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Potassium: Friend or Foe?

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Abstract

The kidney plays an essential role in maintaining homeostasis of blood ion concentrations. Because the concentration gradient of potassium across the cell membrane is a key determinant of the membrane potential of cells, even small deviations in serum potassium from the normal setpoint can lead to severe muscle dysfunction, resulting in respiratory failure and cardiac arrest. Less severe hypo- and hyperkalemia are also associated with morbidity and mortality across various patient populations. In addition, deficiencies in potassium intake have been associated with hypertension and adverse cardiovascular and renal outcomes. This is likely due in part to the interrelated handling of sodium and potassium by the kidney. Here, data on the beneficial effects of potassium on blood pressure and cardiovascular and renal outcomes will be reviewed, along with the physiological basis for these effects. In some patient populations, however, potassium excess is deleterious. Risk factors for the development of hyperkalemia will be reviewed, as well as the risks and benefits of existing and emerging therapies for hyperkalemia.

Keywords

potassium homeostasis; potassium intake; hypokalemia; hyperkalemia; renal physiology; sodium polystyrene sulfonate; patiromer; ZS-9

Introduction

Both hypokalemia and hyperkalemia are associated with adverse consequences. In addition, inadequate potassium intake, even without an abnormality in serum potassium concentration, has also been associated with adverse cardiovascular and renal outcomes. The goal of this review is to discuss publications on the potential benefits and harms of potassium intake on human health. Recent advances illuminating the physiology underlying the beneficial effects of potassium will be reviewed. In some patients, excess potassium intake may result in hyperkalemia; the physiology of this electrolyte disorder will be reviewed, along with clinical risk factors. New data on existing therapies for hyperkalemia management, as well as studies on emerging therapies, will be reviewed. Understanding these principles will guide the clinician in optimizing recommendations for potassium intake in different patient populations. Additionally, clinicians will gain understanding of the risks and benefits of existing and novel therapies for hyperkalemia.

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Potassium: Friend – The Beneficial Effects of Potassium Intake

High blood pressure is the largest threat to human health worldwide [1]. The beneficial effects of potassium salts in promoting natriuresis and diuresis have long been appreciated [2, 3]. Recent studies have provided further evidence of the beneficial effects of potassium intake on blood pressure and clinical outcomes. In a meta-analysis of 21 randomized controlled trials, Aburto et al. found that higher potassium intake resulted in blood pressure lowering in the overall population studied, with more pronounced effects in patients with hypertension or consuming a high sodium diet (Table 1) [4]. Furthermore, analysis of 11 cohort studies with a total of 127,038 participants showed that potassium intake in the range of 90–120 mmol/day was associated with a decreased risk of stroke (RR 0.79, 95% confidence interval 0.68 – 0.93). On the basis of these findings, the World Health Organization recommends daily potassium intake of at least 90 mmol/day (3.5 g/day) [4], while the Institute of Medicine recommends an intake of at least 155 mmol/day (4.5 g/day) for children aged 9–13 years, and 120 mmol/day (4.7 g/day) for older children and adults [5].

The PURE (Prospective Urban Rural Epidemiology) study adds further support to this idea. A global population comprising ~102,000 adults was studied. 24 hour urinary potassium was estimated from spot urine samples. This study found that for any given level of sodium intake, higher potassium intake was associated with decreased blood pressure, and *vice versa*. As in the Aburto study, the modifying effect of potassium was greatest in those individuals consuming the highest sodium diets [6]. This is particularly relevant given high sodium consumption worldwide. In the United States, median sodium intake is 3.4 g/day, with fewer than 10 % of individuals consuming < 2.3 g/day [7], and worldwide, mean sodium intake is 4.9 g, with 3.3 % of individuals consuming < 2.3 g/day [6]. Furthermore, in PURE, high potassium intake, as inferred from urinary excretion, was associated with decreased risk of death or cardiovascular events, while low potassium intake was associated with increased risk of death and cardiovascular events [8]. Low potassium intake also increases the risk of poor renal outcomes: an analysis of patients enrolled in the ONTARGET and TRANSCEND studies found an inverse correlation between dietary potassium intake and estimated glomerular filtration rate (eGFR) decline ≥30 % or chronic dialysis, or proteinuria, with decreased odds of these adverse outcomes at higher levels of dietary potassium, and increased odds with lower potassium intake [9]. Similarly, in a prospective study of Japanese patients with type 2 diabetes who initially had eGFR ≥60 ml/min, higher urinary potassium excretion was associated with a lower risk of renal and cardiovascular events [10], although this was not the case in a cohort with established chronic kidney disease (CKD) [11]. Two prospective cohort studies in pediatric subjects also found associations between higher potassium intake and lower blood pressure [12, 13].

Despite the beneficial effects of potassium, median potassium intake in the United States is estimated to be 66 mmol (2.6 g)/day [7], while worldwide the median potassium intake is 54 mmol (2.12 g)/day [6]. The National Kidney Foundation provides information on the potassium content of various foods at https://www.kidney.org/atoz/content/potassium, and a partial list of high potassium foods is provided in Table 2.

Why is Potassium Beneficial? Recent Advances

It has long been appreciated that potassium has natriuretic and diuretic effects, and therefore the potential to lower blood pressure. In 1935, Keith and Binger reported a series of 60 patients, of whom 80 % had a diuretic response to potassium salts. They demonstrated an increase in urinary sodium excretion in several patients [2]. Subsequent studies further elucidated the relationship between urinary sodium and potassium handling. Womersley and Darragh, studying themselves, demonstrated that severely depleting the diet of potassium (2 mEq K^+/day) caused sodium and water retention in a dietary sodium-dependent fashion [14]. Similarly, in a group of ten healthy men, a low potassium diet (10 mEq K^+/day) resulted in decreased urinary sodium excretion, increased blood pressure, and salt sensitivity [15].

