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Potassium: Friend or Foe?

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This is to acknowledge that Aylin Rodan, MD, PhD has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Rodan will be discussing off-label uses in her presentation.

Biographical Information

Dr. Rodan is a physician-scientist with an interest in electrolyte disorders, hypertension and the underlying epithelial ion transport mechanisms in the kidney driving these clinical syndromes. She obtained a B.S. in Biology with Distinction from Yale University, graduating *magna cum laude,* and began her scientific career there studying the role of endoplasmic reticulum chaperones in protein folding. Dr. Rodan then enrolled in the Medical Scientist Training Program at the University of California San Francisco, where she studied the mechanisms of behavioral changes in *Drosophila melanogaster* in response to alcohol, examining the effects of protein kinase A signaling in different parts of the brain, as well as the role of insulin signaling. After receiving her MD and PhD degrees, she continued at UCSF for internal medicine residency, where she was recognized with the Keith Johnson Award for outstanding second year resident. Dr. Rodan then moved to Dallas for nephrology fellowship training at UT Southwestern, where she deepened her understanding of renal physiology and clinical nephrology, and served as chief fellow. She has been on the faculty of the nephrology division since 2011, and is currently an Assistant Professor. Her laboratory studies ion channels and transporters, and the signaling cascades that regulate them, in the *Drosophila* renal tubule. The goal is to understand these transporters, channels and their regulation in greater mechanistic detail, identify new regulatory factors by performing forward genetic screens, and translate these insights into improved understanding of human kidney disorders. She has received support for her research from a career development award from the NIH, a pilot and feasibility award from the UT Southwestern O'Brien Center, and the Carl Gottschalk Young Investigator Award from the American Society of Nephrology, as well as an award for outstanding genetic research from the Browne Genetic Research Fund. Dr. Rodan also sees patients with general medicine and kidney disorders at Parkland and Zale Lipshy hospitals, and teaches medical, undergraduate and graduate students and housetaff, with an emphasis on renal physiology.

Purpose and Overview:

The purpose of this Grand Rounds presentation is to review 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 risk factors for this electrolyte disorder will be reviewed, as well as management approaches. Understanding of these principles will guide the clinician in optimizing recommendations for potassium intake in different patient populations.

Objectives:

1. Review the beneficial effects of potassium intake on human health
2. Review recent advances in understanding the physiology underlying the beneficial effects of potassium
3. Identify risk factors for hyperkalemia
4. Understand risks and benefits of current treatments for hyperkalemia

Background and Introduction

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, deviations in serum potassium of < 3 mEq/L 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 (1-8). In addition, deficiencies in potassium intake have been associated with hypertension and adverse cardiovascular outcomes. This is likely due to the interrelated handling of sodium and potassium by the kidney. Here, recent data on the beneficial effects of potassium on blood pressure and cardiovascular 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.

Potassium: Friend – The Beneficial Effects of Potassium Intake

High blood pressure is the largest threat to human health worldwide (9). The beneficial effects of potassium salts in promoting natriuresis and diuresis have long been appreciated (10,11). 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) (12). 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 to 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) (12), while the Institute of Medicine recommends an intake of at least 120 mmol/day (4.7 g/day) (13).

Table 1. Effect of higher potassium intake on blood pressure.
Adapted from ref 12.

	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

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 (14). Analysis of participants in the Dallas Heart Study also showed increasing systolic and diastolic blood pressure with increases in the ratio of urinary sodium to potassium in both African-American and non-African-American subjects, with a stronger effect in men than in women (15). 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 (16), and worldwide, mean sodium intake is 4.9 g, with 3.3% of individuals consuming < 2.3 g/day (14). Furthermore, in PURE, high potassium intake, as inferred from urinary excretion, was associated with decreased risk of death or cardiovascular events, primarily driven by decreased risk of death, while low potassium intake was associated with increased risk of death and cardiovascular events (17). However, median potassium intake in the United States is estimated to be 66 mmol (2.6 g)/day (16), while worldwide the median

potassium intake is 54 mmol (2.12 g)/day (14). 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.

