CKJ REVIEW

Dietary potassium and the kidney: lifesaving physiology

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This Review was written in collaboration with NDT Educational.

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ABSTRACT

Potassium often has a negative connotation in Nephrology as patients with chronic kidney disease (CKD) are prone to
develop hyperkalaemia. Approaches to the management of chronic hyperkalaemia include a low potassium diet or
potassium binders. Yet, emerging data indicate that dietary potassium may be beneficial for patients with CKD.
Epidemiological studies have shown that a higher urinary potassium excretion (as proxy for higher dietary potassium
intake) is associated with lower blood pressure (BP) and lower cardiovascular risk, as well as better kidney outcomes.
Considering that the composition of our current diet is characterized by a high sodium and low potassium content,
increasing dietary potassium may be equally important as reducing sodium. Recent studies have revealed that dietary
potassium modulates the activity of the thiazide-sensitive sodium-chloride cotransporter in the distal convoluted tubule
(DCT). The DCT acts as a potassium sensor to control the delivery of sodium to the collecting duct, the potassium-secreting
portion of the kidney. Physiologically, this allows immediate kaliuresis after a potassium load, and conservation of
potassium during potassium deficiency. Clinically, it provides a novel explanation for the inverse relationship between
dietary potassium and BP. Moreover, increasing dietary potassium intake can exert BP-independent effects on the kidney by
relieving the deleterious effects of a low potassium diet (inflammation, oxidative stress and fibrosis). The aim of this
comprehensive review is to link physiology with clinical medicine by proposing that the same mechanisms that allow us to
excrete an acute potassium load also protect us from hypertension, cardiovascular disease and CKD.

Keywords: albuminuria, aldosterone, blood pressure, CKD, hyperkalaemia, hypertension, nutrition

INTRODUCTION

The diet of our hunter-gatherer ancestors consisted mainly of fruit, vegetables and game, and provided small amounts of sodium (Na^+) and large amounts of potassium (K^+). During the late Palaeolithic times, estimated dietary Na^+ intake was ~30 mmol/day (~690 mg/day) and dietary K^+ intake was ~280 mmol/day (~11 g/day) [1]. This is very different from our current diet, which contains large amounts of Na^+ and small amounts of K^+. Studies based on 24-h dietary recalls or urinary excretion estimate that the current average Na^+ intake is between 148 mmol/day (3.4 g/day) [2] and 213 mmol/day (4.9 g/day) [3], and that the average K^+ intake is between 54 mmol/day (2.1 g/day) [3] and 67 mmol/day (2.6 g/day) [2]. This dietary transition may explain, at least in part, the high prevalence of hypertension, cardiovascular disease and chronic kidney disease (CKD) [4–6]. Current evidence links dietary Na^+ intake directly to blood pressure (BP). Accordingly, reducing dietary Na^+ intake decreases BP [3, 7–10]. Based on the assumption that any approach to reduce BP will result in a lower incidence of cardiovascular disease, public health campaigns and research efforts have primarily focused on interventions to reduce dietary Na^+ intake. For example, the World Health Organization recommends a reduction to <2 g/day Na^+ (equivalent to 5 g sodium chloride per day) in adults [11]. On the other hand, strategies to raise dietary K^+ intake have received less attention despite accumulating evidence that higher dietary K^+ intake benefits health. First, several systematic reviews and meta-analyses have shown that increasing dietary K^+ intake decreases BP []. Secondly, large population studies have shown that higher dietary K^+ intake is associated with lower incidence of cardiovascular disease and stroke [3, 12–14]. Thirdly, several observational studies found an association between higher urinary K^+ excretion (as proxy for dietary intake) and better kidney outcomes [15]. Finally, experimental studies have uncovered underlying mechanisms that may explain the health benefits of dietary K^+. Our aim is to review the health effects of dietary Na^+ and K^+, novel physiological insights in Na^+ and K^+ handling by the kidney and how these mechanisms may explain the effects of dietary K^+ on BP, the cardiovascular system and the kidney.

DIETARY SODIUM, POTASSIUM AND HUMAN HEALTH: A BRIEF HISTORY

Globally, hypertension is considered the leading risk factor for cardiovascular and kidney disease, including ischaemic heart disease, congestive heart failure, stroke and CKD [16]. The link between a high-salt (sodium chloride) diet and the incidence of hypertension emerged during the early 1900s [17, 18]. In the 1960s, Dahl [19] found that societies with higher-than-average salt intake also had a higher incidence of hypertension. However, each population also consisted of individuals who did not develop hypertension even though they consistently consumed a high-salt diet. Thus, people can be classified as salt-sensitive or salt-resistant. Dahl et al. suggested that hypertension results from genetic and environmental susceptibility. To demonstrate this, they separated strains of salt-sensitive and salt-resistant rats based on their BP response to high salt [20]. Their findings indicated that salt-sensitivity is a genetic trait, and that salt intake should be seen as an environmental factor. Subsequently, they studied whether dietary K^+ influences salt-sensitive hypertension [21]. One of the reasons to do so was that early findings had shown that dietary Na^+ and K^+ have opposite effects on BP. For example, in 1928, Addison published

a report of five patients with hypertension of various aetiology in whom administration of different K^+ salts decreased BP [22]. In the 1950s, Meneely et al. [23] found that high dietary K^+ intake had prominent anti-hypertensive effects on rats during high dietary Na^+ intake, and increased their lifespan. Dahl et al. found that in rats on a high Na^+ diet, BP was reduced in the groups for which the diet also consisted of high dietary K^+. For example, in Dahl salt-sensitive rats on a high-salt diet for 12 months, rats with a dietary Na^+/K^+ ratio of 10 had a mean systolic BP (SBP) of 157 mmHg, whereas rats on the same NaCl diet with a Na^+/K^+ ratio of 1 had a mean SBP of 127 mmHg [21]. While the effects of K^+ on BP were impressive, at this time, the mechanisms explaining the beneficial effects of dietary K^+ were unknown. Over the following decades, many epidemiologic and interventional studies reported an inverse relationship between dietary K^+ intake and BP. For example, in the 1980s, the INTERSALT investigators studied 24-h urine electrolyte excretion and BP in 10 079 people (aged from 20 to 59 years from 32 countries), and found that 24-h urinary K^+ excretion was inversely associated with BP [7]. This association remained after adjustment for confounders that usually correlate with BP such as urine Na^+ excretion, body mass index and alcohol consumption. The association between BP and the urinary Na^+/K^+ excretion ratio was stronger than the association between BP and either Na^+ or K^+ excretion alone [7]. The INTERSALT study also included a particularly interesting Brazilian Indian population called the Yanomamo and Xingu. Their diet is characterized by a low Na^+ and high K^+ content, similar to our ancestors' diet in Palaeolithic times [1]. In the Yanomamo and Xingu, the urinary Na^+/K^+ ratio was extremely low (<0.01 in the Yanomamo and <0.08 in the Xingu), and there was virtually no BP rise with age [7, 24]. A large meta-analysis of 32 randomized controlled trials (including a total of 2609 participants) between 1981 and 1995 showed that K^+ supplementation (median of 75 mmol/day) caused a significant reduction in SBP by 3.11 mmHg and diastolic BP (DBP) by 1.97 mmHg [25]. The BP-lowering effect was higher when only studies of individuals on a high Na^+ diet were included. Two other smaller meta-analyses also found stronger BP-lowering effects of higher dietary K^+ intake in subjects with hypertension [26, 27]. The Dietary Approaches to Stop Hypertension (DASH)-Sodium study enrolled 412 participants, and showed that the DASH diet, containing ~120 mmol/day K^+, reduced BP [8]. This BP-lowering effect was more prominent in subjects consuming a high Na^+ diet. The fact that the BP-lowering effects of K^+ are more pronounced in individuals that consume a high Na^+ diet suggests that K^+ influences salt-sensitivity. This was further explored by Krishna et al. [28], who performed a randomized placebo-controlled cross-over study in 10 healthy males who were placed on a constant high Na^+ diet (120–200 mmol/day) and a controlled low K^+ diet (10 mmol/day). Participants were randomly supplemented with either placebo or 80 mmol of K^+/day (via potassium chloride tablets) for 9 days, maintaining their dietary K^+ intake at 10 or 90 mmol/day. Each individual was studied on both the low and higher K^+ diets in 4–8 weeks apart. During the low K^+ diet, urinary Na^+ excretion decreased, Na^+ balance became positive (396 ± 63 mmol over the 9-day period) and BP increased (mean arterial pressure increased from 90.9 ± 2.2 to 95.0 ± 2.2 mmHg). During K^+ supplementation, urinary Na^+ excretion was higher and BP decreased (mean arterial pressure decreased from 91.1 ± 1.8 to 88.9 ± 2.3 mmHg). Natriuresis occurred as soon as the participants started with K^+ supplementation. Similar results were observed in 12 patients with essential hypertension [29]. More recently, Aburto et al. [12] conducted a meta-analysis of 21