Potassium is freely filtered at the glomerulus and ~2/3 is reabsorbed in the proximal tubule, and an additional ~25 % in the thick ascending limb of the loop of Henle [16]. Fine-tuning of renal potassium excretion occurs in the aldosterone-sensitive distal nephron (ASDN), comprising the late distal convoluted tubule (DCT), connecting tubule (CNT) and cortical collecting duct (CCD) [17]. In the ASDN, three key factors promote potassium secretion into the tubular lumen: sodium delivery; tubular fluid flow rate; and aldosterone [16]. Sodium reabsorption through the epithelial sodium channel (ENaC) generates the negative luminal charge that drives potassium secretion (Figure 1) [16]. Changes in sodium reabsorption in segments proximal to the ASDN (proximal tubule, thick ascending limb, and DCT) influence sodium delivery to the ASDN, and therefore reabsorption through ENaC and generation of the lumen-negative charge, thereby altering potassium secretion in this segment.

Studies performed in the 1970s and 1980s established that potassium influences proximal sodium reabsorption. For example, intravenous infusions of KCl decrease sodium reabsorption in the proximal tubule [18], while bathing the thick ascending limb in a high potassium bath, as might occur during medullary potassium recycling, decreases sodium reabsorption in that segment [19]. Subsequent studies showed that administration of a high potassium diet or aldosterone to experimental animals results in increased medullary potassium recycling, with increased potassium concentration in the medullary interstitium and decreased sodium reabsorption in the thick ascending limb [20,21]. Contemporary studies have also confirmed that high dietary potassium decreases sodium reabsorption in the thick ascending limb [22].

Effects of potassium on the distal convoluted tubule sodium chloride cotransporter (NCC)

In the past several years, multiple investigators have examined the effect of varying dietary potassium intake on the thiazide-sensitive sodium chloride cotransporter, NCC, which mediates sodium chloride reabsorption in the DCT. These studies have focused on the abundance of total and apical NCC as well as NCC phosphorylation, since NCC phosphorylation increases transport of sodium chloride [23, 24]. A consistent finding has been that high dietary potassium inhibits NCC expression and phosphorylation [25–28], whereas low dietary potassium has the opposite effect, increasing NCC expression and

phosphorylation [29, 30, 28, 31]. In fact, even a single oral potassium “meal” is sufficient to rapidly suppress NCC and increase urinary sodium excretion [32].

Like potassium, a high sodium diet suppresses NCC, while a low sodium diet activates the transporter [29, 33]. How does the kidney handle the combination of high potassium/low sodium or low potassium/high sodium, in which there are opposing signals on NCC? In both cases, the potassium signal dominates. On a high potassium/low sodium diet, NCC is suppressed [26]. This is consistent with human data showing that increasing dietary potassium increases urinary sodium excretion, even in subjects on a very low sodium diet [34]. In animals on a low potassium/high sodium diet, NCC is activated [35,36], and this is also observed in human subjects, as determined by examination of phospho- and total NCC in urinary exosomes [36]. Because the typical Western diet is both high in sodium and low in potassium, the stimulation of NCC by a low potassium diet, even in the face of a high sodium intake, leads to increased NaCl reabsorption by the kidney and hypertension [36].

To summarize, high potassium inhibits sodium chloride reabsorption through NCC in the distal convoluted tubule, shunting sodium downstream to the aldosterone-sensitive distal nephron, where reabsorption through the epithelial sodium channel generates a lumen-negative charge that drives potassium secretion. Conversely, low potassium activates sodium chloride reabsorption in the distal convoluted tubule (Figure 2). In individuals consuming a low potassium/high sodium diet, as is typical in modern society, this leads to plasma volume expansion and increased blood pressure.

Modes of sodium reabsorption in the aldosterone-sensitive distal nephron

In the aldosterone-sensitive distal nephron, there are at least three “modes” of sodium reabsorption, which influence the degree of potassium secretion. Electrogenic reabsorption of sodium by the principal cell, which generates a negative charge in the tubule lumen, can either drive potassium secretion, as described above, or, alternatively, can drive paracellular chloride reabsorption [16]. Claudin-4 and claudin-8 are components of the paracellular pathway that mediate chloride flux [37]. Knockout of either claudin-4 or claudin-8 in mice results in renal salt wasting, and, in the case of claudin-8 knockout, hypokalemia [38, 39], suggesting that decreasing paracellular chloride reabsorption increases potassium secretion. A third pathway is electroneutral sodium chloride reabsorption through non-α-non-β- and β-intercalated cells [40] [41,42] [43], which are also known as “pendrin-positive intercalated cells” based on the presence of the pendrin transporter. Non-electrogenic sodium reabsorption through this pathway is expected to spare potassium secretion.

In conditions of volume depletion or low sodium intake, all modes of sodium reabsorption in the distal nephron are stimulated: electroneutral sodium chloride reabsorption by the sodium chloride cotransporter in the distal convoluted tubule [44]; electroneutral sodium chloride reabsorption by the pendrin-positive intercalated cell [43]; and sodium reabsorption by the epithelial sodium channel in the principal cell of the aldosterone-sensitive distal nephron [45, 46]. However, sodium reabsorption by more upstream segments typically reduces sodium delivery to the principal cell, thereby limiting potassium excretion in the ASDN during low sodium conditions. Like low sodium, low potassium also stimulates sodium chloride reabsorption by the DCT, as discussed above. The pendrin-positive intercalated cell

is also potassium-sensitive, with higher expression of transporters on relatively lower potassium diets [47]. In contrast, epithelial sodium channel activity in the ASDN principal cell is suppressed in conditions of low dietary potassium, even when dietary sodium is also low (Figure 3) [30], thereby sparing potassium secretion. However, in low potassium/high sodium conditions, stimulation of the electroneutral pathways in the distal convoluted tubule and through the pendrin-positive intercalated cells will lead to excess sodium retention, plasma volume expansion, and increased blood pressure.