Table 2. Partial list of high potassium foods. Adapted from https://www.kidney.org/atoz/content/potassium.

High Potassium Foods
apricots
cantaloupe
mango
prunes
butternut squash
beets
carrots
spinach
beans
okra
potatoes
milk
yogurt
nuts (eg peanut butter)

Why is Potassium Beneficial? Recent Advances

It has long been appreciated that potassium has natriuretic and diuretic effects. 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 (10). 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 (18). 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 (19).

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 (20). 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) (21). In this segment, three key factors promote potassium secretion into the tubular lumen: sodium delivery; tubular fluid flow rate; and aldosterone (20). Sodium reabsorption through the epithelial sodium channel (ENaC) generates the negative luminal charge that drives potassium secretion (Figure 1) (20). Changes in sodium reabsorption in segments proximal to the ASDN (proximal tubule, thick ascending limb, and distal convoluted tubule) influence sodium delivery to the ASDN, thereby altering potassium secretion in this segment.

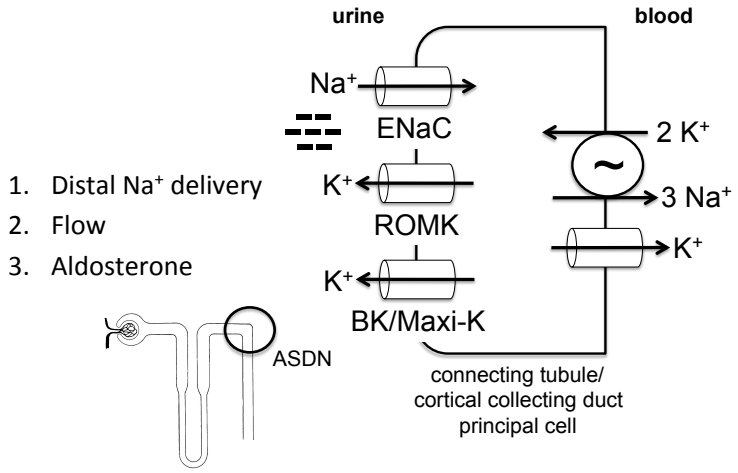

Figure 1. Key determinants or K^+ secretion in the aldosterone-sensitive distal nephron (ASDN). Sodium reabsorption through the epithelial sodium channel (ENaC) generates a lumen-negative charge that drives potassium secretion through the ROMK and BK potassium channels. Therefore, distal sodium delivery is a key determinant of potassium secretion. Tubular lumen flow stimulates EnaC and BK, and effectively lowers luminal potassium concentration. Aldosterone upregulates ENaC and the Na^+/K^+-ATPase, and has additional effects, such as stimulating medullary potassium recycling, that enhance potassium secretion.

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 (22), while bathing the thick ascending limb in a high potassium bath, as might occur during medullary potassium recycling, decreases sodium reabsorption in that

segment (23). 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 (24,25). More recent studies have also confirmed that high dietary potassium decreases sodium reabsorption in the thick ascending limb (26).

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

In recent years, a number of investigators have examined the effect of varying dietary potassium intake in animals on the thiazide-sensitive sodium chloride cotransporter, NCC, which mediates sodium chloride reabsorption in the distal convoluted tubule. 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 (27,28). In some cases clearance studies and blood pressure measurements have been performed. A relative weakness of these studies is that none has directly examined sodium chloride flux in the DCT. Nevertheless, a consistent finding has been that high dietary potassium has a thiazide-like effect, inhibiting NCC expression and phosphorylation (29-32), whereas low dietary potassium has the opposite effect, increasing NCC expression and phosphorylation (32-35). In fact, even a single oral potassium "meal" is sufficient to rapidly suppress NCC and increase urinary sodium excretion (36).

