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VIEWPOINT

Directing two-way traffic in the kidney: A tale of two ions

Lawrence G. Palmer[1]

The kidneys regulate levels of Na^+ and K^+ in the body by varying urinary excretion of the electrolytes. Since transport of each of the two ions can affect the other, controlling both at the same time is a complex task. The kidneys meet this challenge in two ways. Some tubular segments change the coupling between Na^+ and K^+ transport. In addition, transport of Na^+ can shift between segments where it is coupled to K^+ reabsorption and segments where it is coupled to K^+ secretion. This permits the kidney to maintain electrolyte balance with large variations in dietary intake.

Introduction

The kidneys keep track of the electrolytes in the body, matching the rates of excretion in the urine with those of ingestion in the diet. There is now a broad consensus that control of Na^+ and K^+ excretion involves the concerted effort of multiple nephron segments; more proximal portions of the renal tubule reabsorb both ions while distal parts reabsorb Na^+ and secrete K^+ into the urine. This allows simultaneous adjustment of Na^+ and K^+ excretion rates to match rates of uptake from the diet. Furthermore, the coupling of K^+ movement (either in the reabsorptive or secretory direction) to Na^+ transport can be modulated within individual nephron segments. In this Perspective, I will review recent results and current thinking about the cooperation of different parts of the nephron to maintain balance of both Na^+ and K^+. I will also discuss some of the signaling pathways that may be involved.

Na^+ balance

Transport along the nephron

Human kidneys filter about 25 moles of Na^+ each day, almost all of which needs to be reabsorbed to maintain balance. All parts of the renal tubule reabsorb Na^+ (Fig. 1). The major transporters are the Na-H exchanger (NHE3) in the proximal tubule (PT), the Na-K-2Cl cotransporter (NKCC2) in the ascending limb of Henle's loop (TALH), the Na-Cl cotransporter (NCC) in the distal convoluted tubule (DCT), and the epithelial Na channel (ENaC) in the connecting tubule (CNT) and collecting duct (CD; Table 1). Na^+ entering epithelial cells from the urine through these pathways is pumped out into the interstitium by the basolateral Na-pump (Na-K-ATPase).

Two additional routes of reabsorption are less well documented. The inner medullary collecting duct expresses ENaC, but some studies indicate an amiloride-insensitive component of reabsorption that is poorly characterized but can be quite substantial in magnitude (reviewed by Weinstein [1998]). In addition, an electroneutral Na^+ reabsorptive pathway based on Na^+-dependent Cl^-/HCO_3^- exchanger SLC4A8 has been observed in the cortical CD (Leviel et al., 2010). Given the low concentration of HCO_3^- in the tubular fluid of the CD under most conditions, the adequacy of the driving force for Na^+ uptake through this transporter is uncertain under most conditions. These systems will not be discussed further here.

The kidneys can adjust rates of Na^+ excretion to match an enormous range of dietary salt intake. Mean rates of excretion in modern populations range from >200 mmoles/day in parts of Japan, China, and Korea to 0.2 mmoles/day for the Yanamamo people of the Amazon basin (Intersalt Cooperative Research Group, 1988). For reference, the American Heart Association recommends a Na^+ intake (approximately equal to excretion) of <100 meq/day (https://www.heart.org/en/health-topics/high-blood-pressure/changes-you-can-make-to-manage-high-blood-pressure/shaking-the-salt-habit-to-lower-high-blood-pressure).

Regulation of Na^+ excretion

The adaptation to different rates of Na^+ intake can be conveniently studied in rats and mice. For example, switching animals from normal chow to a Na^+-depleted diet produces a dramatic upregulation of ENaC in the collecting duct (Pácha et al., 1993). However, it seems likely that many if not all Na^+-reabsorbing segments participate in the process of Na^+ conservation. Experiments with segment-specific diuretics suggested that the overall response involves enhanced Na^+ reabsorption in proximal segments (PT and TALH) and reduced delivery of Na^+ to the distal nephron, in addition to the activation of distal transport

[1]Department of Physiology and Biophysics, Weill-Cornell Medical College, New York, NY.

Correspondence to Lawrence G. Palmer: lgpalm@med.cornell.edu.