Intrarenal paracrine regulation of the distal nephron by the proximal tubule

What homeostatic responses occur in the kidney as a result of volume depletion and hypokalemia? A recent paper illustrates an integrated response and unveils interesting paracrine regulation between the proximal tubule and distal nephron [48]. In this study, STE20/SPS1-related proline/alanine-rich kinase (SPAK) was knocked out. SPAK is a key activator of NCC, as discussed below, and the SPAK knockout mice have a Gitelman's-like phenotype, with renal salt wasting, volume contraction, and mild hypokalemia (~3.4 mEq/L) [49, 50, 48]; this phenotype is similar to chronic thiazide administration. In response to volume depletion, there is upregulation of the pendrin-positive intercalated cell: the number of these cells increases relative to α-intercalated cells, and there is upregulation of the transport machinery [48]. Ammoniagenesis is upregulated in the proximal cell, presumably in response to hypokalemia, with metabolism of glutamine to α-ketoglutarate. In the SPAK knockout mice, the proximal tubule transport machinery favors transport of the α-ketoglutarate into the lumen, with a three-fold increase in urinary α-ketoglutarate levels [48]. Prior work showed that α-ketoglutarate acts on the seven transmembrane receptor, Oxgr1, to stimulate sodium chloride reabsorption by the pendrin-positive intercalated cell, and inhibits sodium reabsorption through ENaC in the principal cell. These effects will decrease potassium secretion by favoring sodium reabsorption through the electroneutral pathway in the pendrin-positive intercalated cell, and decreasing sodium reabsorption through the electrogenic pathway in the principal cell [51]. Indeed, Oxgr1 is upregulated in the pendrin-positive intercalated cell in the SPAK knockout mice [48]. Since the pendrin-positive intercalated cell also secretes bicarbonate, metabolic alkalosis is also limited [51].

The importance of the pendrin-positive intercalated cell is also illustrated by findings from mice lacking the sodium chloride cotransporter. Mice in which both NCC and pendrin are knocked out have a more dramatic degree of renal salt wasting, volume depletion, and metabolic alkalosis than is seen when either transporter is knocked out individually [52]. Similarly, individuals with Pendred syndrome, carrying mutations in pendrin, have goiter and deafness, but typically do not have renal manifestations at baseline. However, upon challenge with a thiazide diuretic, a child with Pendred syndrome rapidly developed severe volume depletion and hypokalemic metabolic alkalosis [53].

The role of the WNK-SPAK/OSR1 signaling pathway

The first With-no-lysine (WNK) kinase was cloned in 2000 by Cobb and colleagues [54]. The following year, Lifton's group showed that WNK1 and WNK4 are mutated in a human disorder, pseudohypoaldosteronism type II (also called Gordon's syndrome or familial hyperkalemia with hypertension), characterized by hypertension and hyperkalemia [55].

Subsequent work showed that WNKs phosphorylate and activate two related downstream kinases, SPAK and oxidative-stress response (OSR1) (reviewed in [56]). SPAK and OSR1 then phosphorylate the N-termini of the related sodium-coupled chloride cotransporters, which include NCC and the sodium-potassium-2-chloride cotransporters, NKCC1 and NKCC2, resulting in transporter activation [56]. In fact, WNK-SPAK/OSR1 regulation of ion flux through NKCCs is evolutionarily ancient: this pathway regulates transepithelial potassium flux and fluid secretion in the *Drosophila* renal tubule [57, 58]. WNK1 and WNK4 also have a positive regulatory effect on the pendrin-positive intercalated cell [47] and may also positively regulate the paracellular Cl^- reabsorption pathway in the ASDN [56]. *In vivo* studies have confirmed the importance of WNK-SPAK/OSR1 signaling in stimulating sodium reabsorption through NCC in the distal convoluted tubule and NKCC2 in the thick ascending limb [56]. In addition, WNK1 and WNK3 regulate vascular contractility through their regulation of NKCC1 in the vasculature (reviewed in [59]). Thus, WNKs overall promote renal NaCl reabsorption in multiple nephron segments, as well as vasoconstriction (Figure 4), explaining the hypertensive phenotype of gain-of-function alleles of WNK1 and WNK4. The stimulation of electroneutral sodium chloride reabsorption, as well as effects on K^+ secretory channels in the ASDN [56], explains hyperkalemia in these patients.

Because WNK-SPAK/OSR1 signaling is a key regulator of NCC, recent work has focused on the effects of dietary potassium on the WNK-SPAK/OSR1 pathway. A low potassium diet increases WNK phosphorylation [36], as well as SPAK phosphorylation [36, 31, 28], which will increase NCC phosphorylation and activity.

