ABSTRACT

Hyperkalemia is common in patients with impaired kidney function or who take drugs that inhibit the renin-angiotensin-aldosterone axis. During the past decade, substantial advances in understanding how the body controls potassium excretion have been made, which may lead to improved standard of care for these patients. Renal potassium disposition is primarily handled by a short segment of the nephron, comprising part of the distal convoluted tubule and the connecting tubule, and regulation results from the interplay between aldosterone and plasma potassium. When dietary potassium intake and plasma potassium are low, the electroneutral sodium chloride cotransporter is activated, leading to salt retention. This effect limits sodium delivery to potassium secretory segments, limiting potassium losses. In contrast, when dietary potassium intake is high, aldosterone is stimulated. Simultaneously, potassium inhibits the sodium chloride cotransporter. Because more sodium is then delivered to potassium secretory segments, primed by aldosterone, kaliuresis results. When these processes are disrupted, hyperkalemia results. Recently, new agents capable of removing potassium from the body and treating hyperkalemia have been tested in clinical trials. This development suggests that more effective and safer approaches to the prevention and treatment of hyperkalemia may be on the horizon.

J Am Soc Nephrol 27: 981–989, 2016. doi: 10.1681/ASN.2015070751

Disorders of plasma potassium concentration can be rapidly fatal. This fact evokes concern among clinicians and often militates for treatment, even when the indication may not be strong. Although immediate treatment for severe hyperkalemia is clearly effective, such treatment typically does not reduce the total body potassium burden. Thus, definitive treatment usually requires the removal of potassium from the body, most commonly in the urine. When this cannot be achieved or is inadequate, which often occurs in patients with late-stage CKD, clinicians often turn to sodium polystyrene sulfonate (SPS). Although this binding resin has been in use for many years, its efficacy has been questioned, and its risks have clearly been shown. These issues have caused some to argue against the routine use of SPS, whereas others suggest that we are damned if we do but also, damned if we do not.

Recently, two new oral agents for the removal of potassium from the body have been studied in clinical trials. The characteristics of these agents will be discussed below, but their development has occurred in parallel with, but independent of substantial strides in understanding how total body potassium homeostasis is maintained. Although these insights hold the potential to drive more physiologic approaches to potassium disorders, this goal remains unmet. Because hyperkalemia is the most common potassium disorder in patients with CKD and because there are new approaches for treating hyperkalemia, the focus of this review will be on normal potassium homeostasis and hyperkalemia.

GASTROINTESTINAL ABSORPTION AND PLASMA CONCENTRATIONS

Individuals consuming a Western diet typically ingest approximately 50–100 mEq (2–4 g) potassium daily. Approximately 10% is excreted in the stool, and therefore, the vast majority of ingested potassium is eliminated in the urine to maintain steady state. Within the body, the bulk of potassium is inside cells, so that extracellular fluid contains only 50–80 mEq (4 mEq/L × 14 L = 56 mEq). Because dietary intake varies widely, it is not surprising that
elaborate physiologic control systems adjust renal potassium excretion to meet physiologic needs. A single meal may contain more potassium than is present in the plasma, and therefore, it might be expected that a high-K⁺ meal might raise plasma [K⁺] (brackets indicate concentration) substantially; however, plasma [K⁺] is buffered by both renal and extrarenal mechanisms. Thus, large and potentially harmful swings in plasma [K⁺] typically do not occur during the day. Because urinary K⁺ excretion increases rapidly after a meal, some have postulated that there is an undefined gut sensor, which enhances K⁺ excretion. This effect, however, is most apparent when K⁺ is ingested with food, suggesting that it may involve well-recognized metabolic factors, such as insulin. It should also be appreciated that plasma [K⁺] does increase substantially after a potassium-rich meal (Figure 1). In humans, a high-K⁺ meal increased plasma [K⁺] from 0.4 to 0.7 mEq/L, raising plasma aldosterone. Furthermore, steady-state plasma [K⁺] concentrations are strongly modulated by chronic dietary intake, because increasing K⁺ intake from 75 to 400 mEq/L for 3 weeks increased plasma [K⁺] by 0.47 mEq/L and increased plasma aldosterone concentration. The role of such changes in plasma [K⁺] in modulating renal excretion will be addressed below.