randomized controlled trials (including a total of 1892 subjects) and found that increasing dietary K^+ intake to a level of 90 mmol/day reduced SBP and DBP by 3.49 and 1.96 mmHg, respectively, in the overall population. When including only the hypertensive individuals or those on a high Na^+ diet (>4 g Na^+/day), the effects were even stronger: SBP and DBP were reduced by 5.32 and 3.10 mmHg in the hypertensive groups and by 6.91 and 2.87 mmHg in the high Na^+ groups, respectively. Furthermore, increasing dietary K^+ intake to 90–120 mmol/day was associated with a lower risk of stroke in 11 cohort studies (including a total of 127 038 participants). On the basis of this meta-analysis, the World Health Organization recommended a dietary K^+ intake of at least 90 mmol/day [11]. The Institute of Medicine recommends a dietary K^+ intake of 120 mmol/day [30]. This is based mostly on the same studies, but also taking into account the amount of K^+ in the DASH diet (120 mmol/day) [31]. Recently, the Prospective Urban Rural Epidemiology (PURE) study, a cohort study of 102 216 people throughout the world, estimated dietary K^+ intake on the basis of spot urine K^+ excretion, and found that daily K^+ intake modified the effect of Na^+ intake on BP [3]. The researchers divided their participants into three levels of urinary Na^+ excretion (>5 g/day; 3–5 g/day; <3 g/day), and found that within each group, higher urinary K^+ excretion was associated with lower BP. Again, the modifying effect of K^+ on BP reduction was most pronounced in the individuals with hypertension, as well as in the elderly. Of note, the association between urinary K^+ and BP extended to relevant clinical outcomes. PURE showed that a higher urinary K^+ excretion was associated with a lower risk of death or cardiovascular events, and this association remained significant after correction for physical activity, dietary factors and BP [13]. These and other studies on the influence of K^+ on cardiovascular and kidney outcomes will be discussed in more detail in this review. In the next section, we will first review current understanding of Na^+ and K^+ handling in the distal nephron and how this pertains to the BP-lowering effects of K^+.

DISTAL NEPHRON SODIUM AND POTASSIUM HANDLING

Potassium secretion in the distal nephron

The three key factors that regulate K^+ secretion in the aldosterone-sensitive distal nephron (ASDN) are [1] aldosterone, [2] Na^+ delivery and [3] tubular fluid flow rate [32] (Figure 1). The ASDN comprises the late distal convoluted tubule (also called DCT2), the connecting tubule (CNT) and the cortical collecting duct (CCD). The major apical Na^+ transporter for electrogenic Na^+ reabsorption along the ASDN is the epithelial sodium channel (ENaC), which is expressed in principal cells of the DCT2, CNT and CCD, and is upregulated by aldosterone [33]. Electrogenic movement of Na^+ through ENaC generates a lumen-negative transepithelial voltage that drives K^+ secretion through the renal outer medullary K^+ (ROMK) channel. In addition to ROMK channels, the ASDN also expresses big-K^+ channels (BK, or maxi-K^+ channels), which play an important role in flow-dependent K^+ secretion [34]. Therefore, the ASDN is able to switch between electroneutral Na^+ reabsorption [by the sodium-chloride cotransporter (NCC)] to electrogenic Na^+ reabsorption (by ENaC). Accordingly, it is equipped to change urinary K^+ and Na^+ excretion in response to variations in dietary K^+ and Na^+ intake. The natriuresis upon K^+ intake suggests a 'potassium switch' that regulates both K^+ and Na^+ handling
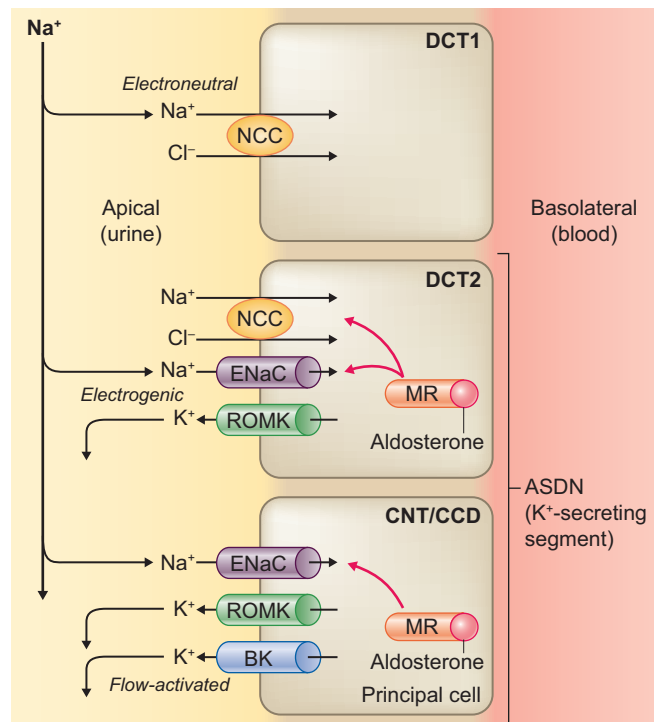

FIGURE 1: Overview of the main apical transport pathways contributing to Na^+ reabsorption and K^+ secretion in the ASDN. In the initial two-thirds of the DCT (DCT1), the apical NCC is the major Na^+ transporter, which mediates electroneutral Na^+ reabsorption. In the final one-third of the DCT (DCT2), NCC is co-expressed with the ENaC and ROMK. K^+ secretion progressively increases in the principal cells of DCT2, CNT and CCD that express ENaC and ROMK. Na^+ reabsorption by ENaC is electrogenic and is regulated by aldosterone. Na^+ reabsorption through ENaC generates a lumen-negative transepithelial voltage that drives K^+ secretion via ROMK. BK channels mediate flow-dependent K^+ secretion in the collecting duct. The three major factors that promote K^+ secretion are (i) Na^+ delivery to CNT/CCD, (ii) tubular flow rate and (iii) aldosterone.

by the kidney. Current insights indicate that this switch occurs in the DCT, which is upstream of the major K^+-secreting segment of the nephron (Figure 1). The potassium switch regulates downstream delivery of Na^+ to the ASDN.

Role of the DCT

Recent insights suggest that the DCT, upstream of the ASDN, acts as a K^+ sensor and affects downstream K^+ handling by regulating Na^+ delivery [35–37]. The electroneutral apical Na^+ transporter in the DCT is the NCC (gene symbol *SLC12A3*) [38, 39], which plays an important role in fine-tuning Na^+ delivery downstream to the ASDN. The functional relevance of the NCC for the handling of Na^+ and K^+ homoeostasis as well as BP is illustrated by two tubulopathies that affect NCC activity, including Gitelman syndrome and Gordon syndrome [40, 41]. Gitelman syndrome is caused by loss-of-function of NCC due to inactivating mutations in *SLC12A3*. Patients with Gitelman syndrome present with urinary Na^+ wasting, hypokalaemia and low-to-normal BP. Conversely, Gordon syndrome, also called familial hyperkalaemic hypertension or pseudohypoaldosteronism Type II, is caused by gain-of-function of NCC due to mutations in genes encoding regulatory proteins of NCC [40, 42–44]. Gordon syndrome patients present with the mirror image of Gitelman syndrome, including salt-sensitive hypertension and hyperkalaemia. NCC is activated by phosphorylation and inactivated by dephosphorylation [45, 46]. Several experimental studies have demonstrated that a low K^+ diet increases total and phosphorylated NCC (pNCC) [36, 47–52], resulting in decreased natriuresis, decreased kaliuresis and elevated BP. This can be reversed by administration of a thiazide diuretic, further supporting a role of NCC [36, 48]. Conversely, acute K^+ loading rapidly dephosphorylates NCC, regardless of whether K^+ is administered in a high K^+ diet [53, 54], through oral gavage [55, 56] or by intravenous infusion [57, 58]. The K^+ loading is followed by increased natriuresis and kaliuresis occurring as soon as 30–60 min. Chronic dietary K^+ loading reduces phosphorylated, total and surface NCC abundance [47, 59–63]. Pooled data from different rat and mouse experiments showed that pNCC levels are inversely correlated with plasma K^+ within the

physiological range [54, 64]. These data indicate that NCC is regulated in response to variations in plasma K^+. High plasma K^+ increases Na^+ delivery to the ASDN and low plasma K^+ decreases Na^+ delivery (Figure 2). The K^+ sensor in the DCT and K^+ secretion in ASDN work in concert in response to dietary K^+. A high K^+ diet dephosphorylates NCC, thereby reducing its activity and inhibiting electroneutral Na^+ reabsorption. In other words, K^+ loading has a thiazide-like effect. This increases Na^+ delivery to the downstream ASDN for electrogenic Na^+ reabsorption by ENaC, causing an electrochemical gradient that drives K^+ secretion through ROMK. Increasing tubular flow also stimulates flow-dependent K^+ secretion through BK (Figure 2). The physiological consequences are natriuresis and kaliuresis. Conversely, low dietary K^+ induces NCC phosphorylation, resulting in electroneutral Na^+ reabsorption through NCC. This will reduce distal Na^+ delivery and prevent Na^+ reabsorption through ENaC and K^+ secretion through ROMK. The physiological consequences are Na^+ retention and K^+ conservation (Figure 2).