The effect of potassium on NCC is opposite to that of sodium chloride: a high salt diet suppresses NCC, while a low salt diet activates the transporter (33,37). How does the kidney handle the combination of high potassium/low sodium or low potassium/high potassium, in which there are opposing signals on NCC? In both cases, the potassium signal appears to dominate. On a high potassium, low sodium diet, NCC is suppressed (30). This is consistent with human data showing that increasing dietary potassium increases urinary sodium excretion, even in subjects on a low sodium diet consisting of 50 mEq (1.1 g) Na^+/day (38). In animals on a low potassium, high sodium diet, NCC is activated (39,40), and this is also observed in human subjects, as determined by examination of phospho- and total NCC in urinary exosomes (40). 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 (40).

To summarize, high potassium inhibits sodium chloride reabsorption 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).

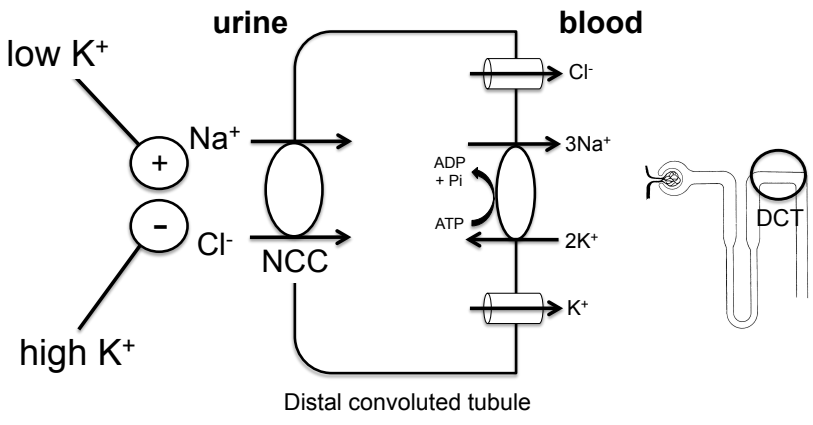

Figure 2. Summary of dietary potassium effects on the thiazide-sensitive sodium chloride cotransporter (NCC). High dietary potassium intake inhibits NCC, increasing sodium delivery to the more distal ASDN where potassium secretion occurs (Figure 1), while low dietary potassium stimulates the transporter. 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.

Modes of sodium reabsorption in the aldosterone-sensitive distal nephron

In the aldosterone-sensitive distal nephron, there are 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 (20). Claudin-4 and claudin-8 are components of the paracellular pathway that mediate chloride flux (41). Knockout of either claudin-4 or claudin-8 in mice results in renal salt wasting, and, in the case of claudin-8 knockout, hypokalemia (42,43). Whether the paracellular pathway is regulated by dietary potassium has not been examined. A third pathway is electroneutral sodium chloride reabsorption through non-α-non-β- and β-intercalated cells (44), which are also known as "pendrin-positive intercalated cells" based on the presence of the pendrin transporter. Recent work has elucidated the transporters involved in this mechanism, which is energized by the basolateral vacuolar H^+-ATPase (45,46). The chloride/bicarbonate exchanger, pendrin, and the sodium-dependent chloride-bicarbonate exchanger (NDCBE, also called SLC4A8) mediate parallel sodium chloride reabsorption on the apical membrane, while the sodium/bicarbonate cotransporter (NBC, also called SLC4A9) and an unknown chloride channel mediate exit across the basolateral membrane (47).

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 (48); electroneutral sodium chloride reabsorption by the pendrin-positive intercalated cell (47); and sodium reabsorption by the epithelial sodium channel in the principal cell of the aldosterone-sensitive distal nephron (49,50). However, sodium reabsorption by more upstream segments typically reduces delivery to the principal cell, thereby limiting potassium excretion. Like low sodium, low potassium also stimulates sodium chloride reabsorption by the distal convoluted tubule, as discussed above. The pendrin-positive intercalated cell is also potassium-sensitive, with higher expression of transporters on relatively lower potassium diets (51). 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) (34).