Two additional sources of variation in plasma K⁺ concentrations are circadian and interindividual. Normal plasma K⁺ concentrations are between 3.5 and 4.5 mEq/L. Although it is often stated that plasma K⁺ is tightly regulated, plasma K⁺ concentration is one of the plasma constituents with the highest circadian variation; in fact, this rhythm is one of the most persistent when diurnal variations in activity, posture, and dietary intake are eliminated. There may also be inherited interindividual differences in plasma [K⁺]; it has been recognized recently that plasma [Na⁺] has a strong heritable component, and it would be surprising if similar factors do not exist for [K⁺].

RENNAL K⁺ HANDLING

Mechanisms of renal K⁺ excretion are well established and reviewed extensively. Potassium is freely filtered, but owing to its primarily intracellular distribution, rates of filtration do not typically determine rates of excretion. In fact, >80%–90% of filtered K⁺ is reabsorbed along the proximal tubule and loop of Henle, so that only 10% of filtered K⁺ is delivered to the distal tubule and collecting duct (CD), even as dietary intake varies. This means that the vast majority of excreted K⁺ is derived from secretion along the distal nephron.

Studies during the early micropuncture era found that K⁺ secretion along the superficial distal tubule, comprising the distal convoluted tubule (DCT) and connecting tubule (CNT), accounted for nearly all K⁺ excretion. However, when in vitro micropuncture became popular, it was easier to use cortical CDs to perfuse; because these segments expressed all components of the K⁺ secretory system and responded to aldosterone, it became common to assign K⁺ secretory primacy to this nephron segment. Molecular insights and reanalysis of extant data, however, made it clear that the late DCT (the DCT2) and CNT play the dominant roles in K⁺ secretion; it seems that the CD plays an important role primarily when the organism is stressed or aldosterone levels are very high.

Like plasma [K⁺] (Figure 2), urinary K⁺ excretion exhibits substantial circadian variation. In humans, the ratio of peak-to-minimum K⁺ excretion is approximately 5:1. Although it might be thought that this relates entirely to dietary intake patterns or plasma [K⁺], this rhythm is maintained, even when diurnal variations in activity, posture, and dietary intake are perturbed, providing evidence that it is related to central clock mechanisms. This type of response has been termed predictive in contrast to reactive, in that it primes the system in anticipation of the need to excrete K⁺.

MECHANISMS OF K⁺ SECRETION

Given the central importance of the distal tubule to K⁺ homeostasis, it is not surprising that this segment of the nephron...
expresses a broad array of transport and regulatory proteins, which enables fine excretory control. A key component of the K+ secretory pathway is the Na+ channel (epithelial sodium channel [ENaC]) (Figure 3). This channel is expressed along the latter part of the DCT (the DCT2),18 the site at which substantial K+ secretion begins.19 ENaC activity depolarizes the luminal membrane of cells, thereby increasing the driving force favoring K+ movement from peritubular space to lumen. ENaC activity is strongly enhanced by aldosterone, which increases K+ secretion secondarily.

The inwardly rectifying K+ channel renal outer medullary K+ (ROMK) is expressed along the entire distal nephron from the thick ascending limb (TAL) through the CDs.20 Its role of mediating regulated K+ secretion, however, only begins at the transition from the DCT1 to the DCT2, the site at which ENaC first appears.18 In the DCT2 and more distal segments, ROMK traffics to the apical membrane in response to dietary K+ loading,20,21 confirming its important role in regulating K+ balance. Although this mechanism of K+ secretion is very important, the observation that people, or mice, that lack functional ROMK lose rather than gain K+22,23 led to the recognition of other mechanisms for K+ secretion along the distal nephron.

Maxi-K channel (BK) also plays an important role in K+ secretion. This channel differs from ROMK, however, in several ways.24 First, although expressed along the distal nephron, it is primarily localized at the apical membrane of intercalated cells. Second, unlike ROMK, it needs to be activated to be open. An important activator of BK is luminal flow, but recently, it has become clear that this channel also plays an important role in aldosterone–regulated K+ secretion. Thus, the increase in urinary K+ excretion in response to a low–salt, high–potassium diet is attenuated in mice lacking BK channels compared with wild-type mice.25 This provides evidence that K+ secretion by BK channels is affected by ENaC activity.