Prioritizing between sodium and potassium

In addition to dietary K^+, dietary Na^+ also regulates NCC phosphorylation. NCC phosphorylation is suppressed by a high Na^+ diet and is promoted by a low Na^+ diet [65]. A relevant question is what happens when there is a high Na^+ diet and a low K^+ diet, characteristic of our current diet. Terker *et al.* [36] showed that NCC is activated by a low K^+ diet despite a high Na^+ diet and that this results in Na^+ retention and a rise in BP. Conversely, of interest is to analyse which signal will dominate in the setting of a low Na^+ and high K^+ diet (the 'Paleolithic' diet). Previously, we combined a low Na^+ and high K^+ diet and showed that there was still a decreased NCC abundance despite a low Na^+ diet and maximal activation of the renin–angiotensin system [61]. The overall result was that potassium-induced natriuresis was maintained, even in the context of a low Na^+ diet. This also illustrates that the effect of high K^+ can override the NCC stimulating effects of angiotensin II and aldosterone [66]. In agreement, Jensen *et al.* found that acute K^+ loading induced NCC dephosphorylation and natriuresis in mice on a high,
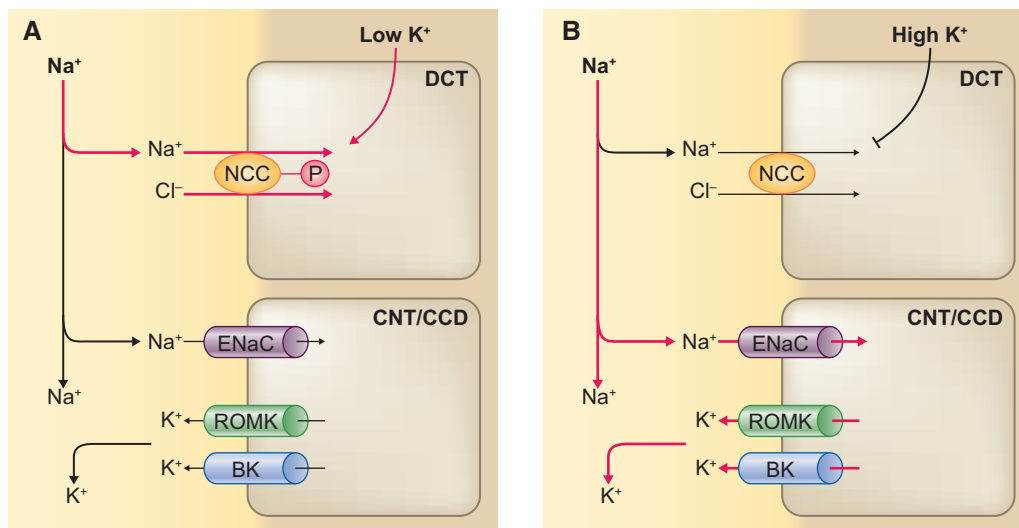

FIGURE 2: Model of how the DCT and ASDN work in concert in response to a low or high K^+ diet. (**A**) A low K^+ diet leads to phosphorylation (activation) of the NCC in the DCT, resulting in increased electroneutral Na^+ reabsorption through NCC. This will reduce Na^+ delivery to the ASDN and inhibit electrogenic Na^+ reabsorption through the ENaC and K^+ secretion through ROMK. (**B**) A high K^+ diet leads to dephosphorylation (inactivation) of NCC, thereby reducing electroneutral Na^+ reabsorption. This increases Na^+ delivery to the ASDN for electrogenic Na^+ reabsorption through ENaC and drives K^+ secretion through ROMK.

normal or low Na$^+$ diet [53]. Taken together, these studies support that K$^+$ homoeostasis is prioritized over Na$^+$ and volume regulation.

LOW POTASSIUM DIET ACTIVATES NCC

When consuming a high Na$^+$ and low K$^+$ diet, the kidneys prioritize conservation of K$^+$ over excretion of Na$^+$ and switch NCC 'on'. During K$^+$ deficiency, this mechanism serves well to inhibit K$^+$ excretion. However, a long-term low K$^+$ diet can cause chronic Na$^+$ reabsorption by upregulating NCC with subsequent plasma volume expansion and hypertension. Therefore, low K$^+$ diet-induced Na$^+$ reabsorption through NCC may be a key driver in the pathogenesis of salt-sensitive hypertension. Recently, several studies have provided insights in the molecular pathways that increase NCC activity during low K$^+$ diet (Figure 3). In the basolateral plasma membrane of DCT cells, potassium conductance is mediated by Kir4.1 (encoded by *KCNJ10*) and Kir5.1 (encoded by *KCNJ16*) [67–69]. These K$^+$ channels form a heterotetramer (Kir 4.1/5.1) which is responsive to plasma K$^+$ and initiates a signalling cascade that results in the phosphorylation of NCC [70–72]. A low extracellular K$^+$ concentration stimulates efflux of K$^+$ through Kir4.1/5.1, leading to membrane hyperpolarization. This leads to chloride efflux through a basolateral voltage-gated Cl$^-$ channel (ClC-Kb), resulting in a reduction in the intracellular Cl$^-$ concentration [73–75]. ClC-Kb requires the beta-subunit barttin for its function [76]. Disruption of any of these transporters blocks NCC phosphorylation. The importance of this pathway has been supported by *in vitro* and *in vivo* studies [36, 70, 73, 77–79]. For example, NCC phosphorylation by low K$^+$ was blocked in *KCNJ10* knockout mice [70, 78], in *ClC-K2* (a murine ortholog of human ClC-Kb) knockout mice [73], and in barttin hypomorphic mice [79]. In humans, loss-of-function mutations in the *KCNJ10* gene cause a syndrome with a Gitelman-like phenotype [80]. Intracellular chloride normally inhibits chloride-sensitive kinases called with-no-lysine (K) kinases (WNKs) by binding to their catalytic domain, and thereby blocking their autophosphorylation (Figure 3) [81]. When intracellular chloride is reduced, this inhibition is relieved and WNKs are able to autophosphorylate [82]. Phosphorylated WNKs activate the intermediary kinases Ste-20-related proline alanine-rich protein kinase (SPAK) and oxidative stress-responsive kinase 1 (OSR1), which activate NCC [36]. Animal studies from several groups have implicated and supported the importance of the intracellular chloride-WNK-SPAK/OSR1-pNCC pathway in the response to a low K$^+$ diet by studying wild-type or genetically altered mice [36, 48–52, 83, 84]. Multiple WNKs exist, but WNK4 appears to be the dominant form in the regulation of NCC. For example, Cl$^-$ inhibits WNK4 kinase activity at lower concentrations than it inhibits other WNKs and these concentrations are analogous to those in the human DCT [64]. Furthermore, WNK4 knockout mice on a low K$^+$ diet failed to increase pNCC [49, 52], whereas WNK1 or WNK3 siRNA knockdown mice still had increased phosphorylation of SPAK/OSR1 and NCC in response to a low K$^+$ diet [36]. The role of WNK4 in Cl$^-$ sensing *in vivo* was further supported by knock-in mice carrying Cl$^-$-insensitive mutant WNK4 (WNK4$^{L319F/L321F}$), which failed to increase total and pNCC in response to dietary K$^+$ restriction [84]. A study in *Drosophila* kidney tubule also found that this chloride-WNK4 sensing mechanism requires the kinase scaffolding protein Mo25 [85, 86]. Taken together, the effect of a low K$^+$ diet on NCC activity is explained by the relationship between Kir4.1/5.1, membrane voltage, intracellular chloride and WNK4-SPAK/OSR1 activation (Figure 3). Furthermore, ubiquitin ligases are also involved in this pathway. For example, Kelch-like 3 (KLHL3) normally degrades WNK4. A low K$^+$ diet increased phosphorylated (inactivated) KLHL3, and this abolished its activity to degrade WNK4, ultimately leading to increased WNK4 activity [87]. However, other signals or additional mechanisms may be present, because in SPAK knockout mice, a low K$^+$ diet was still able to phosphorylate NCC [83], and SPAK/kidney-specific OSR1 double knockout mice on a low K$^+$ diet had variable results with either blunted [36] or absent [51] phosphorylation of NCC.