An unsolved mystery is the mechanism by which the WNK-SPAK/OSR1 pathway senses changes in dietary potassium. One proposal is that changes in extracellular potassium alter the voltage of the distal convoluted cell, driving changes in intracellular Cl^- [36]. A crystallographic study proved that WNK is a chloride-sensitive kinase: chloride binds directly to the active site of WNK, inhibiting the autophosphorylation required for activation [60]. WNK4, the dominant NCC-regulating WNK in the DCT, is particularly Cl^--sensitive *in vitro*, and there is a correlation between plasma potassium concentration and NCC phosphorylation [61]. In cells, WNK activation occurs when intracellular Cl^- is lowered. Whether this also occurs in the DCT is not currently known, but modeling studies support the hypothesis that changes in intracellular Cl^- could explain alterations in transepithelial flux in the DCT in the presence of varying serum potassium [36].

Effects of aldosterone – recent findings

Although the importance of aldosterone in promoting renal potassium excretion has long been understood, new mechanisms for this have been demonstrated. Phosphorylation of the mineralocorticoid receptor on serine 843 occurs in the intercalated cell of the distal nephron and renders the mineralocorticoid receptor insensitive to aldosterone [47]. According to this model, aldosterone upregulates the transport machinery of the pendrin-positive intercalated cell, which would increase electroneutral NaCl reabsorption, as discussed above. In conditions of volume depletion, angiotensin II signaling, or activation of WNK1 and WNK4, Ser 843 is dephosphorylated and the mineralocorticoid receptor is responsive to aldosterone

[47]. In contrast, in high potassium conditions, Ser 843 is phosphorylated and the intercalated cell is unresponsive to aldosterone [47], decreasing electroneutral sodium chloride reabsorption as compared to the electrogenic sodium reabsorption that promotes potassium secretion.

Potassium: Foe – Deleterious Effects of Potassium Excess

Despite the benefits of potassium intake outlined above, potassium excess can be problematic in patients with impaired potassium excretion. The most dreaded complication is ventricular fibrillation [62] leading to sudden death. Therefore, the clinician must understand factors which predispose patients to developing hyperkalemia, and manage this electrolyte complication appropriately when it arises. Fortunately, novel therapies are in development that may advance treatment of hyperkalemia.

Risk factors for hyperkalemia

Potassium is the most abundant intracellular cation and its concentration in the extracellular space is low. This is due to the action of the Na^+/K^+-ATPase, which pumps three Na^+ ions out of the cell in exchange for two K^+ ions. Thus, 98 % of total body potassium (~3400 mEq) is found in intracellular stores, chiefly in muscle, with smaller amounts in red blood cells, liver, and the remaining cells of the body. Only 2 % (~65 mEq) of total body potassium is in the extracellular space [63]. 90 % of ingested potassium is excreted through the kidney, whereas 10 % is excreted in stool [16]. Thus, most cases of hyperkalemia are due either to abnormal shifts of potassium from the intracellular compartment to the extracellular compartment (eg rhabdomyolysis, tumor lysis), or to dysfunction of renal potassium excretion [64].

Because of the importance of aldosterone in maximizing renal potassium excretion, medications and conditions, including congenital disorders, that impair the renin-angiotensin-aldosterone system (RAAS) are frequent culprits in the development of hyperkalemia [65] (Table 3). Because 90 % of potassium excretion occurs through the kidney, decreased GFR is also a powerful predictor of hyperkalemia [66–71].

Recent studies have highlighted the ways in which multiple risk factors for hyperkalemia often exist in patients who develop overt hyperkalemia. Trimethoprim, which inhibits the epithelial sodium channel, is illustrative. In a randomized controlled trial of 97 outpatients treated for various infections with trimethoprim-sulfamethoxazole (TMP) vs. other antibiotics, serum potassium increased in 81 % of the TMP group [72]. This was not clinically significant in most of the patients. However, three patients with additional risk factors for hyperkalemia (older age, impaired GFR, or diabetes mellitus) developed a serum potassium concentration of >6 mEq/L [72]. A quartet of studies has examined the risk of hyperkalemia in older patients (>66 yo) prescribed an ACE (angiotensin converting enzyme) inhibitor, ARB (angiotensin receptor blocker) or the mineralocorticoid receptor antagonist spironolactone, who were subsequently prescribed TMP. Using a nested case-control design, the investigators demonstrated that TMP increased the risk of both hyperkalemia and sudden death in this population when compared to the control antibiotic, amoxicillin [73–76]. Thus, deleterious effects are seen in the presence of a combination of three risk factors for

hyperkalemia – older age; use of an ACE inhibitor, ARB or spironolactone; and use of trimethoprim. Another study found that, of patients admitted to an emergency room with hyperkalemia, 95 % of patients with a serum potassium of >7 mEq/L were taking at least one medication that interferes with potassium secretion, 75 % were taking two such drugs, and 90 % had an impaired GFR [77]. The concept of additive risks – either with dual RAAS blockade, or RAAS blockade in the context of congestive heart failure or CKD – is also consistent with findings from clinical trials [78, 79].

Aldosterone-independent potassium secretion

Two recent studies highlight that the risk of hyperkalemia from RAAS blockade is most pronounced within the first month of initiation. In the first study, 6575 hypertensive patients were studied. Spironolactone was added at a mean dose of 42 mg (in non-CKD patients) or 36 mg (in CKD patients). At 4 weeks, serum potassium increased in both CKD and non-CKD patients, but by 8 weeks, serum potassium normalized in both groups. The incidence of hyperkalemia (serum potassium >5 mEq/L) was 43 % in the non-CKD group at 4 weeks and 50 % in the CKD group, but returned to baseline levels of 3–4 % by 8 weeks [70]. A second study with a different design, a population-based case-control study in a cohort of patients with newly diagnosed congestive heart failure, also found that the odds of hyperkalemia were highest within the first month of initiation of an ACE inhibitor or spironolactone and decreased over time [68].

