sodium transporters NCC, NCC, and ENaC in relation to the effects of loop diuretic drugs. Clin. Pharmacol. Ther. 82, 300–309, https://doi.org/10.1097/01.cpt.6100131

Castaneda-Bueno, M., Vazquez, N., Bustos-Jaines, I., Hernandez, D., Rodriguez-Lobato, E., Pacheco-Alvarez, D. et al. (2010) A single residue in transmembrane domain 11 defines the different affinity for thiazides between the mammalian and flounder NaCl cotransporters. Am. J. Physiol. Renal. Physiol. 299, F1111–F1119, https://doi.org/10.1152/ajprenal.00412.2010

Castrop, H. and Schiessl, I.M. (2014) Physiology and pathophysiology of the renal Na-K-Cl cotransporter (NCC2). Am. J. Physiol. Renal. Physiol. 307, F991–F1002, https://doi.org/10.1152/ajprenal.00342.2013

Ji, W., Foo, J.N., O’Roak, B.J., Zhao, H., Larson, M.G., Simon, D.B. et al. (2008) Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat. Genet. 40, 592–599, https://doi.org/10.1038/ng.118

Nandakumar, P., Morrison, A.C., Grove, M.L., Boerwinkle, E. and Chakravarti, A. (2018) Contributions of rare coding variants in hypotension syndrome genes to population blood pressure variation. Medicine 97, e11865, https://doi.org/10.1097/md.0000000000011865

Monette, M.Y., Rinehart, J., Lifton, R.P. and Forbush, B. (2011) Rare mutations in the human Na-K-Cl cotransporter (NCC2) associated with lower blood pressure exhibit impaired processing and transport function. Am. J. Physiol. Renal. Physiol. 300, F840–F847, https://doi.org/10.1152/ajprenal.00552.2010

Piklidou, M.I., Lasaridis, A.N., Sarafidis, P.A., Tzioias, I.M., Zebekakis, P.E., Dombros, N.V. et al. (2007) Blood pressure and serum potassium levels in hypertensive patients receiving or not receiving antihypertensive treatment. Clin. Exp. Hypertens. 29, 563–573, https://doi.org/10.1080/10641960701744103

Mente, A., O’Donnell, M.J., Ranganarajan, S., McQueen, M.J., Poirier, P., Wiegosz, A. et al. (2014) Association of urinary sodium and potassium excretion with blood pressure. N. Engl. J. Med. 371, 601–611, https://doi.org/10.1056/NEJMoa1311989

Coruzzi, P., Brambilla, L., Brambilla, V., Guerzoni, M., Rossi, M., Parati, G. et al. (2001) Potassium depletion and salt sensitivity in essential hypertension. J. Clin. Endocrinol. Metab. 86, 2857–2862, https://doi.org/10.1210/jcem.86.6.7601

Hoorn, E.J., Gritter, M., Cuevas, C.A. and Fenton, R.A. (2020) Regulation of the renal NaCl cotransporter and its role in potassium homeostasis. Physiol. Rev. 100, 321–356, https://doi.org/10.1152/physrev.00044.2018

Calderone, V., Martelli, A., Piragine, E., Citi, V., Testai, L. and Breschi, M.C. (2018) The renal outer medullary potassium channel (ROMK): an intriguing pharmacological target for an innovative class of diuretic drugs. Curr. Med. Chem. 25, 2627–2636, https://doi.org/10.2174/0929867324666171012120937

Chen, W.K., To, K.F., Tong, J.H. and Law, C.W. (2012) Paradoxical hypertension and salt wasting in Type II Bartter syndrome. Clin. Kidney J. 5, 217–220, https://doi.org/10.1111/j.1757-1249.2012.00206.x

Bao, M., Cai, J., Yang, X. and Ma, W. (2019) Genetic screening for Bartter syndrome and Gitelman syndrome pathogenic genes among individuals with hypertension and hypokalemia. Clin. Exp. Hypertens. 41, 381–388, https://doi.org/10.1080/10641963.2018.1489547

Tobin, M.D., Tomaszewski, M., Braund, P.S., Hajat, C., Raleigh, S.M., Palmer, T.M. et al. (2008) Common variants in genes underlying monogenic hypertension and hypotension and blood pressure in the general population. Hypertension 51, 1658–1664, https://doi.org/10.1161/HYPERTENSIONAHA.108.112664

Fang, L., Li, U. and Welling, P.A. (2010) Hypertension resistance polymorphisms in ROMK (Kir1.1) alter channel function by different mechanisms. Am. J. Physiol. Renal. Physiol. 299, F1359–F1364, https://doi.org/10.1152/ajprenal.00429.2015

Eladari, D., Chambrey, R. and Peti-Peterdi, J. (2012) A new look at electrolyte transport in the distal tubule. Annu. Rev. Physiol. 74, 325–349, https://doi.org/10.1146/annurev-physiol-020911-153225

Royaux, I.E., Suzuki, K., Mori, A., Katoh, R., Everett, L.A., Kohn, L.D. et al. (2000) Pendrin, the protein encoded by the Pendred syndrome gene (PDS), is an apical porter of iodide in the thyroid and is regulated by thyroglobulin in FRTL-5 cells. Endocrinology 141, 839–845, https://doi.org/10.1210/endo.141.7.3703