HIGH POTASSIUM DIET AND NATRIURESIS

Acute potassium-induced natriuresis

Extracellular K$^+$ is a small fraction of total body K$^+$. In order to prevent large fluctuations in extracellular K$^+$ after an acute K$^+$ load, our body is equipped with efficient mechanisms to respond to changes in extracellular K$^+$, namely, by translocating K$^+$ into cells ('shift') and by K$^+$ excretion via the kidneys or the
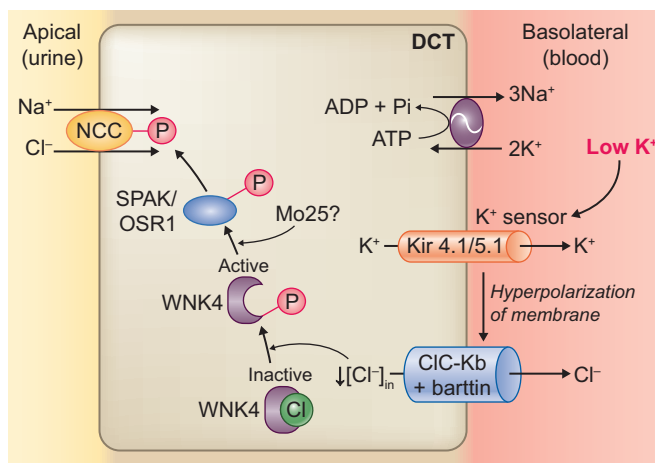

FIGURE 3: Molecular pathways involved in the effects of a low K$^+$ diet on the NCC. A low extracellular K$^+$ concentration is sensed by the K$^+$ channel Kir 4.1/5.1, resulting in efflux of K$^+$ through Kir4.1/5.1. This leads to membrane hyperpolarization and chloride (Cl$^-$) efflux through a basolateral voltage-gated Cl$^-$channel (ClC-Kb/barttin). A reduction in intracellular Cl$^-$ concentration relieves the inhibition of WNK4 autophosphorylation. In turn, phosphorylated WNK4 activates SPAK–OSR1, which phosphorylates NCC. In Drosophila melanogaster kidney tubules, WNK4 phosphorylation of SPAK–OSR1 depends on the scaffold protein Mo25.

gut. These regulations maintain extracellular K^+ within a safe range (between 3.5 and 5.5 mmol/L) [32]. In the kidneys, urinary K^+ excretion is regulated by aldosterone. A rise in plasma K^+ stimulates aldosterone secretion, which acts through the mineralocorticoid receptor to regulate the transcription of multiple genes that control ENaC activity [33, 88, 89]. However, this response occurs relatively late in the kidneys because it involves genomic effects. The kaliuretic effect of dietary K^+ intake precedes the increase in plasma aldosterone and is accompanied by natriuresis [90–92]. Recent insights suggest that this aldosterone-independent mechanism is mediated by acute NCC dephosphorylation in the DCT. NCC inhibition secondary to a high K^+ load induces natriuresis that serves to facilitate kaliuresis. This phenomenon is called K^+-induced natriuresis. Vallon *et al.* [47] were one of the first to report a reduction of NCC abundance and pNCC in mice on a high K^+ diet despite an increase in plasma aldosterone. This indicates that K^+ can dissociate the stimulatory effect of aldosterone on NCC [93–95]. Sorensen *et al.* further characterized that an acute K^+ load dephosphorylated NCC within 15 min and linked this to the natriuresis and kaliuresis starting 30–60 min after the K^+ load. While the kaliuretic response persists ~6 h, the natriuretic response declines earlier (after ~3 h). This decline in natriuresis was likely caused by upregulation of ENaC. Compared to wild-type mice, the K^+-induced early natriuretic effect was blunted in NCC knockout mice, indicating that acute K^+-induced natriuresis primarily depends on a functional downregulation of NCC [55]. This study also supports that K^+-induced NCC dephosphorylation is aldosterone-independent because K^+-loading suppressed NCC phosphorylation in mice lacking the enzyme aldosterone synthase similarly to wild-type mice [55]. Jensen *et al.* found that urinary K^+ excretion rates were attenuated when ENaC was downregulated by a high Na^+ diet or pharmacologically blocked by ENaC inhibition with benzamil [53]. Thus, this study further supports that acute K^+-induced kaliuresis is ENaC dependent. Interestingly, Hunter *et al.* showed that acute NCC inhibition by thiazide diuretics does not always result in kaliuresis [96]. Thus, the effect of thiazide diuretics is not completely similar to the effect of an acute K^+ load. Simply increasing distal Na^+ delivery by NCC inhibition may not be sufficient for the rapid effect that is observed after acute K^+ loading.

Potassium inactivates NCC

The pathways linking the effect of a high K^+ diet to reduced NCC activity are subject of ongoing research. Veiras *et al.* [97] showed that acute K^+ ingestion failed to dephosphorylate NCC in angiotensin II-infused rats that exhibited hypokalaemia secondary to angiotensin II-mediated ENaC upregulation. Normalizing plasma K^+ by K^+ supplementation relieved this. This suggests that plasma K^+ acts as the predominant driver of NCC activity. In contrast to a low K^+ diet, the effect of a high K^+ diet on NCC activity does not only depend on intracellular chloride. Penton *et al.* [58] used kidney slices to test the effect of extracellular K^+ on NCC. This experiment supported the previous observation that the effect of low extracellular K^+ on NCC depends on intracellular chloride. However, rapid dephosphorylation of NCC by high extracellular K^+ was neither blocked in the presence of a Cl^- channel blocker nor by low extracellular Cl^-, and NCC dephosphorylation occurred in the absence of significant changes in SPAK/OSR1 phosphorylation. This suggests that NCC dephosphorylation by high K^+ may occur independent of changes in intracellular chloride. Because of the rapidity of the response, Penton *et al.* [58] hypothesized that activation of protein phosphatases (PPs) may mediate NCC dephosphorylation in response to high extracellular K^+ (Figure 4). Shoda *et al.* [56] further found that an acute K^+ load acutely dephosphorylated NCC in mice independently of the WNK-SPAK/OSR1 cascade. This dephosphorylation of NCC was prevented by a calmodulin inhibitor or a calcineurin inhibitor, suggesting that the effect of high K^+ on the dephosphorylation of NCC is mediated by the calcium-binding protein calmodulin and its downstream PPs such as calcineurin. Whether a high K^+ load increases intracellular calcium and increases the activity of calmodulin and calcineurin requires further study. Studies by Chen *et al.* [84] and Ishizawa *et al.* [98] do support a role for the WNK4-SPAK/OSR1 pathway in modifying NCC phosphorylation after a K^+ load (Figure 4). Chen *et al.* [84] found different responses in acute and chronic K^+ loading in Cl^--insensitive WNK4 knock-in mice. Acute K^+ loading through oral gavage increased plasma K^+ and decreased pNCC in 30 min in wild-type mice, the decrease in pNCC was not observed in WNK4 knock-in mice. However, chronic K^+ loading deactivated NCC in both
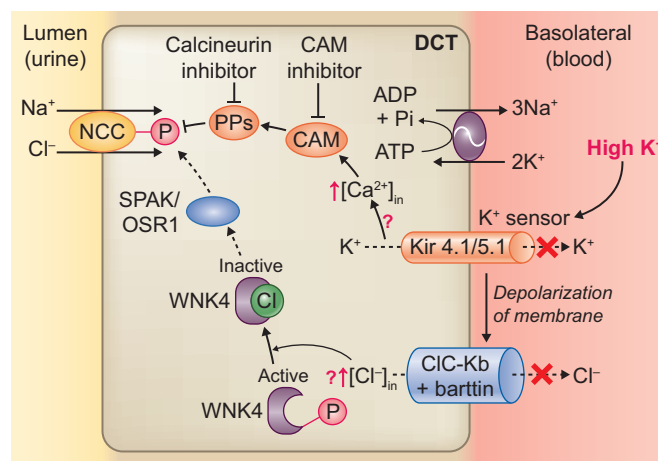

FIGURE 4: Molecular pathways involved in the effects of a high K^+ diet on the NCC. High extracellular K^+ concentration is sensed by K^+ channel Kir4.1/5.1 and causes membrane depolarization. This may lead to an increase in intracellular calcium (Ca^{2+}) through unknown mechanisms. Ca^{2+} stimulates calcium-binding protein calmodulin (CaM) and downstream PPs such as PP3 (calcineurin). This dephosphorylates NCC. In acute K^+ loading, mechanisms that depend on intracellular chloride ($[Cl^-]_{in}$) may also be stimulated through effects dependent on the K^+ channel Kir4.1/5.1. An increase in $[Cl^-]_{in}$ may inhibit WNK4 autophosphorylation. This would prevent SPAK–OSR1 phosphorylation and ultimately, NCC phosphorylation.

wild-type and WNK4 knock-in mice, indicating mechanisms other than Cl$^-$-sensing by WNK4. Whether this is associated with activation of PPs was not reported in this study. Ishizawa *et al.* [98] showed that high extracellular K$^+$ in HEK cells activated calcineurin-mediated dephosphorylation of KLHL3 at serine 433, which in turn decreased WNK4 activity by its ubiquitination to WNK4 and thus limiting NCC phosphorylation. In addition to the downregulation of NCC, experimental studies and mathematical modelling have shown that high K$^+$ also reduces Na$^+$ reabsorption in the proximal tubule [62, 63, 99, 100] and thick ascending limb [62, 101–105]. All these processes serve to enhance Na$^+$ delivery to the ASDN, where Na$^+$ reabsorption leads to K$^+$ secretion. A recent finding *in vivo* and in CCD cells showed that K$^+$ directly influences K$^+$ secretion via ENaC stimulation in the principal cells, independent of plasma aldosterone [106]. This was mediated via basolateral Kir4.1 channels leading to possible changes in intracellular chloride similar to the effects in the DCT. Subsequently, WNK1 stimulates the Type 2 mammalian target of rapamycin (mTOR) complex and serum and glucocorticoid inducible kinase 1 (SGK1), resulting in ENaC activation and thereby K$^+$ secretion. This mechanism acts in concert with aldosterone-dependent mechanisms for K$^+$ excretion [106].