Another transport protein that plays a key role in K+ secretion is the thiazide–sensitive NaCl cotransporter (NCC; gene symbol SLC12A3). Its key role in K+ excretion was not fully appreciated until Gitelman syndrome, which presents with unrelenting K+ wasting, was found to be caused by mutations in SLC12A3.26 Gradually, it has become clear that the unique role of NCC is the result of its specific site of expression and its unique mechanisms of regulation.

NCC expression defines the DCT, which is interposed between the TAL and the CNT. The proximal portion of the DCT (DCT1) expresses NCC27 but not electrogenic Na+ or K+ channels at its apical membrane18,28 (although ROMK can be found in the DCT immunohistochemically,20 it does not seem to contribute to apical K+ conductance28). This means that the transepithelial voltage of the DCT is near zero.29 Thus, the proximal part of the DCT (the DCT1), which reabsorbs NaCl in an electroneutral manner, acts as an insulator, separating the TAL, with its lumen–positive transepithelial voltage, from the CNT, with its lumen–negative transepithelial voltage, driving K+ secretion. NCC activity is exquisitely sensitive to extracellular [K+], which might seem unexpected given that NCC does not transport K+ and the DCT1 secretes little K+.19 In this case, it was the molecular solution to familial hyperkalemic hypertension (also called pseudohypoaldosteronism type 2 or Gordon syndrome) that began to unravel this puzzle.30–32 Familial hyperkalemic hypertension is a rare monogenic hypertensive disease accompanied by hyperkalemia. The phenotype appears as if the Na+-retaining effects of aldosterone are intact, but the kaliuretic effects are not. The molecular solution showed that mutations in WNK kinases or their regulatory proteins cause the disease, in large part by activating NCC33,34; this indicated that NCC plays a key role in determining whether aldosterone (and ENaC) enhances K+ secretion.

Although the reports describing WNK effects have often seemed contradictory and confusing, recently, a consensus view has begun to emerge, which has proven clarifying.35,36 WNK kinases phosphorylate intermediary kinases, SPAK and OxsRI, which can phosphorylate and activate NCC and other cation chloride cotransporters. WNKs also form hetero- or homodimers through their carboxy-terminal tails.37,38 All four WNKs can activate NCC in vitro, but the nature of their effects in vivo depends on both their sites of expression and modifying properties. It has recently become clear that WNKS are inhibited by chloride.39 In fact, WNK4, which is most highly expressed in the DCT, is uniquely chloride sensitive.40
A recent model suggests that plasma [K+] signals to NCC by altering intracellular [Cl–] in the DCT.41,42 It turns out that DCT cells are exceptionally sensitive to changes in plasma [K+]. Thus, when plasma [K+] is high, cell [Cl–] is high, WNKs are turned off, and NCC is suppressed (Figure 3). This occurs, although plasma aldosterone concentrations, which are thought to stimulate NCC in other conditions,43 rise during hyperkalemia (see above).44–48 When plasma [K+] is low, the opposite occurs.41,44 These effects can occur very rapidly, such as when K+ is administered by gavage45 or intravenously47; the rapid decrease in abundance of the phosphorylated form of NCC suggests that high plasma [K+] leads to rapid NCC dephosphorylation. These effects, however, do not occur in isolation. Instead, the same high–[K+] signal also enhances aldosterone secretion by adrenal zona glomerulosa cells.49 Aldosterone activates ENaC in the CNT (and CD). Thus, switching from a low- to a high-K+ diet switches NCC off and ENaC on. Because less of the delivered Na+ load will be reabsorbed by NCC, more will be delivered into the K+ secretory segments, segments primed to secrete K+ through the effects of aldosterone. Although this model is attractive, however, several important details remain to be confirmed.