Everett, L.A., Morsli, H., Wu, D.K. and Green, E.D. (1999) Expression pattern of the mouse ortholog of the Pendred’s syndrome gene (Pds) suggests a key role for pendrin in the inner ear. Proc. Natl. Acad. Sci. U.S.A. 96, 9727–9732, https://doi.org/10.1073/pnas.96.17.9727

Royaux, I.E., Belyantseva, I.A., Wu, T., Kachar, B., Everett, L.A., Marcus, D.C. et al. (2003) Localization and functional studies of pendrin in the mouse inner ear provide insight about the etiology of deafness in pendred syndrome. J. Assoc. Res. Otolaryngol. 4, 394–404, https://doi.org/10.1007/s10162-002-3052-4

© 2022 The Author(s). This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution License 4.0 (CC BY).
65 Royaux, I.E., Wall, S.M., Kaminski, L.P., Everett, L.A., Suzuki, K., Knepper, M.A. et al. (2001) Pendrin, encoded by the Pendred syndrome gene, resides in the apical region of renal intercalated cells and mediates bicarbonate secretion. Proc. Natl. Acad. Sci. U.S.A. 98, 4221–4226, https://doi.org/10.1073/pnas.071516798
66 Wall, S.M., Hassell, R.A., Royaux, I.E., Green, E.D., Chang, J.Y., Shipley, G.L. et al. (2003) Localization of pendrin in mouse kidney. Am. J. Physiol. Renal. Physiol. 284, F229–F241, https://doi.org/10.1152/ajprenal.0147.2002
67 Wall, S.M., Kim, Y.H., Stanley, L., Gajpion, D.M., Everett, L.A., Green, E.D. et al. (2004) NaCl restriction upregulates renal Slc26a4 through subcellular redistribution: role in Cl- conservation. Hypertension 44, 982–987, https://doi.org/10.1161/01.HYP.0000145863.96091.39
68 Kim, Y.H., Pech, V., Spencer, K.B., Beierwaltes, W.H., Everett, L.A., Green, E.D. et al. (2007) Reduced ENaC protein abundance contributes to the lower blood pressure observed in pendrin-null mice. Am. J. Physiol. Renal. Physiol. 293, F1314–F1324, https://doi.org/10.1152/ajprenal.0155.2007
69 Soline, B. and Wagner, C.A. (2021) Regulation of renal pendrin activity by aldosterone. Curr. Opin. Nephrol. Hypertens. 30, 131–137, https://doi.org/10.1097/MNH.0000000000000669
70 Kim, B.G., Yoo, T.H., Yoo, J.E., Seo, Y.J., Jung, J. and Choi, J.Y. (2017) Resistance to hypertension and high Cl(-) excretion in humans with SLC26A4 mutations. Clin. Genet. 91, 448–452, https://doi.org/10.1111/cge.12789
71 Dossena, S., Bizzhanova, A., Nozfiger, C., Bernardelli, E., Ramsauer, J., Kopp, P. et al. (2011) Identification of allelic variants of pendrin (SLC26A4) with loss and gain of function. Cell. Physiol. Biochem. 28, 467–476, https://doi.org/10.1159/000335108
72 Pera, A., Dossena, S., Rodighiero, S., Gandia, M., Botta, G., Meyer, G. et al. (2008) Functional assessment of allelic variants in the SLC26A4 gene involved in Pendred syndrome and nonsyndromic ETA. Proc. Natl. Acad. Sci. U.S.A. 105, 18608–18613, https://doi.org/10.1073/pnas.0805831105
73 Dossena, S., Nozfiger, C., Brownstein, Z., Kanaan, M., Avraham, K.B. and Paulmichl, M. (2011) Functional characterization of pendrin mutations found in the Israeli and Palestinian populations. Cell. Physiol. Biochem. 28, 477–484, https://doi.org/10.1159/000335109
74 Jang, J.H., Jung, J., Kim, A.R., Cho, Y.M., Kim, M.Y., Lee, S.Y. et al. (2014) Identification of novel functional null allele of SLC26A4 associated with enlarged vestibular aqueduct and its possible implication. Audiol. Neurootol. 19, 319–326, https://doi.org/10.1159/000366190
75 Dossena, S., Nozfiger, C., Tamma, G., Bernardelli, E., Vanoni, S., Nowak, C. et al. (2011) Molecular and functional characterization of human pendrin and its allelic variants. Cell. Physiol. Biochem. 28, 451–466, https://doi.org/10.1159/000335107
76 Site, S., Velez, D.R., Gilliani, N.B., Alexander, C.A., George, Jr., A.L. and Williams, S.M. (2008) Haplotype diversity in four genes (CLCNKA, CLCNKB, BSND, NEDD4L) involved in renal salt reabsorption. Hum. Hered. 65, 33–46, https://doi.org/10.1159/000106060
77 Imbrici, P., Tricarico, D., Mangiastori, G., Niccolotti, O., Lograno, M., Conte, D. et al. (2017) Pharmacovigilance database search discloses ClC-K channels as a novel target of the ATP receptor blockers valsartan and olmesartan. Br. J. Pharmacol. 174, 1972–1983, https://doi.org/10.1111/bph.13794