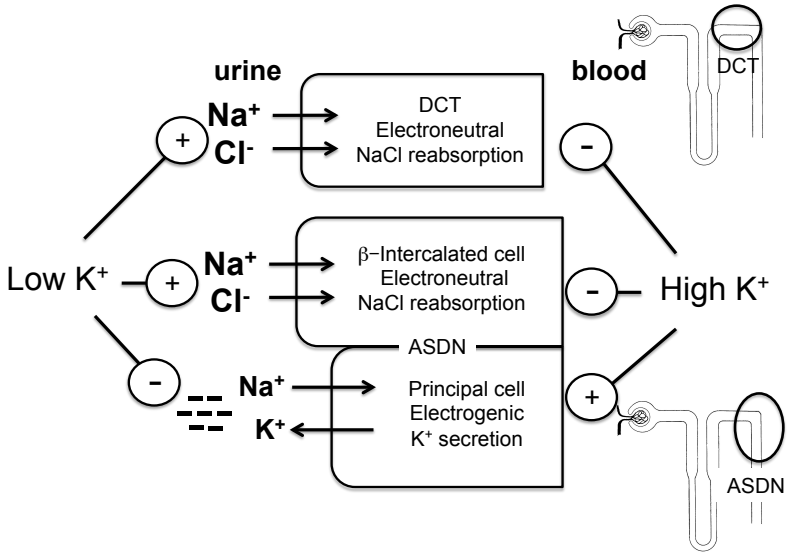

Figure 3. Effects of potassium intake on electroneutral vs. electrogenic Na^+ reabsorption. Similar to a low sodium diet, low dietary potassium intake stimulates electroneutral NaCl reabsorption, decreasing the availability of sodium to ENaC in the ASDN principal cell and thereby limiting K^+ secretion. A low potassium diet also directly inhibits ENaC activity. High dietary potassium has the opposite effect.

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 (52). 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) (52-54); 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, probably through the activation of Notch signaling, and there is upregulation of the transport machinery in the pendrin-positive intercalated cell (52). Ammoniagenesis is upregulated in the proximal cell, presumably in response to hypokalemia. During ammoniagenesis, glutamine is metabolized to α-ketoglutarate. In the SPAK knockout mice, there is a change in the proximal tubule transport machinery that favors transport of the α-ketoglutarate into the lumen, and there is a three-fold increase in urinary α-ketoglutarate levels (52). Prior work showed that α-ketoglutarate stimulates sodium chloride reabsorption by the pendrin-positive intercalated cell, an effect requiring the α-ketoglutarate seven transmembrane receptor, Oxgr1. α-ketoglutarate also appears to inhibit sodium reabsorption through ENaC in the principal cell (55). Indeed, Oxgr1 is upregulated in the pendrin-positive intercalated cell in the SPAK knockout mice (52). Upregulation of electroneutral sodium chloride reabsorption through the pendrin-positive intercalated cell will decrease sodium availability to ENaC, helping to limit potassium losses. Since the pendrin-positive intercalated cell also secretes bicarbonate, metabolic alkalosis is also limited (55).

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 (56). Similarly, individuals with Pendred syndrome, carrying mutations in pendrin, 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 (57). A second patient with Pendred syndrome similarly developed severe hypokalemic metabolic alkalosis during two separate acute illnesses, one in which she had been vomiting and a second with severe infection (58).