All states of high-aldosterone activity, however, are not characterized by K+ wasting. This seems to reflect, in part, NCC activation by angiotensin II. Low-salt diet increases and high-salt diet decreases NCC activity.50 Captopril infusion induces retrieval of NCC from the DCT apical membrane,51 and angiotensin II induces activation of NCC in the absence of adrenal glands,52 an effect that is prevented by losartan.53,54 The effect of angiotensin II on NCC is a WNK4- and SPAK-dependent process.55 In vitro and in vivo experiments revealed that SPAK and NCC are not activated by angiotensin II in the absence of WNK4.53,54 Additionally, angiotensin II through protein kinase C induces phosphorylation of KLHL3, preventing the ubiquitylation and thus, destruction of WNK4.55

Angiotensin II may also play a role in transport along the CD. Angiotensin II has been reported to stimulate the activity and translocation of ENaC to the apical membrane through an aldosterone-independent mechanism,56,57 although it has also been reported that deletion of AT1a receptors along the CD does not reduce ENaC abundance.58 Because angiotensin II may also reduce ROMK activity,59,60 it might be predicted to stimulate sodium reabsorption in the CD but not K+ secretion, which would be inappropriate in states of volume depletion. In other situations, however, angiotensin II has been proposed to increase K+ excretion. Todkar et al.61 suggested that angiotensin enhanced potassium secretion in mice lacking aldosterone.

In addition, during salt depletion, angiotensin II may induce dephosphorylation of the mineralocorticoid receptor in the intercalated cells of the CD, allowing aldosterone to interact with its receptor and thus, increasing Cl– reabsorption by pendrin combined with H+-ATPase.62 The H+-ATPase activation should depolarize the transepithelial voltage and attenuate K+ secretion. In addition, extracellular fluid volume depletion may activate an electroneutral sodium chloride uptake pathway that is dependent on sodium–dependent chloride bicarbonate exchange in parallel with pendrin.63 Thus, the combination of increased activity of NCC, ENaC, and pendrin together with inhibition of ROMK by angiotensin II maximize salt reabsorption while inhibiting K+ secretion in the distal nephron.

**EFFECTS OF K+ INTAKE ON BP**

A natriuretic effect of K+ in humans was reported nearly 80 years ago,64 and BP-lowering effects of K+ supplementation and raising effects of K+ deficit were later reported.65–68 However, dietary K+ has typically received less attention than salt, perhaps because the traditional body fluid model for BP control assigns primacy to Na+.69 It is now clear from large population studies that dietary K+ intake associates inversely with BP.69–71 Although mechanisms involving the sympathetic nervous system, the vasculature, and circulating factors, such as endogenous ouabain, may all play roles in the beneficial effects of high-K+ intake, natriuresis is rarely cited as essential.72,73

Because high-K+ intake will switch off NCC, this would be expected to...
contribute to the ensuing natriuresis. We recently reported that the ability of low-K⁺ intake to increase arterial pressure is absent in mice lacking NCC.⁴¹ These experiments, conducted during concomitant high-salt intake, suggest that NCC and the DCT play essential roles in the beneficial effects of dietary K⁺ loading.

**HYPERKALEMIA**

Two chronic disease processes are responsible for a substantial proportion of hyperkalemic episodes: heart failure and CKD. In these settings, the use of renin-angiotensin-aldosterone system (RAAS) blocking drugs typically contributes.⁷⁴ In individuals with heart failure, low renal blood flow and GFR, poor distal Na⁺ delivery, and the use of drugs that block the RAAS impair K⁺ excretion.⁷⁵,⁷⁶ In the setting of CKD, these same factors are often involved, although low GFR itself is often more obvious.⁷⁷ Because drugs that block the RAAS are among the most effective for treating individuals with both heart failure and CKD and because these drugs contribute substantially to the increased risk for hyperkalemia, RAAS inhibitors often play a role.⁷⁸ This has generated interest within the cardiovascular community in finding ways to achieve the benefits of RAAS blockade, while reducing its potassium retaining effects.

CKD is another major risk factor for hyperkalemia. In a large study of individuals who had been hospitalized, the adjusted rate of potassium ≥5.5 was 7.67 per 100 patient months for individuals with CKD (eGFR<60 ml/min per 1.73 m²) versus 2.3 for those without.⁷⁹ In a much smaller study⁸⁰ of a low-clearance clinic, the prevalence of K≥5.5 mM was 31.5%, with GFR being the most important factor associated with hyperkalemia.