Several conclusions can be drawn from these studies. First, clinicians should monitor serum potassium early after initiation of RAAS blockers, with timely follow-up of abnormal results – an area that has been identified as a safety concern [80, 81]. Second, if hyperkalemia is mild, it may be possible to continue the RAAS blocker, as long as serum potassium is carefully monitored. The improvement in serum potassium that occurs over time is likely due to adaptive changes in the kidney. Although aldosterone is an important mediator of renal (and colonic) potassium excretion, abundant literature describes aldosterone-independent potassium secretion [82–87].

Indeed, a recent paper examined potassium handling in aldosterone synthase knockout mice, which lack the ability to synthesize aldosterone. These mice could tolerate a moderate dietary potassium load, but died on a very high potassium diet. The sodium chloride cotransporter was downregulated to promote distal sodium delivery, and both ENaC and ROMK were upregulated. Interestingly, angiotensin signaling appeared to play a permissive role for potassium secretion, since treatment with losartan rendered the mice unable to handle moderate dietary potassium [88]. This is consistent with clinical data showing that dual RAAS blockade raises serum potassium more than single RAAS blockade [89, 78]. The aldosterone synthase knockout study also found that colonic potassium secretion was entirely aldosterone-dependent [88], consistent with clinical data showing that hyperkalemia complicates the use of eplerenone in patients on hemodialysis [90].

Preventing hyperkalemia in high-risk patients

The prevention of hyperkalemia in high-risk patients has previously been reviewed [65]. Management includes discontinuation of NSAIDs and hyperkalemic herbal preparations; use

of diuretics; correcting metabolic acidosis; and prescribing a low potassium diet. If these measures are unsuccessful, lower doses or discontinuation of medications that cause hyperkalemia may be necessary [65].

While hyperkalemia is problematic, hypokalemia is also associated with worse outcomes in patients with CKD. For example, a potassium concentration below 4 mEq/L, even in the range of 3.5 – 3.9 mEq/L, was associated with increased mortality in a population with CKD and congestive heart failure [91]. Two other studies also found a U-shaped association between serum potassium and mortality in patients with CKD, with increased mortality, cardiovascular events, and end-stage renal disease in patients with a serum potassium below 4 mEq/L [69, 92]. Thus, even mild degrees of hypokalemia confer increased risk of mortality. Therefore, a low potassium diet should not routinely be prescribed in patients with normal serum potassium concentrations, particularly if they are on loop or thiazide diuretics that result in renal potassium wasting. However, there is a linear association between the risk of hyperkalemia and dietary potassium intake in patients with CKD, so patients should be appropriately monitored [9].

Hyperkalemia management

Management of hyperkalemia has been reviewed [93]. Acutely, an electrocardiogram should be immediately obtained to assess for cardiac toxicity, and intravenous calcium administered if electrocardiographic changes are present. The second step involves shifting potassium from the extracellular space to the intracellular space using insulin and beta agonist therapy. These increase uptake of potassium through the Na^+/K^+-ATPase into muscle. Interestingly, even in patients with “insulin resistance” in terms of glucose uptake in response to insulin, uptake of potassium is not impaired [94]. Finally, potassium must be definitively eliminated either through the kidney, the gut, or dialysis. Because most potassium excretion is through the kidney, in a patient who is not oliguric or anuric, loop diuretics can be effective in eliminating potassium by increasing distal delivery of sodium and distal flow rates. Large doses of a loop diuretic may be needed in patients with impaired GFR. For patients with hypovolemia, concomitant administration of isotonic fluids can help prevent worsening volume depletion, and in patients with a prerenal decrease in GFR due to hypovolemia, saline alone may be sufficient to improve GFR and resolve hyperkalemia.

Until recently, sodium polystyrene sulfonate (SPS) was the only approved potassium-binding resin in the United States for gastrointestinal elimination of potassium. However, the safety of this medication was called into question when reports began to emerge of cases of colonic necrosis [95], and SPS with 70 % sorbitol now carries a black box warning [96]. The estimated incidence of this complication, based on the largest available study, is 0.14 %, with a number needed to harm of 1395 [97]. Another potential adverse effect of SPS is extracellular volume expansion: a 60 g dose of SPS contains 65 mEq of sodium.

A second question that has been raised is whether SPS is effective in lowering potassium [95, 93]. A small randomized controlled study was recently published, in which 33 outpatients with CKD and baseline serum potassium of 5.0 – 5.9 mEq/L were randomized to placebo or 30 g SPS daily. At the end of 1 week, serum potassium in the SPS group was 1.04 mEq/L lower than the placebo group. However, hypocalcemia and hypomagnesemia

occurred in a substantial fraction of the SPS group (19 % and 31 % respectively) [98]. A larger retrospective study of inpatients evaluated the response to a single dose of SPS. The investigators observed a dose-dependent decrease in serum potassium, ranging from 0.82 ± 0.48 mEq/L for the 15 g dose, to a 1.40 ± 0.42 mEq/L decrease for the 60 g dose. 94 % of patients normalized serum potassium with a single dose, though the mean starting potassium concentration was <6 mEq/L in all four groups [99]. A second retrospective study also demonstrated dose-dependent decreases in serum potassium concentration after SPS administration [100].