The role of the WNK-SPAK/OSR1 signaling pathway

The first With-no-lysine (WNK) kinase was cloned at UT Southwestern in 2000 by Melanie Cobb and colleagues (59). The following year, Rick Lifton's group showed that WNK1 and WNK4 were mutated in a human disorder, pseudohypoaldosteronism type II (also called Gordon's syndrome or familial hyperkalemia with hypertension), characterized by hypertension and hyperkalemia (60). Subsequent work showed that WNKs phosphorylate and activate two related downstream kinases, SPAK and oxidative-stress response (OSR1) (61-63). 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 (28,61,63-69). 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 (70,71). WNK1 and WNK4 also have a positive regulatory effect on the pendrin-positive intercalated cell (51) and may also positively regulate the paracellular Cl^- reabsorption pathway in the ASDN (72,73). *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 (26,53,54,74-79). In addition, WNK1 and WNK3 regulate vascular contractility through their regulation of NKCC1 in the vasculature (53,80,81). Thus, WNKs overall promote renal NaCl reabsorption and 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 the

inhibitory effects of WNK1 and WNK4 on the ASDN K^+ secretory channel ROMK (renal outer medullary K^+ channel, Kir1.1) (82-86), explains hyperkalemia in these patients.

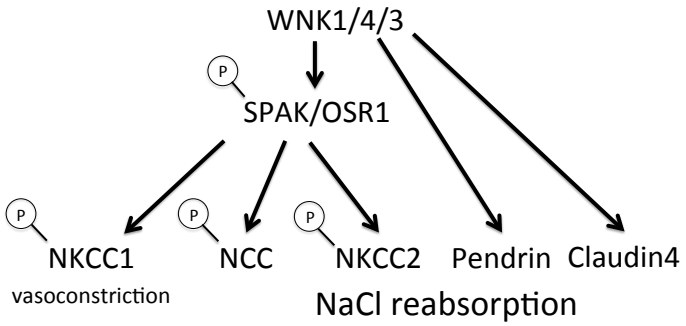

Figure 4. WNK kinases stimulate vasoconstriction and NaCl reabsorption. WNK kinases phosphorylate and activate two related kinases, SPAK and OSR1. SPAK and OSR1 phosphorylate the N-terminus of the related sodium-coupled chloride cotransporters, NKCC1 in the vasculature, NCC in the distal convoluted tubule, and NKCC2 in the thick ascending limb of the loop of Henle. In addition, WNKs have positive regulatory effects on pendrin in the β-intercalated cells and paracellular transport in the ASN, mediated by claudin-4. The overall effect of WNK signaling is to promote vasoconstriction and NaCl reabsorption.

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. One study found that, although total amounts of phospho-SPAK (the active form of the kinase) are increased in cortical homogenates in response to a high-potassium diet, the subcellular distribution of phospho-SPAK was shifted (30). A low potassium diet increases WNK phosphorylation (40), as well as SPAK phosphorylation (32,35,40). This likely explains at least part of the increase in NCC phosphorylation. However, at least part of the upregulation in NCC phosphorylation appears to be independent of SPAK and OSR1 (32,35,40), suggesting the existence of an additional "potassium-sensitive" kinase.

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^- (40). Work performed at UT Southwestern recently proved that WNK is a chloride-sensitive kinase: chloride binds directly to the active site of WNK, inhibiting its autophosphorylation and activation (87). In cells, WNK activation occurs when intracellular Cl^- is lowered. Whether this also occurs in the distal convoluted tubule, a transporting epithelium, is not known. Additionally, the effects of a low potassium diet on NCC phosphorylation are also seen in the absence of a change in serum potassium (40). Ongoing studies in my laboratory are investigating whether intracellular Cl^- regulates transepithelial ion transport.

Effects of angiotensin II and aldosterone

Another incompletely understood area is the integration of angiotensin and aldosterone signaling in the response to dietary sodium and potassium. A simple model is that aldosterone stimulates potassium secretion when angiotensin II levels are low, and promotes sodium reabsorption over potassium secretion when angiotensin II levels are high. However, two examples illustrate limitations of this model. First, both aldosterone and angiotensin II independently stimulate NCC phosphorylation when dietary sodium is low (88,89). However, as discussed above, in the face of a low sodium, high potassium diet – in which aldosterone is stimulated both by the low sodium AND the high potassium, and renin and angiotensin levels are similar to low sodium alone – NCC phosphorylation is suppressed (30). Thus, opposite effects on NCC phosphorylation are observed when angiotensin II and aldosterone levels are high, depending on dietary potassium intake. Indeed, experiments have shown that dietary potassium intake suppresses NCC phosphorylation independent of aldosterone or its downstream mediator Sgk1 (serum and glucocorticoid regulated kinase 1) (33,36). Second, aldosterone synthase knockout mice, which cannot make aldosterone, but which have elevated angiotensin II levels, are able to upregulate ENaC and handle moderate amounts of dietary