**TREATMENT OF HYPERKALEMIA**

As noted above, there are many strategies for treating hyperkalemia both acutely and chronically; most of these have been in routine use for many years.⁸¹ When treatment is urgent, treatment is first aimed at cell membrane stabilization with intravenous calcium. Although this approach is effective, its duration of action is <60 minutes, making additional treatments necessary. The typical secondary treatments are insulin and glucose or in rare situations, inhaled β-agonists. These shift potassium into cells, with durations of action of ≤6 hours. Definitive treatment must, however, remove K⁺ from the body. When kidney function permits, loop diuretics combined with intravenous saline (depending on the effective arterial blood volume) are the first line of treatment. Dialysis is typically used for individuals with inadequate kidney function. However, frequently, physicians turn to oral K⁺ binding resins to achieve K⁺ removal; today, this is almost always SPS (Kayexalate and others). Calcium polystyrene sulfonate is much less commonly used. Sterns et al.¹ estimated that the typical community hospital dispenses 2000 doses of SPS per year. SPS was approved by the Food and Drug Administration (FDA) in 1958, well before today’s rigorous standards for efficacy were established, and some have questioned whether it is, in fact, efficacious.¹ This issue of efficacy, however, has been complicated by increasing concerns about safety.

SPS can be constipating, and therefore, it has commonly been administered with sorbitol to induce osmotic diarrhea. Case reports, however, noted that SPS, often combined with sorbitol, could induce intestinal necrosis in patients, which was frequently fatal. In 2009, the FDA placed a Black Box warning on the use of SPS with sorbitol on the basis of this information. More recently, however, a comprehensive review found a substantial number of patients with intestinal necrosis that occurred with SPS without sorbitol.² Harel et al.² urge caution in the use of SPS, but others have argued that the common clinical use and the infrequency of complications suggest that SPS is usually well tolerated and effective.³,⁸²

The concerns about safety and efficacy have prompted interest in developing new agents to treat hyperkalemia. Two have recently been evaluated in prospective trials and seem to be effective. The first is sodium zirconium cyclosilicate (ZS-9), an oral, inorganic, nonsystemic cation exchanger, which was designed to preferentially entrap monovalent cations in the gastrointestinal tract. ZS-9 has a microporous framework structure and exhibits >25-fold selectivity for potassium over Ca²⁺ or Mg²⁺. Unlike SPS, ZS-9 does not swell within the gastrointestinal tract.

ZS-9 has been evaluated in several recent trials (Figure 4). In one,⁸⁴ 753 individuals with moderate hyperkalemia (5–6.5 mEq/L) were randomized to placebo or one of several doses of ZS-9. There was a significant dose–dependent reduction of plasma [K⁺] at 48 hours that ranged from 0.46 to 0.73 mEq/L at doses from 2.5 to 10 g per dose. During a maintenance phase of the study, ZS-9

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**Figure 4.** ZS-9 and SPS lower plasma K⁺ concentration. ZS-9 versus placebo indicates results of ZS-9 extracted from Figure 1.⁸⁴ ZS-9 (10 g) is drawn from data in Kosiborod et al.⁸⁶. Effects of SPS and SPS + sorbitol are from Gruy-Kapral et al.⁹². Note that the data are not necessarily comparable but shown for illustration. Modified from Kosiborod et al.⁸⁶ and Gruy-Kapral et al.⁹², with permission.
was also more effective than placebo at preventing plasma [K+] from rising.

In another study involving the same group,85 253 individuals with plasma [K+] ≥5.1 mmol/L were given 10 g ZS-9 three times daily for 48 hours in an initial open-label phase. At 24 hours, the decrease in [K+] was 0.7 mmol/L, and at 48 hours, it was 1.1 mmol/L, both values significantly different from zero. Those who achieved normokalemia at the end of this phase were then randomized to placebo or different doses of ZS-9 for days 8–28. There was a significant dose–dependent relation between dose and plasma [K+] at the end of this period, with a difference of 0.7 mmol/L at the highest dose (15 g three times per day). Dose-dependent edema was the major observed side effect, occurring in 14% of patients taking a high dose of ZS-9 versus only 2% treated with placebo.85