78 Le, B.T. and Duong, C.M. (2020) Two novel mutations in the CLCNKB gene leading to classic Bartter syndrome presenting as syncope and hypertension in a 13-year-old boy. BMJ Case Rep. 13, e233872, https://doi.org/10.1136/brc-2019-233872
79 Jeck, N., Waldegger, S., Lampert, A., Boehmer, C., Waldegger, P., Lang, P.A. et al. (2004) Activating mutation of the renal epithelial chloride channel ClC-Kb predisposing to hypertension. Hypertension 43, 1175–1181, https://doi.org/10.1161/01.HYP.0000129824.12959.f0
80 Site, S., Velez, D.R., Gilliani, N.B., Naris, T., Moore, J.H., George, Jr., A.L. et al. (2009) CLCNKB–T481S and essential hypertension in a Ghanaian population. J. Hypertens. 27, 298–304, https://doi.org/10.1097/JHJ.0b013e3283140c9e
81 Kuboku, Y., Tomoki, H., Tanaka, C., Barnõ, M., Okuda, T., Inamoto, N. et al. (2006) Association of sixty-one non-synonymous polymorphisms in forty-one hypertension candidate genes with blood pressure variation and hypertension. Hypertens. Res. 29, 611–619, https://doi.org/10.1291/hypres.29.611
82 Chen, X., Zhou, B., Hou, X., Xing, J., Zou, S., Wu, X. et al. (2015) Associations between CLCNKA_B tag SNPs with essential hypertension and interactions between genetic and environmental factors in an island population in China. Clin. Exp. Hypertens. 37, 519–525, https://doi.org/10.3109/10641963.2015.1013124
83 Jeck, N., Waldegger, P., Doroszewicz, J., Seyberth, H. and Waldegger, S. (2004) A common sequence variation of the CLCNKB gene strongly activates ClC-Kb chloride channel activity. Kidney Int. 65, 190–197, https://doi.org/10.1111/j.1523-1755.2004.00363.x
84 Sahbani, D., Strumbo, B., Tedeschi, S., Conte, E., Camerino, G.M., Benetti, E. et al. (2020) Functional study of novel Bartter’s syndrome mutations in ClC-Kb and rescue by the accessory subunit barttin toward personalized medicine. Curr. Opin. Nephrol. Hypertens. 29, F1198–F1209, https://doi.org/10.1097/MNH.0000000000000669
85 Yu, Y., Xu, C., Pan, X., Ren, H., Wang, W., Meng, X. et al. (2010) Identification and functional analysis of novel mutations of the CLCNKB gene in Chinese patients with classic Bartter syndrome. Clin. Genet. 77, 155–162, https://doi.org/10.1111/j.1399-0004.2009.01288.x
86 Hadchouel, J., Ellison, D.H. and Gamba, G. (2016) Regulation of renal electrolyte transport by WNK and SPAK–OSR1 kinases. Annu. Rev. Physiol. 78, 367–389, https://doi.org/10.1146/annurev-physiol-050815-105431
87 O’Reilly, M., Marshall, E., Speirs, H.J. and Brown, R.W. (2003) WNK1, a gene within a novel blood pressure control pathway, tissue-specifically generates radically different isoforms with and without a kinase domain. J. Am. Soc. Nephrol. 14, 2447–2456, https://doi.org/10.1097/01.ASN.0000088930.97681.3B
88 Mederle, K., Mriot, K., Paliege, A., Carota, I., Bachmann, S., Castrop, H. et al. (2013) Loss of WNK3 is compensated for by WNK3/SPAK axis in the kidney. Am. J. Physiol. Renal. Physiol. 304, F1198–F1209, https://doi.org/10.1152/ajprenal.00288.2012
89 Yang, C.L., Angell, J., Mitchell, R. and Ellison, D.H. (2003) WNK kinases regulate thiazide-sensitive Na-Cl cotransport. J. Clin. Invest. 111, 1039–1045, https://doi.org/10.1172/JCI17443
90 Paccheo-Alvarez, D., Carrillo-Perez, D.L., Mercado, A., Leyva-Rios, K., Moreno, E., Hernandez-Mercado, E. et al. (2020) WNK3 and WNK4 exhibit opposite sensitivity with respect to cell volume and intracellular chloride concentration. Am. J. Physiol. Cell. Physiol. 319, C371–C380, https://doi.org/10.1152/ajpcell.00488.2019

© 2022 The Author(s). This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution License 4.0 (CC BY).
Chavez-Canales, M., Zhang, C., Soukaseum, C., Moreno, E., Pacheco-Alvarez, D., Vidal-Petiot, E. et al. (2014) WNK-SPAK-NCC cascade revisited: WNK1 stimulates the activity of the Na-Cl cotransporter via SPAK, an effect antagonized by WNK4. Hypertension 64, 1047–1053, https://doi.org/10.1161/HYPERTENSIONAHA.114.04306