potassium, but are unable to do so when treated with the angiotensin receptor blocker, losartan (90). There is some evidence that angiotensin II can directly stimulate sodium reabsorption through ENaC in isolated perfused cortical collecting ducts (91). Thus, at least in some situations, angiotensin II signaling appears important for maintaining potassium homeostasis in the face of dietary intake.

Additional work illustrates that aldosterone can have different effects depending on dietary potassium intake. 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 (51). According to this model, aldosterone upregulates the transport machinery of the pendrin-positive intercalated cell, which would increase 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 (51). In contrast, in high potassium conditions, Ser 843 is phosphorylated and the intercalated cell is unresponsive to aldosterone (51). An unanswered question is how intercalated cells, which lack 11-β-hydroxysteroid dehydrogenase, protect themselves from activation of the mineralocorticoid receptor by cortisol.

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 (92) leading to sudden death. Indeed, hyperkalemia has been associated with increased risk of both ventricular arrhythmias and death (4,6,8). 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 (93). 90% of ingested potassium is excreted through the kidney, whereas 10% is excreted in stool (20). 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 (94).

Because of the importance of aldosterone in maximizing renal potassium excretion, medications and conditions that impair the renin-angiotensin-aldosterone system (RAAS) are frequent culprits in the development of hyperkalemia (95). These include diabetes mellitus, advanced age, beta blockers and nonsteroidal anti-inflammatory drugs (NSAIDs), which decrease renin secretion; direct renin inhibitors; angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs); impaired aldosterone synthesis due to adrenal insufficiency or aldosterone synthase inhibitors (heparin, ketoconazole); mineralocorticoid receptor antagonists (spironolactone, eplerenone); and blockers of the epithelial sodium channel (amiloride, triamterene, trimethoprim and pentamidine) (95). Because 90% of potassium excretion occurs through the kidney, decreased glomerular filtration rate (GFR) is also a powerful predictor of hyperkalemia (2,4,8,96-98).

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 (99). In this relatively healthy population (mean age 46, creatinine 0.9 mg/dL, 17% diabetic), this was not clinically significant in most of the patients. However, three patients developed a serum potassium concentration of > 6 mEq/L; the mean age of these three patients was 63, two had a creatinine of > 1.1 mg/dL, and one was diabetic (99). A quartet of studies has examined the risk of hyperkalemia in older patients (>66 yo) prescribed an ACE inhibitor, ARB 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 (100-103). 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 recent 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 (104). In a third study, ACE inhibitors and trimethoprim were the most common medications associated with hyperkalemia in hospitalized patients, 70% of whom had underlying CKD (105). The concept of additive risks – either with dual RAAS blockade, or RAAS blockade in the context of congestive heart failure or chronic kidney disease – is also consistent with findings from clinical trials (106,107).

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. 40% were diabetic, 12% had stage 3 chronic kidney disease (CKD), and 25% were on RAAS blockade. 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 (97). 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: in the 1st month, the odds ratio for hyperkalemia was 10.68 with spironolactone [95% confidence interval (CI), 6.61-17.26] and 5.47 with ACE inhibitor (95% CI, 3.66-8.19), whereas after 12 months, the odds ratio for spironolactone was 2.17 (95% CI, 1.76-2.66) and for ACE inhibitor was 1.39 (95% CI, 1.13-1.72) (96).

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 (108,109). 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 (110-115).