Chronic adaptation to a high potassium diet

Chronically, a high K$^+$ diet intake leads to compensatory changes that attenuate the initial natriuresis and help to preserve Na$^+$ balance. This decline in natriuresis is ENaC dependent and could be partially explained by the delay in reaching the peak levels of aldosterone after an acute K$^+$ load [55, 107]. Interestingly, NCC knockout mice exhibit a blunted K$^+$-induced early natriuretic response compared with wild-type mice [55]. Structural adaptation was observed in mouse models of persistent NCC inhibition or activation. For example, Grimm *et al.* identified the activation of an α-ketoglutarate paracrine signalling system and distal nephron remodelling process in SPAK-deficient mice (a model for persistent NCC inhibition) [108].

Both mechanisms act together to induce Na$^+$ reabsorption in the CNT and CCD to compensate for the loss of NCC function. In constitutively active SPAK mice (a model for persistent NCC activation), the same investigators found delayed restoration of urinary K$^+$ excretion and plasma K$^+$ to the levels of wild-type mice upon thiazide treatment within 3 days [109]. They concluded that NCC hyperactivity drives the cellular remodelling in the ASDN with a reduction in CNT mass and attenuation in ENaC and ROMK, whereas NCC inhibition could reverse this remodelling. Therefore, during chronic K$^+$ loading, NCC was persistently inhibited and compensatory mechanisms were activated. This adaptation attenuates K$^+$-induced natriuresis by an acute K$^+$ load [110]. Evaluating cellular remodelling of nephron segments in other genetically modified animals (e.g. WNK4 knockout, Cl$^-$-insensitive WNK4 knock-in mice or ENaC knockout mice) may explain alterations in Na$^+$ and K$^+$ handling in acute and chronic responses to dietary K$^+$ [86].

GUT–KIDNEY KALIURETIC SIGNALLING

How K$^+$ is 'sensed' remains an unanswered question, as well as how the signal is conveyed from the gut to the kidney and whether this depends on plasma K$^+$ (Figure 5). Rabinowitz *et al.* [111] challenged the traditional view of feedback control that is that high plasma K$^+$ during a high K$^+$ diet is the major factor to trigger aldosterone-mediated transcellular K$^+$ shift and kaliuresis. In studies in sheep, they found that meal-induced kaliuresis was not accompanied by a change in plasma aldosterone and only subtle changes in plasma K$^+$. The authors proposed the idea of feedforward control by proposing that kaliuresis is initiated before the rise in plasma K$^+$, by a mechanism controlled by K$^+$ sensing in the gut. Lee *et al.* [112] further provided evidence for this 'gut factor' in rats by finding that intra-gastric K$^+$ infusion with meal provokes a significant increase in urinary K$^+$ excretion without a rise in plasma K$^+$, while intra-portal and systemic K$^+$ infusion do increase plasma K$^+$. Complementing these experimental data, Preston *et al.* [113] conducted a physiological study in healthy human volunteers by comparing the
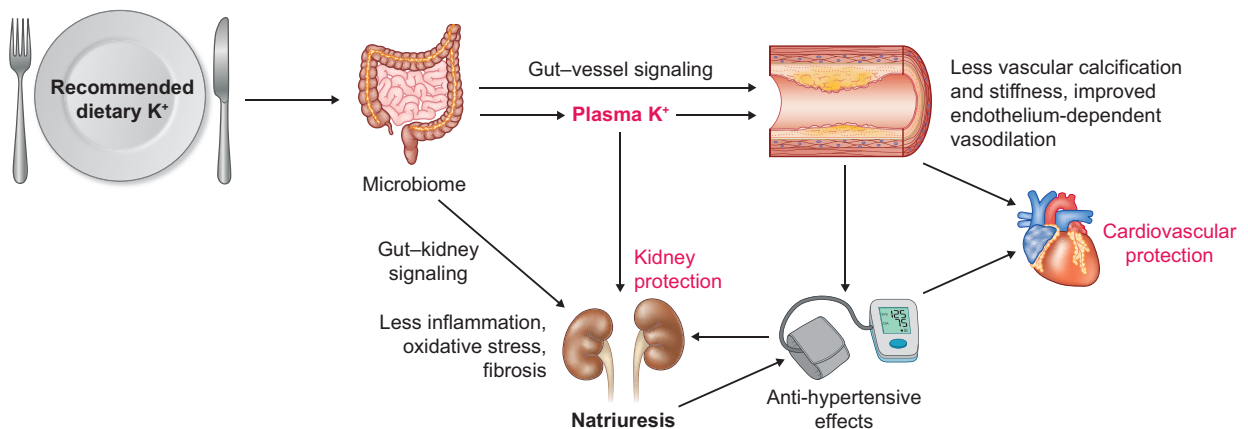

FIGURE 5: Working hypothesis of how dietary K$^+$ may confer cardiovascular and kidney protection. The effects of dietary K$^+$ may either be relayed through its effect on the microbiome and its metabolites (gut–vessel and gut–kidney signalling) or through plasma K$^+$. The protective effects of K$^+$ can be mediated both through BP-dependent and -independent mechanisms.

kaliuretic effect in three conditions: oral K^+ load only, K^+-deficient meal only, or an oral K^+ load plus a K^+-deficient meal. Results showed that a significant increase in kaliuresis, without changes in plasma K^+, was observed in the group with K^+ plus meal. This kaliuresis remained intact following pharmacological blockade of the mineralocorticoid receptor with eplerenone, supporting the existence of a gut–kidney kaliuretic signalling that regulates urinary K^+ excretion by a feedforward mechanism, independently of plasma K^+ and plasma aldosterone. Although these studies support a 'gut factor', another possibility to explain feedforward control could be that a minor rise in the K^+ concentration in peritubular capillaries by dietary K^+ may be sufficient to mediate NCC inhibition [114]. Possible signalling molecules for the 'gut factor' remain to be determined. Recent studies provide new insights into gut–kidney cross-talk by showing that gut microbiota-derived short chain fatty acids can affect BP and kidney function (Figure 5). The G protein-coupled receptor Gpr41 and olfactory receptor Olfr78 in the afferent arteriole of the kidney respond to these short chain fatty acids to regulate BP via vascular resistance or renin secretion [115, 116]. Similarly, dietary sodium has been shown to influence BP regulation through direct effects on the microbiome [117]. In summary, although the 'gut factor' remains unclear, the physiological implication would be that both feedback control and feedforward control work in concert to maintain K^+ and Na^+ homoeostasis.