RAAS blockers are effective for the treatment of conditions which simultaneously predispose to hyperkalemia, such as congestive heart failure and diabetic nephropathy [101–105]. Given the limitations of SPS outlined above, intense effort has been focused on developing new potassium-lowering drugs. Two agents are in advanced clinical trials. Patiromer, also known as RLY5016, is a non-absorbed polymer that binds potassium in the gastrointestinal tract. Results from the PEARL-HF [106], OPAL-HK [107] and AMETHYST-DN [108] studies are summarized in Table 4. Patiromer effectively decreases serum potassium concentrations in high-risk patients on RAAS blockers, including those with heart failure, CKD, and diabetic nephropathy. The most frequent adverse events are hypomagnesemia and gastrointestinal side effects, but the number of patients studied (648) has been relatively small and the longest follow-up to date has been one year. Furthermore, whether patiromer has beneficial effects on clinical outcomes beyond hyperkalemia is unknown. Nevertheless, patiromer was approved by the Food and Drug Administration in October 2015, albeit with a black box warning that it may bind other orally administered drugs and decrease their intestinal absorption [109]. Therefore, the warning recommends that patiromer should be administered six hours apart from other orally administered medications – a challenge for patients with multiple comorbidities on many medications. Simultaneously, the FDA also required further studies on SPS to determine whether it also binds orally administered medications [110].

Sodium zirconium cyclosilicate, also known as ZS-9, is a non-absorbed microporous compound whose pore size renders it highly selective for potassium ions as compared to calcium or magnesium ions [111]. ZS-9 has been evaluated in three clinical trials to date [112] [113] [114], which are summarized in Table 5. ZS-9 rapidly lowered serum potassium concentrations, and the effect was maintained for up to 4 weeks. Hypomagnesemia was not observed, presumably because of the high selectivity of ZS-9 for potassium, but GI side effects and edema were seen in patients on higher doses of the drug. Finally, the investigators of the prior trials analyzed 45 patients with baseline serum potassium of 6.0 mEq/L who received a 10 g dose of ZS-9. They reported that after a single 10 g dose, serum potassium decreased by 0.4 mEq/L at 1 hour, 0.6 mEq/L at 2 hours, and 0.7 mEq/L at 4 hours. The median time to a serum potassium level <6.0 mEq/L was 1.07 hours, and the median time to a serum potassium level <5.5 mEq/L was 4 hours [115]. In contrast, after an 8.4 g dose of patiromer, the first statistically significant reduction in serum potassium occurred after 7 hours, and was modest – 0.21 mEq/L. The median time to a serum potassium <5.5 mEq/L (from a starting point of 5.93 mEq/L) was 12.7 hours, occurring after a second dose of patiromer was administered at hour 10. Thus, patiromer appears to act less

rapidly than ZS-9 in lowering serum potassium acutely [116]. Like patiromer, the effects of ZS-9 on clinical outcomes beyond serum potassium concentration have not been evaluated.

Summary

Dietary potassium intake lowers blood pressure and is associated with decreased risks of cardiovascular morbidity, overall mortality and progression of renal disease. Some of the benefits from potassium are likely due to the interrelated handling of sodium and potassium in the kidney. Specifically, potassium inhibits sodium reabsorption by the kidney, while a low potassium diet enhances renal sodium reabsorption, even with a concomitant high sodium diet. Therefore, current guidelines recommend dietary potassium intake in the range of 90 to 120 mmol/day, well above usual intake in American and worldwide populations. In some patients, however, excess dietary potassium intake results in hyperkalemia. Patients at risk include older patients and those with CKD, congestive heart failure, or diabetes mellitus, especially with concomitant use of medications that inhibit the RAAS, whether as an on-target effect (eg ACE inhibitors, ARBs or mineralocorticoid receptor antagonists), or as an off-target effect (eg trimethoprim). Appropriate monitoring is required when using these beneficial medications in high-risk populations. Concerns about the toxicity of SPS for hyperkalemia management have led to the development of two new drugs: patiromer, which has recently been approved in the United States, and sodium zirconium cyclosilicate (ZS-9), for which the Food and Drug Administration has accepted a new drug application filing.

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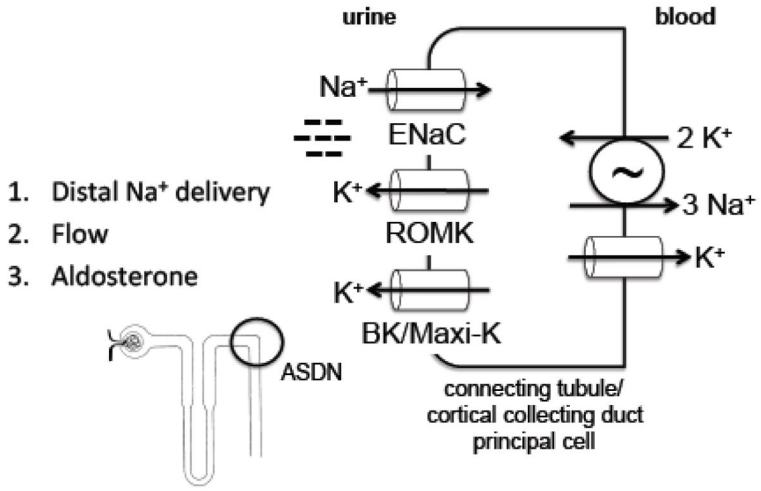

Figure 1.

Key determinants of potassium secretion in the aldosterone-sensitive distal nephron (ASDN). Sodium reabsorption through the epithelial sodium channel (ENaC) generates a lumen-negative charge that drives potassium secretion through the ROMK and BK potassium channels. Therefore, distal sodium delivery is a key determinant of potassium secretion. Tubular lumen flow stimulates ENaC and BK, and effectively lowers luminal potassium concentration, thereby increasing the driving force for potassium secretion. BK expression is low in neonates, limiting flow-stimulated potassium secretion and facilitating potassium retention at this stage of development [117]. Aldosterone upregulates ENaC and the Na+/K+-ATPase, and has additional effects, such as stimulating medullary potassium recycling, that enhance potassium secretion.