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 (90). This is consistent with clinical data showing that dual RAAS blockade raises serum potassium more than single RAAS blockade (106,116). The aldosterone synthase knockout study also found that colonic potassium secretion was entirely aldosterone-dependent (90), consistent with recent clinical data showing that hyperkalemia complicates the use of eplerenone in patients on hemodialysis (117).

Preventing hyperkalemia in high-risk patients

The prevention of hyperkalemia in high-risk patients has previously been reviewed (95). 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 (95).

While hyperkalemia is problematic, hypokalemia is also associated with worse outcomes in patients with chronic kidney disease. 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 (3). A second study also found a U-shaped association between serum potassium and mortality in patients with CKD, with increased mortality and end-stage renal disease in patients with a serum potassium below 4 mEq/L (2). Furthermore, an analysis of patients enrolled in the ONTARGET and TRANSCEND studies found an inverse correlation between dietary potassium intake and 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 (118). Thus, as with the general population, dietary potassium restriction is associated with increased morbidity, while 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. 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 (118).

Hyperkalemia management

Management of hyperkalemia has been recently reviewed (119). 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 (120). 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 very 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.

Currently, sodium polystyrene sulfonate (SPS) is 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 (121), and SPS with 70% sorbitol now carries a black box warning (122). A more recent study linked prescriptions of SPS to pathologic diagnoses of colonic necrosis. Of 1860 outpatient prescriptions, there were no cases of colonic necrosis. Of 5144 inpatient prescriptions, 3 cases of colonic necrosis occurred, for an incidence of 0.14% and a number needed to harm of 1395 (123). The three patients who developed this complication were > 65 years old, in the intensive care unit, and had an estimated GFR of < 30 ml/min (123). 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 (119,121). One of the largest studies to examine this question evaluated 122 inpatients in a single-center Veterans Administration hospital. The mean age was 69 yo, 79% of the patients had hypertension, 34% had diabetes mellitus, 38% had CKD, 69% had acute kidney injury, 26% congestive heart failure, and 49% were prescribed a medication known to cause hyperkalemia. The investigators evaluated the response to a single dose of SPS. They 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 (124). A study of 154 hyperkalemic episodes in hospitalized patients, 95% of which were treated with SPS, also demonstrated dose-dependent decreases in serum potassium concentration after SPS administration (105).

RAAS blockers are effective for the treatment of conditions which simultaneously predispose to hyperkalemia, such as congestive heart failure and diabetic nephropathy (125-129). 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 nonabsorbed polymer that binds potassium in the gastrointestinal tract. Three recent studies have examined the safety and efficacy of this agent. PEARL-HF examined 105 patients with heart failure with an indication for spironolactone who either had CKD and were receiving ACE-I, ARB or beta blocker therapy, or who had a documented history of discontinuation of a RAAS blocker or beta blocker due to hyperkalemia. Patients were randomized to receive spironolactone either with or without patiromer and were monitored for 4 weeks. Potassium increased in the spironolactone + placebo group, with 25% of patients experiencing K > 5.5 mEq/L during the study, but decreased in the spironolactone + patiromer group, with 7% of patients experiencing K > 5.5 mEq/L. However, there was a 47% incidence of serum K < 4 mEq/L. Hypomagnesemia also was more common in the patiromer group, with 24% of patients developing serum Mg^{2+} < 1.8 mg/dL, as were gastrointestinal disorders (130). OPAL-HF examined patients with chronic kidney disease, evenly split between stages 3 and 4 CKD, on RAAS blockade; 57% of the subjects were diabetic, 42% had heart failure, 17% were on dual RAAS blockade and 54% were on diuretics. In the single-blind treatment phase, 76% of the 237 patients on patiromer maintained a potassium concentration in the target range of 3.8 to 5 mEq/L during 4 weeks of study. Dose-adjustments of patiromer were required in 60% of patients, mostly on days 3 and 7. The 107 patients who achieved a serum potassium concentration in the target range by 4 weeks were then randomized to a placebo-controlled, single-blind randomized withdrawal phase. By the end of 8 weeks, 43% of patients in the patiromer arm developed hyperkalemia at some point, as compared to 90% in the placebo group. 94% of patients in the patiromer arm were able to continue RAAS blockers, as compared to only 44% in the placebo group. The main adverse events were constipation and hypomagnesemia, which required magnesium replacement in 9 patients (131). AMETHYST-DN examined 306 patients with diabetic nephropathy on dual RAAS blockade with an ACE-I or ARB and spironolactone. Similar potassium-lowering efficacy was seen as compared to OPAL-HF, this time with more prolonged drug treatment to one year. The most common adverse events were constipation and hypomagnesemia, and hypokalemia (K < 3.5 mEq/L) was seen in 5.6%