Zambrowicz, B.P., Abun, A., Ramirez-Solis, R., Richter, L.J., Piggott, J., Beltrand-Rio, H. et al. (2003) Wnk1 kinase deficiency lowers blood pressure in mice: a gene-trap screen to identify potential targets for therapeutic intervention. Proc. Natl. Acad. Sci. U.S.A. 100, 14109–14114, https://doi.org/10.1073/pnas.2336103100

Wilson, F.H., Disse-Nicodeme, S., Choahe, K.A., Ishikawa, K., Nelson-Williams, C., Desitter, I. et al. (2001) Human hypertension caused by mutations in WNK kinases. Science 293, 1107–1112, https://doi.org/10.1126/science.1062840

Laiлотi, M.D., Zhang, J., Volkman, H.M., Kahle, K.T., Hoffmann, K.E., Toka, H.R. et al. (2006) Wnk4 controls blood pressure and potassium homeostasis via regulation of mass and activity of the distal convoluted tubule. Nat. Genet. 38, 1124–1132, https://doi.org/10.1038/ng1877

Yang, S.S., Morimoto, T., Rai, T., Chiga, M., Sohara, E., Ohno, M. et al. (2007) Molecular pathogenesis of pseudohypoaldosteronism type II: generation and analysis of a Wnk4(K561A+) knockin mouse model. Cell Metab. 5, 331–344, https://doi.org/10.1016/j.cmet.2007.03.009

Shi, R., Li, J., He, J., Meng, Q., Gian, Z., Shi, D. et al. (2018) Association of with-no-lysine kinase 1 and serine/threonine kinase 39 gene polymorphisms and haplotypes with essential hypertension in Tibetans. Environ. Mol. Mutagen. 59, 151–160, https://doi.org/10.1002/em.22140

Newhouse, S., Farrall, M., Wallace, C., Holm, Z., Burke, B., Howard, P. et al. (2009) Polymorphisms in the WNK1 gene are associated with blood pressure variation and urinary potassium excretion. PLoS ONE 4, e5003, https://doi.org/10.1371/journal.pone.0005003

Osada, Y., Miyachi, R., Goda, T., Kasezawa, N., Horiike, H., Iida, M. et al. (2009) Variations in the WNK1 gene modulates the effect of dietary intake of sodium and potassium on blood pressure determination. J. Hum. Genet. 54, 474–478, https://doi.org/10.1038/jhg.2009.64

Liu, F., Zheng, S., Mu, J., Chu, C., Wang, W., Wang, Y. et al. (2013) Common variation in with-no-lysine kinase 1 (Wnk1) and blood pressure responses to dietary sodium or potassium interventions- family-based association study. Circ. J. 77, 169–174, https://doi.org/10.1253/circj.CJ-12-0900

Ghodsian, N., Ismail, P., Ahmadloo, S., Heidari, F., Haghighizadeh, P., Atalaihia Eskhoo, S. et al. (2016) Novel association of WNK4 gene, Ala589Ser polymorphism in essential hypertension, and type 2 diabetes mellitus in Malaysia. J. Diabetes Res. 2016, 8219543, https://doi.org/10.1155/2016/8219543

Nortlander, A.E., Salehe, M.A., Pandey, A.K., Itani, H.A., Wu, J., Xiao, L. et al. (2017) A salt-sensing kinase in T lymphocytes, SGK1, drives hypertension and hypertensive end-organ damage. JCI Insight 2, e92801, https://doi.org/10.1172/jci.insight.92801

Raikwar, N.S., Liu, K.Z. and Thomas, C.P. (2012) A regulated NH2-terminal Sgk1 variant with enhanced function is expressed in the collecting duct. Am. J. Physiol. Renal. Physiol. 303, F1527–F1533, https://doi.org/10.1152/ajprenal.00191.2012

Raikwar, N.S., Snyder, P.M. and Thomas, C.P. (2008) An evolutionarily conserved N-terminal Sgk1 variant with enhanced stability and improved function. Am. J. Physiol. Renal. Physiol. 295, F1440–F1448, https://doi.org/10.1152/ajprenal.90239.2008

Huang, D.Y., Boini, K.M., Osswald, H., Friedrich, B., Artunc, F., Ullrich, S. et al. (2006) Resistance of mice lacking the serum- and glucocorticoid-inducible kinase SGK1 against salt-sensitive hypertension induced by a high-fat diet. Am. J. Physiol. Renal. Physiol. 291, F1264–F1273, https://doi.org/10.1152/ajprenal.00299.2005

Lang, F. and Shumilina, E. (2013) Regulation of ion channels by the serum- and glucocorticoid-inducible kinase SGK1. FASEB J. 27, 3–12, https://doi.org/10.1096/fj.12-218230

Vallon, V. and Lang, F. (2005) New insights into the role of serum- and glucocorticoid-inducible kinase SGK1 in the regulation of renal function and blood pressure. Curr. Opin. Nephrol. Hypertens. 14, 59–66, https://doi.org/10.1097/01.mnh.000014552-20050100-000010