DIETARY POTASSIUM AND BP

Besides NCC regulation, dietary K^+ may also exert effects on blood vessels, nerves and the intra-kidney renin–angiotensin system that may contribute to BP effects (Figure 5). Studies have shown that K^+ depletion activates renin, angiotensin II and endothelin-1 in the kidney independent of the systemic renin–angiotensin system. The activated intra-kidney renin–angiotensin system is associated with structural changes in the kidney and salt-sensitive hypertension [118–120]. For example, Suga et al. [118] showed that rats made hypokalaemic by a low K^+ diet exhibited tubulointerstitial injury, hypoxia and an imbalance in local vasoactive mediators that favours vasoconstriction. There was evidence for upregulation of angiotensin-converting enzyme at sites of tubulointerstitial injury, increased cortical-to-plasma angiotensin II ratio, increased endothelin-1 in both the cortex and the medulla, reduced urinary prostaglandin E2, and a decrease in kallikrein. Moreover, these rats demonstrated salt-sensitive hypertension that was not corrected after normalizing plasma K^+. Beneficial effects of K^+ are also mediated through neural effects. For example, K^+ may regulate Na^+ excretion and BP by modulating the activity of the kidney's sympathetic nervous system (SNS). Fujita and Sato [121] evaluated the effect of K^+ supplementation on the kidney's SNS in rats treated with deoxycorticosterone acetate (DOCA), a model of salt-sensitive hypertension. They found that the norepinephrine turnover rate in the kidney was significantly increased in DOCA-salt rats, and that K^+-supplemented DOCA-salt rats decreased but not completely inhibited this effect. K^+-supplemented DOCA-salt rats also showed attenuated Na^+ retention and an antihypertensive response. These results confirmed previous reports showing that kidney SNS activation impairs natriuresis, and that kidney denervation increases urinary Na^+ excretion [122, 123]. Studies also support that kidney SNS activation is an important factor influencing salt-sensitive hypertension in obese animal models [124–126]. Mu et al. [127] linked SNS activity and salt-sensitive hypertension to NCC

activation in the DCT, which was mediated by stimulation of β1-adrenergic receptors. The β1-adrenergic stimulation of NCC possibly involves the WNK4–OSR1 pathway [128] and the Kir4.1 channel in the DCT [129]. A recent study showed that β1-adrenergic stimulation of NCC involves PP1 inhibitor-1 (I-1), which is an endogenous inhibitor of PP1. Stimulation of β1-adrenergic receptors results in changes in cyclic adenosine monophosphate (cAMP) and stimulates a protein kinase A-dependent phosphorylation of I-1, which in turn inhibits PP1-dependent NCC dephosphorylation [130]. K^+ supplementation may decrease but not completely inhibit this pathway through decreasing SNS activity. Aside from modifying the activity of the SNS in the kidney, Zicha et al. [131] found that a high K^+ diet may attenuate sympathetic vasoconstriction and result in an antihypertensive effect in immature salt-sensitive Dahl rats; however, this mechanism is absent in adult salt-loaded rats and in rats with established salt-sensitive hypertension. Similar findings were reported by Dietz et al. [132] in stroke-prone spontaneously hypertensive rats. They showed that a high K^+ diet partially reversed salt-induced changes in noradrenaline metabolism, resulting in improved neuronal uptake of noradrenaline, attenuated sensitivity of vascular smooth muscle to noradrenaline and reduced release of noradrenaline into the plasma. All these changes attenuate sympathetic vasoconstriction. Direct effects of K^+ on vascular tone may be mediated through endothelium-dependent vasodilation. In patients with essential hypertension, local K^+ infusion facilitates endothelium-dependent vasodilation induced by acetylcholine. This effect appears to be mediated by nitric oxide production from endothelial cells and was independent of mean arterial BP [133]. This finding is consistent with experimental data. For instance, aortic endothelium-dependent relaxation was reduced in salt-sensitive Dahl rats, whereas a high K^+ diet significantly enhanced endothelium-dependent relaxation to acetylcholine independent of changes in BP [134]. Zhou et al. [135] also showed that K^+ supplementation improves endothelium-dependent relaxation by increasing endothelial nitric oxide in the carotid arteries of salt-loaded Dahl salt-sensitive rats. K^+ can also influence endothelial cell structure. For example, in various studies, Oberleithner et al. [136–138] showed that high extracellular K^+ significantly reduces the stiffness of vascular endothelial cells by changing endothelial cell structure and increasing the release of nitric oxide, whereas high extracellular Na^+ and aldosterone prevented these changes. One clinical study also supported the notion that K^+ has effects on vascular tone independent of the kidney. In this study, Dolson et al. [139] studied 11 anuric haemodialysis patients who initially received haemodialysis with a dialysate containing 2.0 mmol/L K^+ and were then randomly allocated to groups with a dialysate K^+ of either 3.0 or 1.0 mmol/L for at least 1 month. All groups showed a reduction in BP during haemodialysis because of fluid removal. However, patients with a 1.0 mmol/L K^+ dialysate showed significantly increased BP 1-h post-dialysis, whereas patients with a 3.0 mmol/L K^+ dialysate did not exhibit this 'rebound hypertension'.

DIETARY POTASSIUM AND CARDIOVASCULAR RISK

A high Na^+ and low K^+ diet contribute to hypertension, which increases the burden of cardiovascular and kidney disease. K^+ supplementation is proposed to block this vicious cycle by BP reduction via natriuresis, attenuation of SNS activity or direct

vascular effects, which in turn, improve cardiovascular and kidney health (Figure 5). A high K^+ diet may also provide BP-independent protective effects such as anti-inflammatory, anti-fibrotic and antioxidant effects, improvement of endothelial function and prevention of atherosclerosis [140]. The beneficial effects of increasing dietary K^+ intake on BP and cardiovascular outcomes are becoming increasingly evident from epidemiological, clinical and experimental studies.

Epidemiological studies

Higher dietary K^+ intake is associated with reduced BP and a lower risk of stroke. However, Aburto *et al.* [12] found no significant associations with incident cardiovascular disease. This may be attributable to the lack of adequately powered randomized trials. Subsequent data from the large-scale PURE study did show inverse associations between urinary K^+ excretion, major cardiovascular events and mortality. Compared with a urinary K^+ excretion <1.5 g/day, individuals with higher urinary K^+ excretion had a decreased risk of cardiovascular events and death [13]. A more recent analysis of the PURE cohort showed that although Na^+ intake has a positive association with BP across communities, the association between dietary Na^+ intake and cardiovascular events revealed a J-shaped relationship. There was a linear association between dietary K^+ intake and cardiovascular outcomes [14]. This supports the role of dietary K^+ in cardiovascular protection but also indicates that the effects of dietary Na^+ and K^+ on cardiovascular events are complex and cannot be explained solely by the BP-lowering effects.

Clinical trials

The potential cardioprotective effects of high K^+ intake are also supported by clinical intervention studies. For example, a long-term intervention study in Taiwan analysed the effect of K^+-enriched salt on cardiovascular mortality. Five kitchens were randomized to prepare meals with K^+-enriched salt (experimental group, $n = 768$) or regular salt (control group, $n = 1213$). After a follow-up of 31 months, the incidence of cardiovascular deaths reduced by nearly 40% and the life expectancy was longer among participants in the experimental group [141]. These effects may be primarily attributable to K^+ because the increase in urinary K^+-to-creatinine ratio was greater than the decrease in urinary Na^+-to-creatinine ratio (76 versus 17%, respectively). However, it is unclear whether this cardiovascular benefit was dependent on BP due to a lack of BP measurements. In a recent population-level salt-substitution study in Peru (involving a total of 2376 individuals from six villages), regular table salt (sodium chloride) was replaced by K^+-enriched salt (25% potassium chloride) using a stepped-wedge cluster randomized trial design [142]. This intervention decreased SBP and DBP by 1.29 mmHg and 0.76 mmHg, respectively. Again, the BP-lowering effect was most pronounced in subjects with hypertension and in older individuals. In addition, the incidence of hypertension was reduced by 51% among participants without hypertension at baseline. This BP-lowering effect was likely attributable to K^+, because of higher 24-h urinary K^+ and similar Na^+ excretion at the end of the intervention. Currently, a large-scale cluster-randomized controlled trial in 600 villages (20 996 participants at high cardiovascular risk) in northern rural mainland China is investigating the effect of long-term potassium-salt substitution (70% sodium chloride and 30% potassium chloride) on cardiovascular outcomes (follow-up of 5 years). In this study, the primary outcomes are fatal and non-fatal stroke and the secondary outcomes are total major vascular events (non-fatal stroke, non-fatal acute coronary syndrome or death from cardiovascular or cerebrovascular causes) and total mortality [143]. Pending these results, potassium-enriched salt substitutes are increasingly recognized as a potential means of lowering BP at population scale [144]. There is also evidence that dietary K^+ can exert BP-independent effects on vascular function. He *et al.* [145] conducted a placebo-controlled crossover trial comparing K^+ chloride with K^+ bicarbonate in 42 pre-hypertensive individuals. Compared with placebo, both K^+ chloride and K^+ bicarbonate had significant beneficial effects on cardiovascular parameters (improved endothelial function, increased arterial compliance, decreased left ventricular mass and improved left ventricular diastolic function) despite the fact that the BP-lowering effect was modest during the K^+ treatment (possibly because they consumed a relatively low Na^+-high K^+ diet at baseline). A recent meta-analysis explored which vascular functions are improved by dietary K^+ supplementation and found that this was primarily the case for pulse pressure [146]. Overall, the cardiovascular benefits of dietary K^+ are likely attributable to both BP-dependent and BP-independent effects (Figure 5).