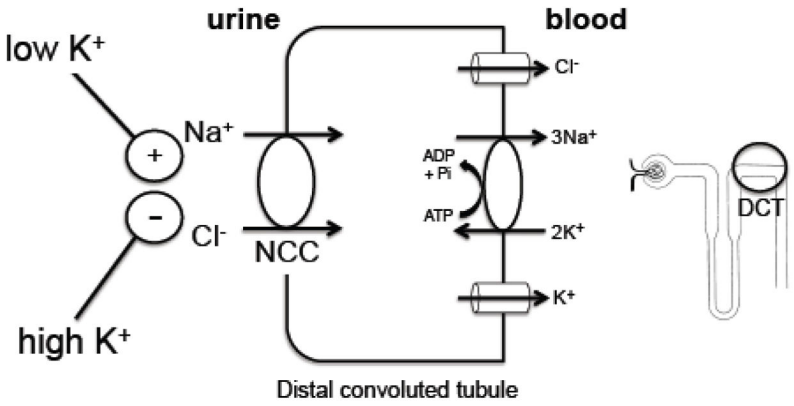

Figure 2.

Summary of dietary potassium effects on the thiazide-sensitive sodium chloride cotransporter (NCC). High dietary potassium intake inhibits NCC, increasing sodium delivery to the more distal aldosterone-sensitive distal nephron (ASDN) where potassium secretion occurs (Figure 1), while low dietary potassium stimulates the transporter. This occurs in both low and high dietary sodium conditions. Thus, in the face of a low potassium/high sodium diet, NCC is activated and NaCl reabsorption is increased, resulting in extracellular volume expansion and hypertension.

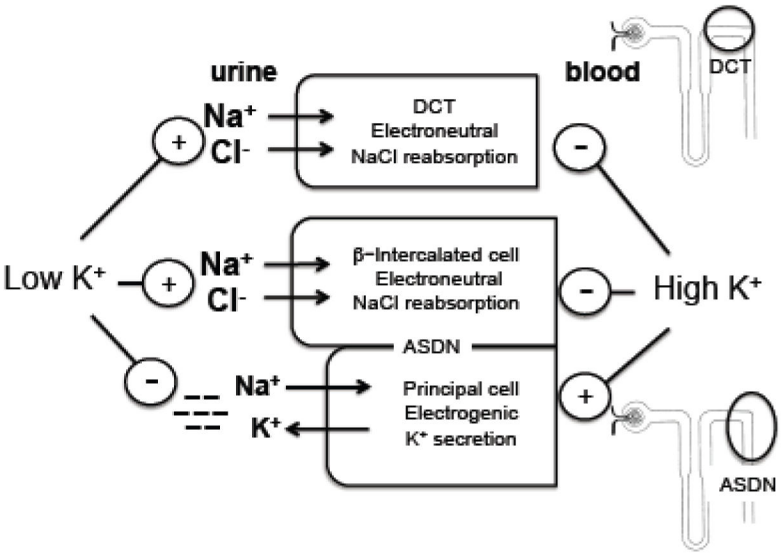

Figure 3.

Effects of potassium intake on electroneutral vs. electrogenic sodium reabsorption. Similar to a low sodium diet, low dietary potassium intake stimulates electroneutral NaCl reabsorption, decreasing the availability of sodium to ENaC in the aldosterone-sensitive distal nephron (ASDN) principal cell and thereby limiting potassium secretion. A low potassium diet also directly inhibits ENaC activity. High dietary potassium has the opposite effect.

DCT: distal convoluted tubule

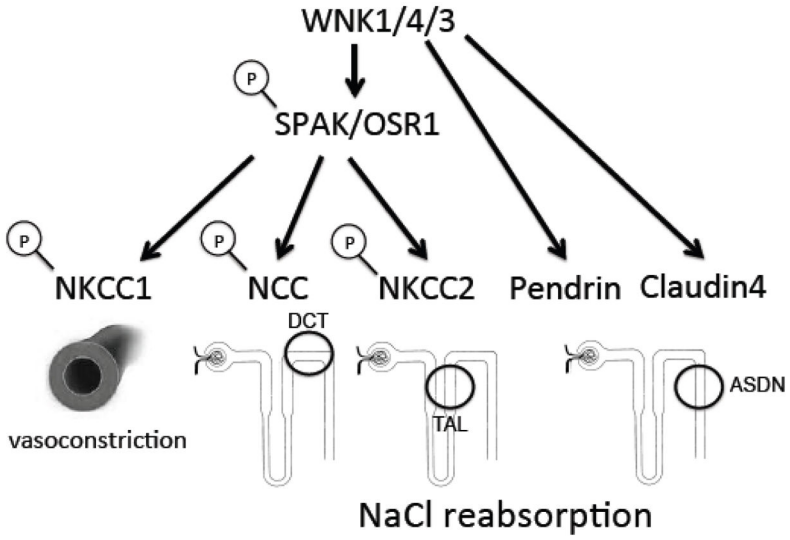

Figure 4.

WNK kinases stimulate vasoconstriction and NaCl reabsorption. WNK kinases phosphorylate and activate two related kinases, SPAK and OSR1. SPAK and OSR1 phosphorylate the N-terminus of the related sodium-coupled chloride cotransporters, NKCC1 in the vasculature, NCC in the distal convoluted tubule, and NKCC2 in the thick ascending limb of the loop of Henle. Phosphorylation results in transporter activation, leading to vasoconstriction and increased sodium chloride reabsorption in multiple nephron segments. In addition, WNKs have positive regulatory effects on pendrin in the β-intercalated cells and paracellular chloride transport in the ASDN, mediated by claudin-4, which again will increase renal sodium chloride reabsorption. The overall effect of WNK signaling is to promote vasoconstriction and NaCl reabsorption.