In a follow-up letter to the editor, the same group culled from the initial results 45 patients whose plasma [K+] was ≥6.0 mmol/L. For individuals who received 10 g, the plasma [K+] had declined by 0.4 mmol/L at 1 hour, 0.6 mmol/L at 2 hours, and 0.7 mmol/L at 4 hours. By 4 hours, 80% of individuals had plasma [K+] values ≤6.0.86

Patiromer is a second new agent recently investigated. Patiromer consists of the polymer anion (the active moiety patiromer) and a calcium-sorbitol counterion complex. It is a nonabsorbed cation exchange polymer that binds K+ in the lumen of the gastrointestinal tract and like ZS-9, does not swell appreciably in liquids. During the development of patiromer, calcium fluoride was identified as a degradation product, and efforts were undertaken to develop a more stable compound, resulting in a calcium-sorbitol counterion complex. Because serum fluoride did not rise substantially when patients were treated for ≤1 year, investigators have concluded that fluoride toxicity is not a concern. Unlike in SPS, sorbitol is not added as a laxative but at very small amounts to stabilize the complex.

In a trial,87 243 patients with stage 3 or 4 CKD who were receiving RAAS blockade and whose plasma [K+] was between 5.1 and 6.5 were enrolled. In an initial phase, all patients received patiromer at a dose that depended on enrollment plasma [K+]. At the end of 4 weeks, those who achieved target [K+] values were randomized to continue patiromer or receive placebo. During the subsequent 4 weeks, the mean [K+] declined by 1 mmol/L. As in the trial with ZS-9, plasma [K+] increased more when patients were randomized to placebo than to active treatment. Several side effects have been noted with patiromer, most notably hypomagnesemia (in 8.6% of patients in one study88); this led to the administration of magnesium supplements to some subjects. Because hypomagnesemia may be associated with cardiac arrhythmias,89 this may be a concern in patients with disordered plasma [K+]. A variety of gastrointestinal side effects were also noted.

As noted by editorialists,90,91 these studies show efficacy of the new agents in lowering plasma [K+] when monitored over time. In maintenance studies, they were clearly superior to placebo in attenuating a rise. Unfortunately, in neither study was the active drug compared with SPS, and therefore, we are left without comparative effectiveness information. Furthermore, although the drugs were generally well tolerated, the incidence and effect of the noted side effects will need further study. Furthermore, because the incidence of intestinal necrosis with SPS is low,2 a comparison of safety profiles will require monitoring of many more patients receiving the agents. Thus, the role of these agents in either intermediate-term treatment of hyperkalemia or maintenance therapy awaits further trials. These agents are expected to be evaluated by the FDA during the next year, a process that will involve careful consideration of their efficacy and toxicity.

CONCLUSIONS

The intake of K+ is increasingly appreciated as an important determinant of human health, and higher K+ intake is associated with lower BP and mortality in the population as a whole. Although many factors may contribute, it seems clear that important effects of K+ involve kidney salt transport. Potassium acts directly on DCT cells, where it inhibits NCC activity. Because K+ also stimulates aldosterone secretion, this means that high-K+ diets elicit a natriuresis by turning off NCC but turning on ENaC. Because ENaC cannot fully compensate for the Na+ rejected by the DCT, natriuresis ensues. Although high-K+ intake is healthful for most, individuals with CKD and heart failure, especially when treated with RAAS inhibitors, are at risk for hyperkalemia, a potentially deadly complication. Here, physicians have long relied on SPS to treat hyperkalemia that is unresponsive to simpler approaches. Two new nonabsorbable agents have recently shown efficacy in treating hyperkalemia. It is hoped that their role in standard of care will be defined by studies comparing them directly with more traditional approaches.

ACKNOWLEDGMENTS

Work in the authors’ laboratories has been supported by National Institutes of Health Grants 2R01DK051496-15A1 and 5T32DK067864-10 to D.H.E. and Department of Veterans Affairs Grant 11BX002228-01A1 to D.H.E. A.S.T. was supported by American Heart Association Pre-doctoral Fellowship Award 3PRE14090030 and National Institute of Diabetes and Digestive and Kidney Diseases Grant 5T32DK067864-08.

DISCLOSURES

None.

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