Experimental studies

Experiments in stroke-prone spontaneously hypertensive rats showed that a high K^+ diet reduces the size of cerebral infarcts, decreases vessel wall thickness and increases vascular compliance independently of changes in BP [147]. Several studies have shown that K^+ supplementation may attenuate inflammation and oxidative stress. For example, in salt-loaded Dahl salt-sensitive rats, K^+ supplementation attenuated salt-induced acceleration of neointima proliferation, adventitial macrophage infiltration and generation of reactive oxygen species in cuffed arteries despite the small reduction in BP. This indicates a potential vascular protective effect of K^+ via its antioxidant activities [148]. Sun *et al.* linked dietary K^+ intake to vascular smooth muscle cell calcification. In an atherogenic animal model and an *ex vivo* tissue model, low K^+ induced differentiation and calcification of vascular smooth muscle cells and promoted vascular calcification, whereas a high K^+ inhibited these responses [149]. Compared with low K^+-fed mice, a high K^+ diet concurrently reduced aortic pulse wave velocity, which is an indicator of arterial stiffness.

DIETARY POTASSIUM AND CKD

The close relationship between BP, cardiovascular disease and kidney disease has led to the hypothesis that dietary K^+ may also protect the kidney. Indeed, such effects are being supported by emerging evidence both from epidemiological studies in humans and experimental data from animal models.

Epidemiological studies

Several observational studies have analysed the association between urinary K^+ excretion and kidney outcomes (Figure 6). These studies are heterogeneous in terms of baseline kidney function and method to assess urinary K^+ excretion. Below we will discuss these studies; they were also included in a systematic review [150]. Three studies were conducted in populations with preserved kidney function [estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2]. First, Araki *et al.* [151] studied the association of a single baseline 24-h urine K^+ excretion with
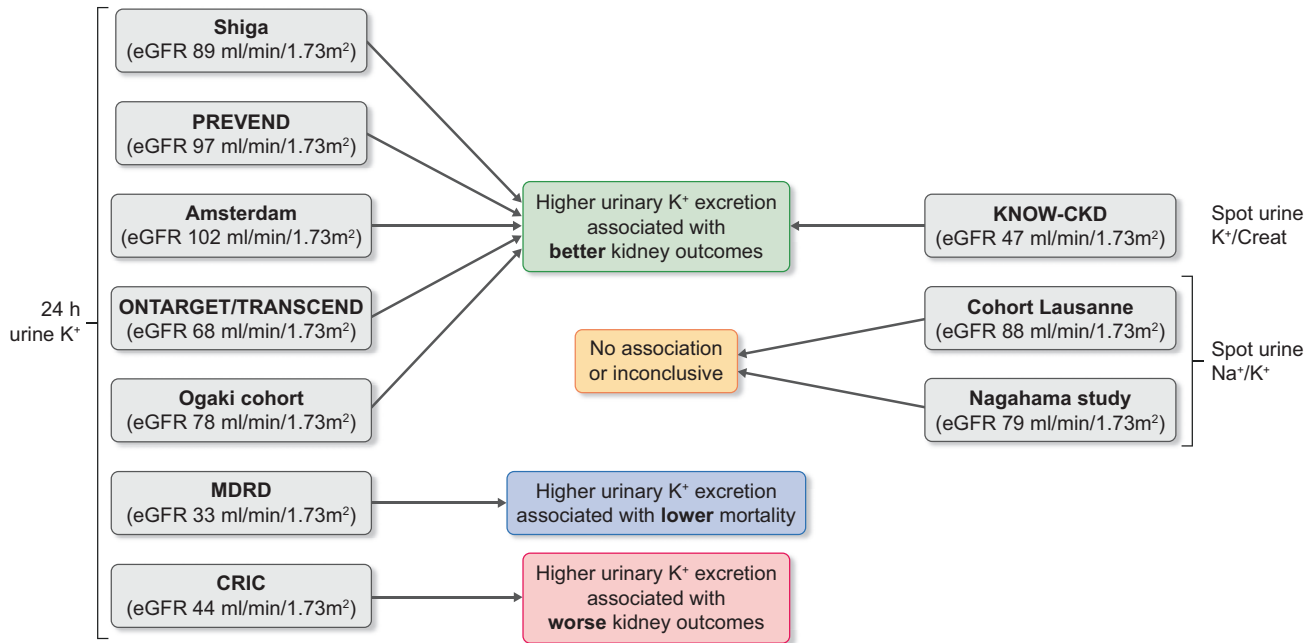
FIGURE 6: Overview of cohort studies that analysed the association between urinary K$^+$ or urine Na$^+$/K$^+$ (as proxy for dietary intake) and kidney outcomes. The average baseline eGFR is shown for each cohort.

the incidence of kidney and cardiovascular events in 623 Japanese patients with Type 2 diabetes. After a median follow-up period of 11 years, a urinary K$^+$ excretion >1.72 g/day was associated with lower incidence of kidney replacement therapy or cardiovascular events and 50% decline in eGFR or progression to CKD Stage 4 compared with patients who had a urinary K$^+$ excretion of <1.72 g/day. Furthermore, patients in the highest quartile of urinary K$^+$ excretion (>2.9 g/day) had a significantly lower rate of annual eGFR decline. Secondly, Kieneker *et al.* analysed the association between two 24-h urine K$^+$ excretions with the risk of CKD (defined as newly developed eGFR <60 mL/min/1.73 m^2 or albuminuria >30 mg/24 h, or both) in the population-based Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort (5315 individuals) [152]. During a median follow-up of 10.3 years, they showed that each 21 mmol/day (1 SD) decrement in urinary K$^+$ excretion was independently associated with a 16% higher risk of *de novo* CKD even after adjustment for confounders and other possible mediators. This association was more pronounced in individuals with hypertension. Thirdly, Olde Engberink *et al.* conducted a retrospective cohort study (involving a total of 541 patients) in the outpatient setting showing that higher urinary K$^+$ excretion (>82 mmol/day based on two 24-h urine collections) was associated with a lower risk of 60% eGFR decline or start of kidney replacement therapy after a median follow-up time of 16 years [153]. Two studies were conducted in populations including patients with and without CKD. Smyth *et al.* performed a *post hoc* analysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomised Assessment Study in ACE-

Intolerant Subjects with Cardiovascular Disease (TRANSCEND) cohorts (involving a total of 28 879 participants with a mean eGFR of 68 mL/min/1.73 m^2) and found that higher 24-h urinary K$^+$ excretion (estimated from a fasting morning urine sample) was associated with a lower risk of eGFR decline, progression of proteinuria and initiation of dialysis [154]. Of interest, subgroup analysis showed a loss of this association in individuals with more severe CKD (eGFR <45 mL/min/1.73 m^2). Nagata *et al.* [155] evaluated the association of 24-h urinary K$^+$ excretion with kidney outcomes and death in Japanese patients with diabetes (involving a total of 1230 patients with eGFR >30 mL/min/1.73 m^2) with a mean follow-up of 5.5 years. They found that higher 24-h urinary K$^+$ excretion (2.0–3.0 g/day) was associated with a lower risk of 30% eGFR decline or death compared with patients with urinary K$^+$ excretion <1.5 g/day. Similarly, a subgroup analysis of patients with eGFR between 30 and 60 mL/min/1.73 m^2 showed a loss of statistical significance between urinary K$^+$ excretion and outcomes. Two studies evaluated the association between spot urine Na$^+$/K$^+$ ratio with kidney function decline in the general population. Deriaz *et al.* conducted a longitudinal population-based study (including a total of 4141 adults with a mean baseline of eGFR 88 ± 15 mL/min/1.73 m^2), and their results showed that a high urinary Na$^+$ excretion and high urine Na$^+$/K$^+$ ratio was associated with faster kidney function decline; however, there was no significant association between urine K$^+$ excretion and kidney outcomes [156]. Another study also analysed spot urine Na$^+$/K$^+$ (7063 participants, ~15% CKD) and revealed a trend similar to that described by Deriaz *et al.* [156] but concluded that a single determination of the urinary Na$^+$/K$^+$ ratio does not have sufficient prognostic utility in assessing