DCT: distal convoluted tubule, TAL: thick ascending limb, ASDN: aldosterone-sensitive distal nephron

Table 1

Effect of higher potassium intake on blood pressure

Created using data from [4]; further details in text

	SBP (mmHg)	DBP (mmHg)
Overall population	−3.49	−1.96
Hypertensive subjects	−5.32	−3.10
High Na^+ (> 4g/day) intake	−6.91	−2.87

SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 2

Partial list of high potassium foods

Created using data from https://www.kidney.org/atoz/content/potassium and https://ndb.nal.usda.gov

High Potassium Foods	mEq K^+ per 100 g
apricots	7
cantaloupe	7
mango	4
prunes	19
butternut squash	7
beets, boiled	8
carrots, raw	8
spinach, cooked	12
beans, baked	9
potatoes, baked	15
milk	5
yogurt	4
nuts (eg peanut butter)	14

Table 3

Drugs and Conditions which Increase Risk for Hyperkalemia
Diabetes mellitus
Advanced age
Beta-blockers
Nonsteroidal anti-inflammatory drugs
Angiotensin converting enzyme inhibitors
Angiotensin receptor blockers
Adrenal insufficiency, congenital adrenal hyperplasia
Aldosterone synthase deficiency or inhibitors (heparin, ketoconazole)
Loss-of-function mutations in the mineralocorticoid receptor or antagonists (spironolactone, eplerenone, drosperinone)
Loss-of-function mutations in the epithelial sodium channel or inhibitors (amiloride, triamterene, trimethoprim, pentamidine)
Decreased glomerular filtration rate

Table 4
Summary of 3 clinical trials examining patiromer safety and efficacy

Created using data from [106–108]

Study	Patients	Drug	Outcome	Adverse effect
PEARL-HF [106]	105 pts with CHF+CKD or prior discontinuation of RAAS blocker or beta blocker due to hyperkalemia	Spironolactome + patiromer or placebo, 4 weeks	Placebo: 25% K > 5.5 mEq/L Patiromer: 7% K > 5.5 mEq/L	24% of patiromer patients Mg < 1.8 mg/dL
OPAL-HK [107]	237 pts with CKD stages 3/4 on RAAS blockade	Patiromer, 8 weeks Dose adjustments required in 60% of patients, mostly on days 3 and 7	After drug withdrawal: Hyperkalemia in 90% in placebo group vs. 43% in patiromer group Able to continue RAAS blocker: 44% in placebo group vs. 94% in patiromer group	9 patients in patiromer group required Mg replacement
AMETHYST-DN [108]	306 pts with diabetic nephropathy on ACE-I/ARB + spironolactone	Patiromer, 1 year	Significant decrease in serum K^+ throughout the study period	Hypomagnesemia; constipation; 30% of patients discontinued treatment

CHF, congestive heart failure. CKD, chronic kidney disease. RAAS blocker, renin-angiotensin-aldosterone system blocker. ACE-I, angiotensin converting enzyme inhibitor. ARB, angiotensin receptor blocker.

Table 5

Summary of 3 clinical trials examining safety and efficacy of sodium zirconium cyclosilicate (ZS-9)

Created using data from [112–114]

Study	Patients	Drug	Outcome	Adverse effect
Phase 2, double-blind, placebo controlled dose-escalation study [112]	90 pts with CKD stage 3	ZS-9: 0.3 g, 3 g, or 10 g × 48 hours	K^+ lowering 2 days: 0.3 g, −0.39 mEq/L 3 g, −0.42 mEq/L 10 g, −0.92 mEq/L	GI side effects, esp at 10 g dose
Phase 3, two-stage, double-blind, placebo-controlled [113]	753 pts with hyperkalemia, K^+ 5.0–6.5 mEq/L CKD - 75% DM - 60% CHF - 40% RAAS blockers - 67%	ZS-9: placebo, 1.25 g, 2.5 g, 5 g or 10 g × 2 days. If K 3.5–4.9 mEq/L after 2 days (543 pts), received same ZS-9 dose vs. placebo × 2 weeks.	Dose-dependent lowering of serum K^+ in first 48 hours. Days 2–14, maintenance of serum K^+ in ZS-9 groups vs increase in placebo groups	Similar between placebo and ZS-9 groups
HARMONIZE [114]	258 pts with hyperkalemia, serum $K^+ \geq 5.1$ mEq/L CKD - 66% DM - 66% CHF - 36% RAAS blockers - 70%	ZS-9 10 g × 2 days (open-label), then placebo or ZS-9 5 g, 10 g or 15 g × 4 weeks	92% achieved normokalemia during the first 2 days of ZS-9 10 g. Median time to normalization, 2.2h. During 4 week maintenance phase, mean serum K^+ by dose: placebo, 5.1 mEq/L 5 g, 4.8 mEq/L 10 g, 4.5 mEq/L 15 g, 4.4 mEq/L	Hypokalemia in ~10% of patients in 10 g and 15 g groups; edema in 2.4% of placebo group, 2.2% of 5 g group, 5.9% of 10 g group and 14.3 % of 15 g groups

CKD, chronic kidney disease. GI, gastrointestinal. DM, diabetes mellitus. CHF, congestive heart failure. RAAS, renin-angiotensin-aldosterone system.