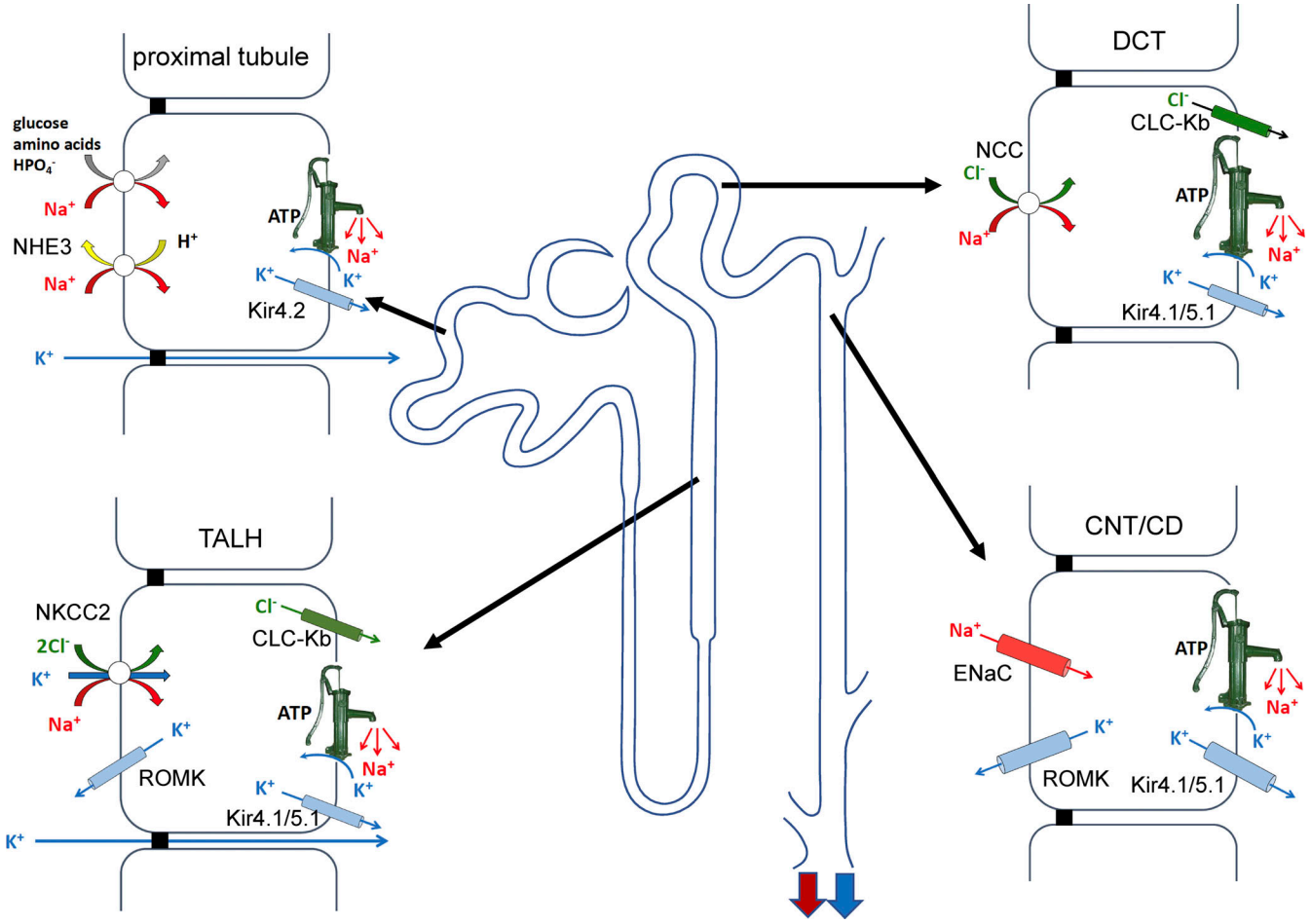

Figure 1. **Major epithelial transport systems for Na^+ and K^+ and their position along the nephron.** Segments of the renal tubule illustrated are the PT, TALH, DCT, and the CNT/CCD.

machinery (Frindt et al., 2018). Another study came to very similar conclusions based on measurements of renal Na^+ transporter proteins in mice; the overall as well as the surface expression of NHE3, NKCC2, and NCC were inversely related to the amount of Na^+ in the diet (Udwan et al., 2017). Thus, Na^+ reabsorption likely increases in all segments in response to Na^+ restriction (Fig. 2).