kidney function decline [157]. Three studies mainly focused on patients with CKD. Leonberg-Yoo *et al.* evaluated the association between time-updated average urinary K^+ excretion, kidney failure (defined as start of kidney replacement therapy) and all-cause mortality in a *post hoc* analysis of the Modification of Diet in Renal Disease cohort [158]. These patients have advanced CKD (812 patients with CKD Stages G3–5, measured GFR 32.6 ± 12.0 mL/min/1.73 m²). The results showed an inverse association between urine K^+ excretion and all-cause mortality, but there was no association with kidney failure. Kim *et al.* investigated the relationship between spot urinary K^+-to-creatinine ratio and kidney outcomes in the Korean KNOW-CKD Study (including 1821 patients with CKD Stages G1–G5) [159]. During 5326 person-years of follow-up, the lowest quartile of urinary K^+-to-creatinine ratio was associated with increased risk of CKD progression (>50% decrease in eGFR from baseline values and the onset of end-stage kidney disease). These results were also evident in a subgroup analysis in which only patients with an eGFR <45 mL/min/1.73 m² were included. He *et al.* [160] conducted a prospective study and evaluated the association of 24-h urinary K^+ excretion with kidney outcomes in the Chronic Renal Insufficiency Cohort (CRIC, including 3939 patients with eGFR 20–70 mL/min/1.73 m²). Surprisingly, their data demonstrated that high urinary K^+ excretion was associated with a higher risk of incident end-stage kidney disease and halving of eGFR. Other studies focused more generally on the association between healthy dietary patterns (which are typically K^+ rich) and kidney outcomes. A recent meta-analysis included 18 cohort studies of non-CKD populations and demonstrated that a healthy dietary pattern was associated with a lower risk of incident CKD, and a lower incidence of albuminuria, but not with a lower incidence of eGFR decline [161]. Another meta-analysis conducted by the same group showed that a plant-based dietary pattern among patients with established CKD was associated with lower mortality, but not with the risk of end-stage kidney disease [162]. A recent review also recommends plant-based diets for both primary and secondary prevention of CKD [163]. Some cohort studies used food frequency questionnaire to evaluate the association between dietary K^+ intake and kidney outcomes [164–166]. For example, Mun *et al.* recently studied the association of dietary K^+ with eGFR <60 mL/min/1.73 m² and >15% decline in eGFR in Korean rural populations with CKD Stage 2 (involving a total of 5064 patients) [166]. Compared with the subjects in the lowest quartile of dietary K^+ intake (<1236 mg/day), patients in the highest quartile of dietary K^+ intake (>2323 mg/day) had a 40% lower risk of CKD development and patients in all quartiles had a 28–46% lower risk of eGFR decline during the follow-up period of 47 months. However, this association was only statistically significant in subjects with hypertension. Two other studies also showed that higher K^+ intake is associated with better kidney outcomes [159, 165], while another study showed no association [164]. Taken together, the majority of these observational studies demonstrate that diets rich in K^+ were associated with better kidney outcomes in the overall population or patients with early-stage CKD (Figure 6) [151, 152, 154, 155, 165, 166].

Experimental studies

In rats, a K^+-deficient diet leads to tubulointerstitial injury with macrophage infiltration and interstitial collagen deposition, development of salt-sensitive hypertension and decline in kidney function [118, 167]. K^+ depletion also caused proximal tubular hypertrophy and a marked increase in angiotensin II Type 1

receptor density in healthy rats and those subjected to subtotal nephrectomy. These changes may explain the mechanisms of the deleterious effects of K^+ deficiency on the kidney [168]. Conversely, in prehypertensive Dahl salt-sensitive rats, adding K^+ to high salt diets reduced progression of kidney injury (preventing 30–50% of the tubular lesions and 20% of the glomerular lesions) decreased arteriolar wall thickness and diminished the severity of arteriolar lesions, and this occurred independent of BP [169]. Ellis *et al.* [170] also reported a reduction in albuminuria and improvement in hypertensive kidney lesions in K^+-supplemented, salt-loaded spontaneously hypertensive rats. In the 5/6th nephrectomy model of CKD, high dietary K^+ intake decreased interstitial fibrosis and suppressed inflammation [171]. More specifically, high dietary K^+ intake resulted in less collagen Types I and III deposition in the kidney, less macrophage infiltration, lower expression of the inflammatory cytokines interleukin-1 beta and intercellular adhesion molecule 1, and decreased activation of nuclear factor kappa B (NF-κB). In this rat CKD model, the kidney protective effects were linked to a reduction in transforming growth factor beta (TGF-β), a key mediator of kidney fibrosis, upregulation of Smad7 (a negative regulator of TGF-β and NF-κB) and lower BP. Similar kidney protective effects were observed in another rat CKD model (albumin overload) [172]. A K^+-induced upregulation of the kinin–kallikrein system reduced BP, proteinuria and tubulointerstitial fibrosis. These effects were also accompanied by increased Smad7 production and downregulation of the TGF-β pathway [172–174]. *In vitro*, bradykinin prevented albumin-induced tubular phenotypic changes and the expression of mesenchymal markers, and inhibited TGF-β expression. All of these effects were reversed by pharmacological blockage of the kinin pathway [174]. These results support that the K^+-induced upregulation of the kinin–kallikrein system may protect the kidney. Although experimental evidence supports the kidney protective effects of dietary K^+, clinical intervention studies are necessary to establish if these findings also extend to humans.

PERSPECTIVES

The evidence for a beneficial effect of dietary K^+ on human health is strengthening. Although the ideal dietary K^+ content is unknown, data from association studies consistently suggest that a low K^+ diet is harmful. This implies that increasing dietary K^+ intake to recommended levels (90–120 mmol/day) could be an effective public health strategy to reduce hypertension and cardiovascular disease. Because hypertension and cardiovascular diseases are very prevalent in patients with CKD, there are good reasons to believe that patients with CKD may also benefit from increasing dietary K^+. This assumption is now increasingly supported by both experimental and epidemiological

Table 1. Knowledge gaps

i. Is potassium-induced natriuresis (with NCC dephosphorylation) preserved in CKD?

ii. Does CKD cause a switch from urinary K^+ excretion to gastro-intestinal K^+ excretion or intracellular redistribution?

iii. In CKD, do the beneficial effects of dietary K^+ outweigh the risks of hyperkalaemia?

iv. Are the positive effects of dietary K^+ mediated by plasma K^+ and, if so, are they concentration dependent?

v. What is the effect of dietary K^+ on phosphate balance and fibroblast growth factor 23?

data (Figures 5 and 6). However, several caveats apply and several knowledge gaps remain (Table 1). First, association studies do not prove causality. For example, high K^+ or healthier diets may not only be rich in K^+ but also in alkaline-rich fruits and vegetables. The anion accompanying K^+, other nutrients, lower protein, higher fibre content and lower phosphate content in these plant-based diets may have contributed to the outcomes. Indeed, alkali therapy will help to correct the metabolic acidosis of CKD, which in turn may slow CKD progression [175–178]. Also of interest is a potential interaction between K^+ and phosphate in patients with CKD. An observational study conducted in healthy individuals showed that a Western diet, which is poor in K^+ and rich in phosphate, is characterized by higher fibroblast growth factor 23 and found an inverse association with a low K^+ intake [179]. In mice, a high Na^+-low K^+ diet increases urinary calcium and phosphate excretion [180]. Studies have shown that K^+ supplementation increases the tubular phosphate reabsorption capacity in rats [181] and increases serum phosphate in healthy individuals [182], indicating a possible interaction between K^+, phosphate and fibroblast growth factor 23. Another important consideration is that it matters how dietary K^+ intake is assessed (Figure 6). Although most studies use 24-h urine excretions, weekly or monthly rhythms may influence daily excretions [183, 184]. Indeed, multiple 24-h measurements may better predict outcomes better than a single one [185]. Repeated spot urine Na^+/K^+ ratios have shown to be strongly correlated to 24-h urine Na^+/K^+ ratios in patients with CKD Stages G1–3 but not CKD Stages G4–5 [186]. With declining kidney function, more K^+ may be excreted by the gastrointestinal tract or redistributed internally. Racial differences in K^+ homoeostasis also make the relationship between K^+ excretion and CKD more difficult to interpret [187]. Compared with urinary K^+ excretion, food frequency questionnaires suffer from recall bias, inaccuracies in the natural K^+ content in food composition tables, and do not account for K^+ additives. If more conclusive evidence for a beneficial effect of increasing dietary K^+ in patients with CKD becomes available, this must be weighed against the risk of hyperkalaemia [188]. The prevalence of plasma K^+ >5.0 mmol/L is estimated to be 12–18% in patients with CKD compared with 3–4% of patients without CKD [189–191]. Based on epidemiological data, the lowest risk of all-cause mortality is estimated at plasma K^+ between 4.0 and 4.5 mmol/L and even mild hyperkalaemia has been associated with higher risk of mortality [189]. However, the ideal plasma K^+ range appears to be higher in patients with kidney disease [192, 193]. It is also not clear whether the positive effects of dietary K^+ are mediated by plasma K^+ and, if so, whether this is concentration dependent (Table 1). Put provocatively, one could argue that the beneficial effects of renin–angiotensin inhibitors are partly related to their effect on plasma K^+. To address some of these questions, we are currently conducting a randomized clinical trial in which patients with progressive CKD Stage G3b or G4 are being treated with potassium chloride, potassium citrate, or placebo for 2 years [194]. The primary endpoint of this study is eGFR decline, while secondary outcomes include 24-h BP and albuminuria. We hope that such intervention studies will contribute to stronger clinical evidence to support the recent exciting insights in the physiology and epidemiology of potassium homoeostasis.

FUNDING

CONFLICT OF INTEREST STATEMENT

Dr. Vogt reports support from Vifor Fresenius Medical Care Renal Pharma and AstraZeneca, both outside the submitted work. Dr. De Borst reports support from Vifor Fresenius Medical Care Renal Pharma, Astra Zeneca, Amgen, Sanofi Genzyme, Bayer, Kyowa Kirin, and Pharmacosmos, all outside the submitted work.

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