Van Beusecum, J.P., Barbaro, N.R., McDowell, Z., Aden, L.A., Xiab, L., Pandey, A.K. et al. (2019) High salt activates CD11c(+) antigen-presenting cells via SGK (serum glucocorticoid kinase) 1 to promote renal inflammation and salt-sensitive hypertension. Hypertension 74, 555–563, https://doi.org/10.1161/HYPERTENSIONAHA.119.112761

Pasham, V., Rotte, A., Xu, S., Yang, W., Bhandaru, M., Rixehepaj, R. et al. (2013) Uprogration of intestinal NHE3 following saline ingestion. Kidney Blood Press. Res. 37, 48–57, https://doi.org/10.1007/s10034-012-0218-30

He, P., Lee, S.J., Lin, S., Seidler, U., Lang, F., Fejes-Toth, G. et al. (2011) Serum- and glucocorticoid-induced kinase 3 in recycling endosomes mediates acute activation of Na(+)/H(+) exchanger NHE3 by glucocorticoids. Mol. Biol. Cell 22, 3812–3825, https://doi.org/10.1091/mbc.e11-04-0328

Panchapakesan, U., Pollock, C. and Saad, R. (2011) Renal epithelial growth factor receptor: its role in sodium and water homeostasis in diabetic nephropathy. Clin. Exp. Pharmacol. Physiol. 38, 84–88, https://doi.org/10.1111/j.1440-1681.2010.05472.x

Lang, F. and Stournaras, C. (2013) Serum and glucocorticoid inducible kinase, metabolic syndrome, inflammation, and tumor growth. Hormones (Athens) 12, 160–171, https://doi.org/10.4103/0973-6375.128270

Pacak, V., Böhmer, C., Palmada, M., Sebohm, G., Strutz-Seebohm, N. and Vallon, V. (2006) (Patho)physiological significance of the serum- and glucocorticoid-inducible kinase isoforms. Physiol. Rev. 86, 1151–1178, https://doi.org/10.1152/physrev.00050.2005

Strazzullo, P. and Galletti, F. (2007) Genetics of salt-sensitive hypertension. Curr. Hypertens. Rep. 9, 25–32, https://doi.org/10.1007/s11906-007-0006-6

Chen, C., Chen, G., Li, Y., Yang, Z., Taylor, E. and Zhao, L. (2021) A G-quadruplex nanoswitch in the SGK1 promoter regulates isoform expression by K/Na balance and resveratrol binding. Biochim. Biophys. Acta Gen. Subj. 1865, 129778, https://doi.org/10.1016/j.bbagen.2020.129778

Busjahn, A., Aydin, A., Uhmann, R., Krasko, C., Bähring, S., Szelести, T. et al. (2002) Serum- and glucocorticoid-regulated kinase (SGK1) gene and blood pressure. Hypertension 40, 256–260, https://doi.org/10.1161/01.HYP.0000030153.19366.26

Busjahn, A. and Luft, F.C. (2003) Twin studies in the analysis of minor physiological differences between individuals. Cell. Physiol. Biochem. 13, 51–58, https://doi.org/10.1007/s006290030204

von Wovern, F., Berglund, G., Carlson, J., Månsson, H., Hedblad, B. and Melander, O. (2005) Genetic variance of SGK-1 is associated with blood pressure, blood pressure change over time and strength of the insulin-diastolic blood pressure relationship. Kidney Int. 68, 2164–2172, https://doi.org/10.1111/j.1523-1755.2005.00672.x
118 Rao, A.D., Sun, B., Saxena, A., Hopkins, P.N., Jeunemaitre, X., Brown, N.J. et al. (2013) Polymorphisms in the serum- and glucocorticoid-inducible kinase 1 gene are associated with blood pressure and renin response to dietary salt intake. *J. Hum. Hypertens.* **27**, 176–180, https://doi.org/10.1038/jh.2012.22

119 Li, C., Yang, X., He, J., Hixon, J.E., Gu, D., Rao, D.C. et al. (2014) A gene-based analysis of variants in the serum/glucocorticoid regulated kinase (SGK) genes with blood pressure responses to sodium intake: the GenSalt Study. *PloS ONE* **9**, e98432, https://doi.org/10.1371/journal.pone.0098432

120 Chu, C., Wang, Y., Wang, M., Mu, J.J., Liu, F.G., Wang, L. et al. (2015) Common variants in serum/glucocorticoid regulated kinase 1 (SGK1) and blood pressure responses to dietary sodium or potassium interventions: a family-based association study. *Kidney Blood Press. Res.* **40**, 424–434, https://doi.org/10.1159/000368518

121 Zhang, D., Gu, D., He, J., Hixon, J.E., Rao, D.C., Li, C. et al. (2017) Associations of the serum/glucocorticoid regulated kinase genes with BP changes and hypertension incidence: the Gensalt study. *Am. J. Hypertens.* **30**, 95–101, https://doi.org/10.1093/ajh/hpw122