K^+ balance

Transport along the nephron

Handling of K^+ by the kidneys also involves multiple nephron segments (Malnic et al., 2007; Welling, 2013; McDonough and Youn, 2017; Fig. 1). The PT reabsorbs much of filtered K^+ (about 800 mmoles/day) through a paracellular pathway. Fluid reabsorption concentrates luminal K^+, providing a diffusion gradient which, together with the high permeability of tight junctions, permits paracellular transport of the ion. In the TALH, urine K^+ is taken up into the cell by NKCC2, with some recycling through K^+ channels in the luminal membrane. Some of the recycled K^+ is also reabsorbed through the paracellular pathway, driven by a lumen-positive transepithelial voltage (Mandon et al., 1993). The rest is returned to the blood through basolateral K^+ channels (Kir4.1/5.1) and KCl cotransporters (KCC4) contributing to net K^+ reabsorption (Weinstein and Krahn, 2010).

These processes will normally leave less K^+ in the urine than needs to be excreted for K^+ balance. This problem is corrected by the secretion of additional K^+ back to the urine by the distal segments CNT and CCD. This process entails uptake into the cell through the Na/K pump and electrodiffusion into the urine through K^+ channels in the luminal membrane. Both steps are coupled to the reabsorption of Na^+, enzymatically at the pump and electrically at the apical membrane. Renal outer medullary K (ROMK) channels can account for most of K^+ secretion under basal conditions and dietary K^+ challenge (Yang et al., 2021). However, Ca^{2+}-activated BK channels can contribute to K^+ secretion, especially under conditions of high urine flow rates (Woda et al., 2001) or when ROMK channels are genetically deleted (Bailey et al., 2006).

Regulation of K^+ excretion

The kidneys are also able to match urinary excretion to a wide range of dietary K^+ intake. Transport of Na^+ and K^+ is interdependent, and the ability to simultaneously match both Na^+ and K^+ intakes depends on qualitative and quantitative differences in the coupling of the two fluxes along the nephron. In proximal

Table 1. **Molecular identification of renal transport proteins implicated in Na^+ and K^+ homeostasis**

Segment	Transporter	Gene	Pole	Function	Ref.
PT	NHE3	Slc9a3	Apical	Na^+ reabsorption	Bobulescu and Moe (2009)
	Kir4.2/5.1	Kcnj15/16	Basolateral	K^+ recycling	Lin et al. (2022)
	TASK-2	Kcnk5	Basolateral	K^+ recycling	Warth et al. (2004)
TALH	NKCC2	Slc12a1	Apical	K^+, Cl^- reabsorption	Bazua-Valenti et al. (2016)
	ROMK	Kcnj1	Apical	K^+ secretion	Welling and Ho (2009)
	Kir4.1/5.1	Kcnj10/16	Basolateral	K^+ reabsorption	Wang and Lin (2022)
	KCC4	Slc12a7	Basolateral	K^+, Cl^- reabsorption	Bazua-Valenti et al. (2016)
	CLCKb	Clcnkb	Basolateral	Cl^- reabsorption	Teulon et al. (2018)
DCT	NCC	Slc12a3	Apical	Na^+, Cl^- reabsorption	Hoorn et al. (2020)
	Kir4.1/5.1	Kcnj10/16	Basolateral	K^+ recycling	Wang and Lin (2022)
	CLCKb	Clcnkb	Basolateral	Cl^- reabsorption	Teulon et al. (2018)
CD/PC	ENaC	Scnn1	Apical	Na^+ reabsorption	Garty and Palmer (1997)
	ROMK	Kcnj1	Apical	K^+ secretion	Welling and Ho (2009)
	Kir4.1/5.1	Kcnj10/16	Basolateral	K^+ recycling	Wang and Lin (2022)
CD/IC	pendrin	Slc26a4	Apical	Cl^- reabsorption	Wall et al. (2020)
	AE1	Slc4a1	Basolateral	Cl^- recycling	Wall et al. (2020)
	CLCKb	Clcnkb	Basolateral	Cl^- reabsorption	Wall et al. (2020)
	BK	Kcnma1	Apical	K^+ secretion	Carrisoza-Gaytan et al. (2016)

CD/PC, principal cells of collecting duct; CD/IC, intercalated cells of collecting duct.