of patients. 30% of patients discontinued treatment (132). Patiromer releases calcium in exchange for potassium. No clinically relevant changes in calcium or phosphate levels were observed in AMETHYST-DN (132). However, current guidelines suggest limiting calcium intake in patients with CKD due to risk for vascular calcification (133), and whether calcium release from patiromer will be problematic over time is not known. In summary, patiromer effectively decreases serum potassium concentrations in high-risk patients on RAAS blockers, including those with heart failure, chronic kidney disease, 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.

Sodium zirconium cyclosilicate, also known as ZS-9, is a non-absorbed microporous compound whose pore size renders it highly selective for potassium ion as compared to calcium or magnesium ions (134). ZS-9 has been evaluated in three clinical trials to date. The first trial was a randomized, double-blind placebo-controlled dose-escalation study that examined the effect of ZS-9 at 3 doses over 2 days in 90 patients with stage 3 chronic kidney disease and serum potassium between 5.0 and 6.0 mEq/L; mean baseline potassium was 5.0-5.2 mEq/L. ZS-9 dose-dependently lowered serum potasium (135). A phase 3 trial used a two-stage, double-blind strategy to evaluate ZS-9 in 753 patients. This study enrolled adults with a serum potassium of 5.0 to 6.5 mEq/L. Patients were randomized to receive placebo or one of 4 doses of ZS-9 for 48 hours. Those who achieved a serum potassium of 3.5 to 4.9 mEq/L (543 patients) were then randomized to receive either the same ZS-9 dose as in the initial stage, or placebo, and were followed for an additional 2 weeks. 75% of patients had CKD, 67% were on RAAS blockers, 60% had diabetes, and 40% had heart failure. ZS-9 dose-dependently lowered serum potassium during the first 48 hours. In patients randomized to placebo in the second stage, serum potassium increased, whereas patients in the ZS-9 arm maintained a stable serum potassium concentration. Rates of adverse events were similar between the ZS-9 and placebo groups (136). The HARMONIZE trial evaluated 258 patients. 66% had CKD, 36% heart failure, 66% diabetes mellitus, and 70% were on a RAAS blocker. All patients were treated with 10 g open-label ZS-9 for 2 days. 92% achieved normokalemia, with a median time to normalization of 2.2 hours. These patients were then randomized to placebo or one of three doses of ZS-9, and were followed for an additional 4 weeks. There was a dose-dependent effect of ZS-9 on the mean serum potassium. Between 80% (lowest dose) and 94% (highest dose) of patients on ZS-9 maintained serum K < 5.1 mEq/L, as compared to 46% of the placebo group. ~10% of patients became hypokalemic. More patients in the highest-dose group developed edema (14%), but this group also contained a higher proportion of patients with CKD and heart failure (137). 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 (138). 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 and overall mortality. 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 chronic kidney disease, congestive heart failure, or diabetes mellitus, especially with concomitant use of medications that inhibit the renin-angiotensin-aldosterone system, whether as an on-target effect (eg ACE inhibitors, angiotensin receptor blockers 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. Management of hyperkalemia has not changed in recent years, but concerns about the toxicity of sodium polystyrene sulfonate have led to the development of two new drugs, patiromer and sodium zirconium cyclosilicate, that may be approved for use in the near future.

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