122 Jolicouer-Martineau, A., Wazana, A., Szekely, E., Steiner, M., Fleming, A.S., Kennedy, J.L. et al. (2019) Alternating optimization for G x E modelling with weighted genetic and environmental scores: Examples from the MAVAN study. *Psychol. Methods* **24**, 196–216, https://doi.org/10.1037/met0000175

123 Soleimani, M., Barone, S., Xu, J., Shull, G.E., Siddiqui, F., Zahedi, K. et al. (2012) Double knockout of pendrin and Na-CI cotransporter (NCC) causes severe salt wasting, volume depletion, and renal failure. *Proc. Natl. Acad. Sci. U.S.A.* **109**, 13366–13373, https://doi.org/10.1073/pnas.1202671109

124 Patel-Chamberlin, M., Varasteh Kia, M., Xu, J., Barone, S., Zahedi, K. and Soleimani, M. (2016) The role of epithelial sodium channel ENaC and the apical Cl-/HCO3- exchanger pendrin in compensatory salt reabsorption in the setting of Na-CI cotransporter (NCC) inactivation. *PloS ONE* **11**, e0150918, https://doi.org/10.1371/journal.pone.0150918

125 Xu, J., Barone, S., Brooks, M.B. and Soleimani, M. (2013) Double knockout of carbonic anhydrase II (CAII) and Na(+)-Cl(-) cotransporter (NCC) causes salt wasting and volume depletion. *Cell. Physiol. Biochem.* **32**, 173–183, https://doi.org/10.1159/000356637

126 Hachoueli, J., Souksem, C., Busst, C., Zhou, X.O., Baudrie, V., Zurrer, T. et al. (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**, 18109–18114, https://doi.org/10.1073/pnas.1006128107

127 Loffing, J., Valtton, V., Loffing-Cueni, D., Arnegger, F., Richter, K., Pietri, L. et al. (2004) Altered renal distal tubule structure and renal Na(+) and Ca(2+) handling in a mouse model for Gitelman's syndrome. *J. Am. Soc. Nephrol.* **15**, 2276–2288, https://doi.org/10.1097/01.ASN.0000138324.18569.63

128 Grimm, P.R., Lazo-Fernandez, Y., Delpire, E., Wall, S.M., Dorsey, S.G., Weinman, E.J. et al. (2015) Integrated compensatory network is activated in the mouse kidney: role of pendrin in mineralocorticoid-induced hypertension. *J. Clin. Invest.* **125**, 2136–2150, https://doi.org/10.1172/JCI78558

129 Mistry, A.C., Wynne, B.M., Yu, L., Tomilin, V., Yue, Q., Zhou, Y. et al. (2016) The sodium chloride cotransporter (NCC) and epithelial sodium channel ENaC in the mouse kidney: role of pendrin in mineralocorticoid-induced hypertension. *J. Hum. Hypertens.* **30**, F131–F144, https://doi.org/10.1007/s00424-013-1356-3

130 Frische, S., Kwon, T.H., Frokiaer, J., Madsen, K.M. and Nielsen, S. (2003) Regulated expression of pendrin in rat kidney in response to chronic NH4Cl or NaHCO3 loading. *Am. J. Physiol. Renal. Physiol.* **284**, F584–F593, https://doi.org/10.1152/ajprenal.00254.2002

131 Kim, G.H., Martin, S.W., Fernandez-Llama, P., Masilamani, S., Packer, R.K. and Knepper, M.A. (2000) Long-term regulation of renal Na-dependent cation-chloride-coupled cotransporters via the STE20-related kinases, SPAK and OSR1. *J. Am. Soc. Nephrol.* **11**, 2276–2288, https://doi.org/10.1161/01.HYP.0000088321.67254.87

132 Quentin, F., Chambrey, R., Inth-Trang-Tan, M.M., Fysekidis, M., Cambillau, M., Paillard, M. et al. (2004) The Cl-/HCO3- exchanger pendrin in the rat kidney is regulated in response to chronic alterations in chloride balance. *Am. J. Physiol. Renal. Physiol.* **287**, F1179–F1188, https://doi.org/10.1152/ajprenal.00712.2004

133 Kusche-Vihrog, K., Jegg, P. and Oberleithner, H. (2014) The role of ENaC in vascular endothelium. *Pflugers Arch.* **466**, 851–859, https://doi.org/10.1007/s00424-013-1356-3

134 Bazua-Valenti, S., Castaneda-Bueno, M. and Gamba, G. (2016) Physiological role of SLC12 family members in the kidney. *Am. J. Physiol. Renal. Physiol.* **311**, F131–F144, https://doi.org/10.1152/ajprenal.00071.2016

135 Richardson, C., Rafiei, F.H., Karlsson, H.K., Molelekii, N., Vandewalle, A., Campbell, D.G. et al. (2008) Activation of the thiazide-sensitive Na+-Cl-cotransporter by the WNK-regulated kinases SPAK and OSRI. *J. Cell Sci.* **121**, 675–684, https://doi.org/10.1242/jcs.025312