segments (PCT, TALH), K^+ reabsorption is coupled to Na^+ reabsorption. However, in the CNT/CD, K^+ secretion is coupled to Na^+ reabsorption (Fig. 3). This complexity helps the kidney regulate the two ions at the same time, essentially by allowing it to simultaneously solve two equations:

$$[Na^+ \text{ excretion}] = [\text{filtered } Na^+ \text{ load}] - [\text{proximal } Na^+ \text{ reabsorption}] - [\text{distal } Na^+ \text{ reabsorption}]. \quad (1)$$

$$[K^+ \text{ excretion}] = [\text{filtered } K^+ \text{ load}] - Q_{prox}[\text{proximal } Na^+ \text{ reabsorption}] + Q_{dist}[\text{distal } Na^+ \text{ reabsorption}]. \quad (2)$$

Q_{prox} and Q_{dist} are coupling constants relating the net fluxes of Na^+ and K^+, respectively. The filtered loads are considered to be constant, while Na^+ reabsorption rates and the coupling constants are variable. This simple formulation suggests two ways in which K^+ excretion can be modulated at constant rates of Na^+ excretion. Either the coupling constants can be changed, or the proportion of Na^+ reabsorbed in proximal versus distal segments can be adjusted.

Regulation of Na/K coupling

The coupling of Na^+ and K^+ reabsorption in the proximal tubule is presumably roughly constant. Changes in coupling could, in principle, be accomplished by modulating the ion selectivity of the paracellular pathway to cations (Günzel and Yu, 2013), but there is no evidence that this occurs. Coupling could also be affected by changes in the transepithelial voltage, although it is only a few millivolts, which will alter paracellular K^+ flux. Electrogenic Na^+ reabsorption, for example through the Na-glucose cotransporter, will make the tubular lumen more negative, impeding K^+ reabsorption. However, no linkage between proximal tubule voltage and K^+ homeostasis has been established.

In the TALH, coupling of Na^+ and K^+ transport varies. Micropuncture measurements showed that an acute K^+ load decreased the reabsorption of K^+ more than that of Na^+ in this segment (Sufit and Jamison, 1983). More dramatically, when mice are fed a diet with high K^+ and low Na^+ contents, the TALH switches from Na^+-coupled reabsorption to Na^+-coupled K^+ secretion (Wang et al., 2017). How this occurs has not been demonstrated, but it could be achieved by decreasing the ratio of apical to basolateral K^+ conductances. The apical ROMK conductance in the TALH is not strongly influenced by diet (Lu et al., 2004). However, if basolateral K^+ conductance were reduced, K^+ entering the cell through the Na/K pump would tend to flow out of the cell across the luminal membrane. There are no direct measurements of basolateral K^+ conductance in the TALH under these conditions. However, in DCT, which is the segment immediately downstream, a high-K^+ diet reduces the abundance of putative Kir4.1/5.1 channels in basolateral membrane (Wang et al., 2018).

Coupling can also change in the CNT/CCD. Here, apical K^+-channel activities increase with high and decrease with low dietary K^+ intake (Wang et al., 1990; Palmer et al., 1994; Wei et al., 2001; Frindt et al., 2009; Yang et al., 2021). Currents through ROMK (Kir1.1) channels can change as much as