136 Moriguchi, T., Urushiyama, S., Hisamoto, N., Iemura, S., Uchida, S., Natsume, T. et al. (2005) WNK1 regulates phosphorylation of cation-chloride-coupled cotransporters via the STE20-related kinases, SPAK and OSR1. *J. Biol. Chem.* **280**, 42685–42693, https://doi.org/10.1074/jbc.M510042200

137 Loffing, J., Vallton, V., Loffing-Cueni, D., Arnegger, F., Richter, K., Pietri, L. et al. (2004) Altered renal distal tubule structure and renal Na(+) and Ca(2+) handling in a mouse model for Gitelman's syndrome. *J. Am. Soc. Nephrol.* **15**, 2276–2288, https://doi.org/10.1161/01.HYP.0000088321.67254.87

138 Bazua-Valenti, S., Castaneda-Bueno, M. and Gamba, G. (2016) Physiological role of SLC12 family members in the kidney. *Am. J. Physiol. Renal. Physiol.* **311**, F131–F144, https://doi.org/10.1152/ajprenal.00071.2016

139 Richards, C., Rafiei, F.H., Karlsson, H.K., Molelekii, N., Vandewalle, A., Campbell, D.G. et al. (2008) Activation of the thiazide-sensitive Na+-Cl-cotransporter by the WNK-regulated kinases SPAK and OSRI. *J. Cell Sci.* **121**, 675–684, https://doi.org/10.1242/jcs.025312

140 Moriguchi, T., Urushiyama, S., Hisamoto, N., Iemura, S., Uchida, S., Natsume, T. et al. (2005) WNK1 regulates phosphorylation of cation-chloride-coupled cotransporters via the STE20-related kinases, SPAK and OSR1. *J. Biol. Chem.* **280**, 42685–42693, https://doi.org/10.1074/jbc.M510042200

141 Viñes, A.C., Deak, M., Morrice, N.A. and Alessi, D.R. (2005) The WNK1 and WNK4 protein kinases that are mutated in Gordon's hypertension syndrome phosphorylate and activate SPAK and OSR1 protein kinases. *Biochem. J.* **391**, 17–24, https://doi.org/10.1042/BJ20051180
142 Castaneda-Bueno, M., Cervantes-Perez, L.G., Vazquez, N., Uribe, N., Kantesaria, S., Morla, L. et al. (2012) Activation of the renal Na+:Cl- cotransporter by angiotensin II is a WNK4-dependent process. Proc. Natl. Acad. Sci. U.S.A. 109, 7929–7934, https://doi.org/10.1073/pnas.1209047110

143 Takahashi, D., Mori, T., Nomura, N., Khan, M.Z., Araki, Y., Zeniya, M. et al. (2014) WNK4 is the major WNK positively regulating NCC in the mouse kidney. Biochi. Rep. 34, e00107, https://doi.org/10.1016/j.bior.2014.08.020

144 Huang, C.L., Yang, S.S. and Lin, S.H. (2008) Mechanism of regulation of renin-angiotensin system by WNK kinases. Curr. Opin. Nephrol. Hypertens. 17, 519–525, https://doi.org/10.1097/MNH.0b013e32830e5d50

145 Richardson, C., Sakamoto, K., de los Heros, P., Deak, M., Campbell, D.G., Prescott, A.R. et al. (2011) Regulation of the NKCC2 co-transporter by SPK1/OSR1-dependent and -independent pathways. J. Cell Sci. 124, 789–800, https://doi.org/10.1242/jcs.077220

146 Rinehart, J., Kahle, K.T., de los Heros, P., Vazquez, N., Meade, P., Wilson, F.H. et al. (2005) WNK3 kinase is a positive regulator of NKCC2 and NCC, renal cation-Cl- co-transporters required for normal blood pressure homeostasis. Proc. Natl. Acad. Sci. U.S.A. 102, 16777–16782, https://doi.org/10.1073/pnas.0508303102

147 Yang, C.L., Zhu, X. and Ellison, D.H. (2007) The thiazide-sensitive Na-Cl cotransporter is regulated by a WNK kinase signaling complex. J. Clin. Invest. 117, 3403–3411, https://doi.org/10.1172/JCI32033

148 Wilson, F.H., Kahle, K.T., Sabath, E., Laloiiti, M.D., Rapson, A.K., Hoover, R.S. et al. (2003) Molecular pathogenesis of inherited hypertension with hyperkalemia, regulates the K+ channel ROMK1 (Kir1.1).

149 Liu, Z., Xie, J., Wu, T., Truong, T., Auchus, R.J. and Huang, C.L. (2011) Downregulation of NCC and NKCC2 cotransporters by kidney-specific WNK1 revealed by gene disruption and transgenic mouse models. Hum. Mol. Genet. 20, 855–866, https://doi.org/10.1093/hmg/ddl525

150 Argaiz, E.R., Chavez-Canales, M., Ostronsky-Frid, M., Rodriguez-Gama, A., Vazquez, N., Gonzalez-Rodriguez, X. et al. (2018) Kidney-specific WNK1 isoform (KS-WNK1) is a potent activator of WNK4 and NCC. Am. J. Physiol. Renal. Physiol. 315, F734–F745, https://doi.org/10.1152/ajprenal.00145.2018

151 Xu, B.E., Stippec, S., Chu, P.Y., Lazrak, A., Li, X.J., Lee, B.H. et al. (2005) WNK1 activates SGK1 to regulate the epithelial sodium channel. Proc. Natl. Acad. Sci. U.S.A. 102, 10315–10320, https://doi.org/10.1073/pnas.0504422102

152 Heise, C.J., Xu, B.E., Deaton, S.L., Cha, S.K., Cheng, C.J., Earnest, S. et al. (2010) Serum and glucocorticoid-induced kinase (SGK) 1 and the epithelial sodium channel are regulated by multiple with no lysine (WNK) family members. J. Biol. Chem. 285, 25161–25167, https://doi.org/10.1074/jbc.M110.103432

153 Ring, A.M., Cheng, S.X., Leng, Q., Kahle, K.T., Rinehart, J., Laloiiti, M.D. et al. (2007) WNK4 regulates activity of the epithelial Na+ channel in vitro and in vivo. Proc. Natl. Acad. Sci. U.S.A. 104, 4020–4024, https://doi.org/10.1073/pnas.0611727104

154 Leng, Q., Kahle, K.T., Rinehart, J., MacGregor, G.G., Wilson, F.H., Canessa, C.M. et al. (2006) WNK3, a kinase related to genes mutated in hereditary hypertension with hyperkalemia, regulates the K+ channel ROMK1 (Kir1.1). J. Physiol. 571, 275–286, https://doi.org/10.1113/jphysiol.2005.092202

155 Kahle, K.T., Wilson, F.H., Leng, Q., Laloiiti, M.D., O’Connell, A.D., Dong, K. et al. (2003) WNK4 regulates the balance between renal NaCl reabsorption and K+ secretion. Nat. Genet. 35, 372–376, https://doi.org/10.1038/ng1271

156 Wu, P., Gao, Z.X., Xu, S.T., Ellison, D.H., Hadchouel, J., Teulon, J. et al. (2018) Role of WNK4 and kidney-specific WNK1 in mediating the effect of high dietary K+ intake on ROMK channel in the distal convoluted tubule. Am. J. Physiol. Renal. Physiol. 315, F223–F230, https://doi.org/10.1152/ajprenal.00500.2018

157 Cheng, C.J., Baum, M. and Huang, C.L. (2013) Kidney-specific WNK1 regulates sodium reabsorption and potassium secretion in mouse cortical collecting duct. Am. J. Physiol. Renal. Physiol. 304, F397–F402, https://doi.org/10.1152/ajprenal.00589.2012

158 Valinsky, W.C., Touyz, R.M. and Shrier, A. (2018) Aldosterone, SGK1, and ion channels in the kidney.

159 Iadecola, C., Yaffe, K., Biller, J., Bratzke, L.C., Faraci, F.M., Gorelick, P.B. et al. (2016) Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. Hypertension 68, e67–e94, https://doi.org/10.1161/HYP.0000000000000653

160 Drummond, G.R., Vinh, A., Guzik, T.J. and Sobey, C.G. (2019) Immune mechanisms of hypertension. Nat. Rev. Immunol. 19, 517–532, https://doi.org/10.1038/s41577-019-0160-5

161 Liu, Y., Rafferty, T.M., Rhee, S.W., Webber, J.S., Song, L., Ko, B. et al. (2017) CD8+ T cells stimulate NaCl co-transporter NCC in distal convoluted tubules leading to salt-sensitive hypertension. Nat. Commun. 8, 14037, https://doi.org/10.1038/ncomms14037

162 Saleh, M.A., Norlander, A.E. and Madhurst, M.S. (2016) Inhibition of interleukin-17A but not interleukin-17F signaling lowers blood pressure and reduces end-organ inflammation in angiotensin II-induced hypertension. JACC Basic Transl. Sci. 1, 606–616, https://doi.org/10.1016/j.jbts.2016.07.009

163 Furusho, T., Sohara, E., Mandai, S., Kikuchi, H., Takahashi, N., Fujimaru, T. et al. (2020) Renal TNAIalpha activates the WNK phosphorylation cascade and contributes to salt-sensitive hypertension in chronic kidney disease. Kidney Int. 97, 713–727, https://doi.org/10.1016/j.kint.2019.11.021

164 Kamat, N.V., Thabet, S.R., Xiao, L., Saleh, M.A., Kirabo, A., Madhurst, M.S. et al. (2015) Renal transporter activation during angiotensin-II hypertension is blunted in interferon-gamma-/- and interleukin-17A-/- mice. Hypertension 65, 569–576, https://doi.org/10.1161/HYPERTENSIONAHA.114.04975

165 Zhang, J., Rudemiller, N.P., Patel, M.B., Karlovich, N.S., Wu, M., McDonough, A.A. et al. (2016) Interleukin-1 receptor activation potentiates salt reabsorption in angiotensin II-induced hypertension via the NKCC2 co-transporter in the nephron. Cell Metab. 23, 360–368, https://doi.org/10.1016/j.cmet.2015.11.013