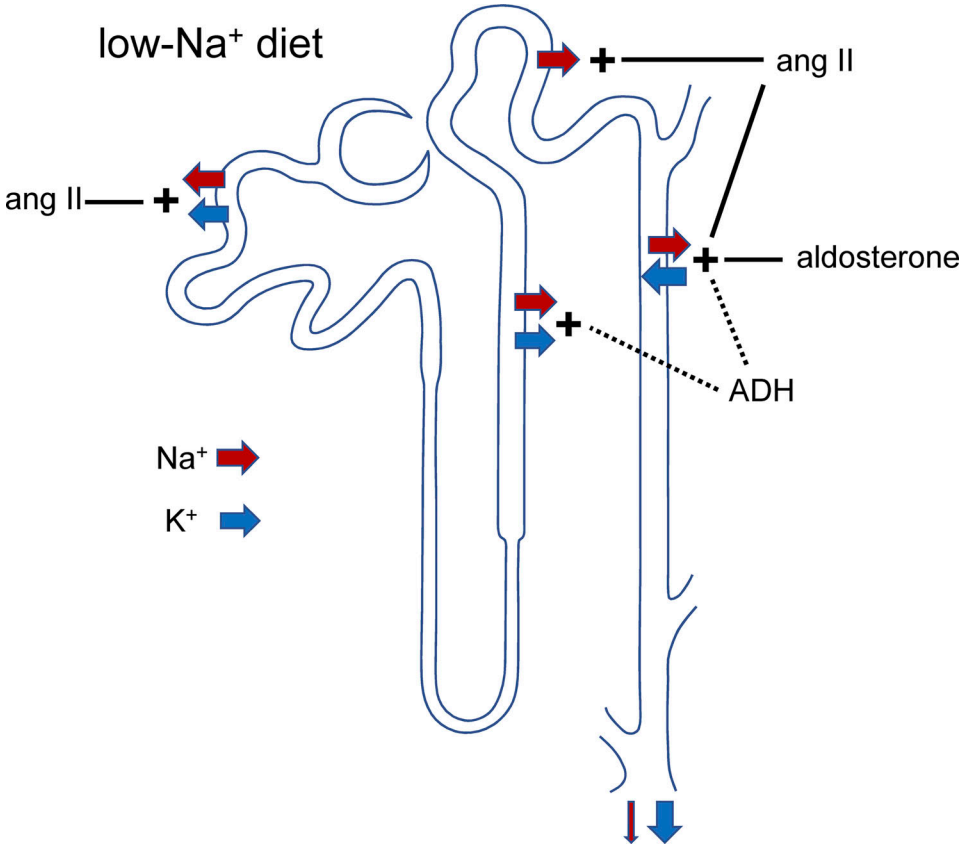

Figure 2. **Changes in Na^+ and K^+ transport by the kidney when dietary Na^+ intake is low.** + symbols indicate increased transepithelial movement of ions. Solid lines represent well-established signaling systems for regulating transport under these conditions. Dashed lines represent pathways that regulate transport but have not been shown to be involved in the response to reduced Na^+ intake. The net result is that urinary Na^+ excretion is reduced while K^+ excretion remains constant.

sevenfold as dietary K^+ varies from low to high levels. Increasing apical K^+ permeability will increase the fraction of reabsorbed Na^+ that is balanced by K^+ secretion rather than by Cl^- reabsorption.

As in the TALH, inhibiting basolateral K^+ channels in the CNT/CCD might be expected to enhance the coupling of K^+ secretion to Na^+ reabsorption; more K^+ entering the cell through the pump would exit across the luminal membrane into the urine. However, basolateral K^+ conductance increases, rather than decreases, when dietary K^+ intake is high (Gray et al., 2005; Tomilin et al., 2018). In rabbit CCD, high rates of Na^+ transport obtained with chronic adrenal steroid administration can produce basolateral membrane potentials sufficiently large to drive K^+ uptake into the cell from the interstitial fluid (Sansom et al., 1989). Under these conditions, an increase in basolateral K^+ conductance could enhance K^+ secretion through electrodiffusion across both basolateral and apical membranes (Gray et al., 2005).

Regulating Cl^- reabsorption can also alter transepithelial Na/K coupling in the CD. Pendrin is a Cl^-/HCO_3^- exchanger expressed on the apical membrane of B-type intercalated cells in the CCD, where it facilitates HCO_3^- secretion into the urine (Wall et al., 2020). When both H^+-secreting and HCO_3^--secreting cells are simultaneously active, pendrin can also participate in electrogenic transepithelial Cl^- reabsorption that can couple to ENaC-dependent Na^+ reabsorption (Pech et al., 2007; Fig. 4). In principle, this system could facilitate NaCl reabsorption while minimizing K^+ secretion when both Na^+ and K^+ need to be conserved.

Switching sites of Na^+ reabsorption

Eqs. 1 and 2 can also be satisfied simultaneously by changing the relative amounts of Na^+ reabsorbed in proximal versus distal segments (Fig. 3). For example, shifting Na^+ transport from proximal to distal parts of the nephron can increase K^+ excretion at constant overall rates of Na^+ excretion.

Decreased Na^+ reabsorption in response to a K^+ challenge has been extensively documented in the DCT. This segment transports little K^+ itself, at least in the early parts of the segment where Na^+ reabsorption is primarily through NCC (Weinstein, 2005). However, decreasing Na^+ transport through NCC will balance increased Na^+ uptake in exchange for K^+ in the CNT and CD.

Evidence that this occurs comes largely from measurements of the phosphorylation state of the NCC cotransporter. Phosphorylation by SPAK kinase is essential for activating the transporter (Subramanya and Ellison, 2014). An acute load of K^+ through the diet or IV infusion dephosphorylates NCC (Sorensen

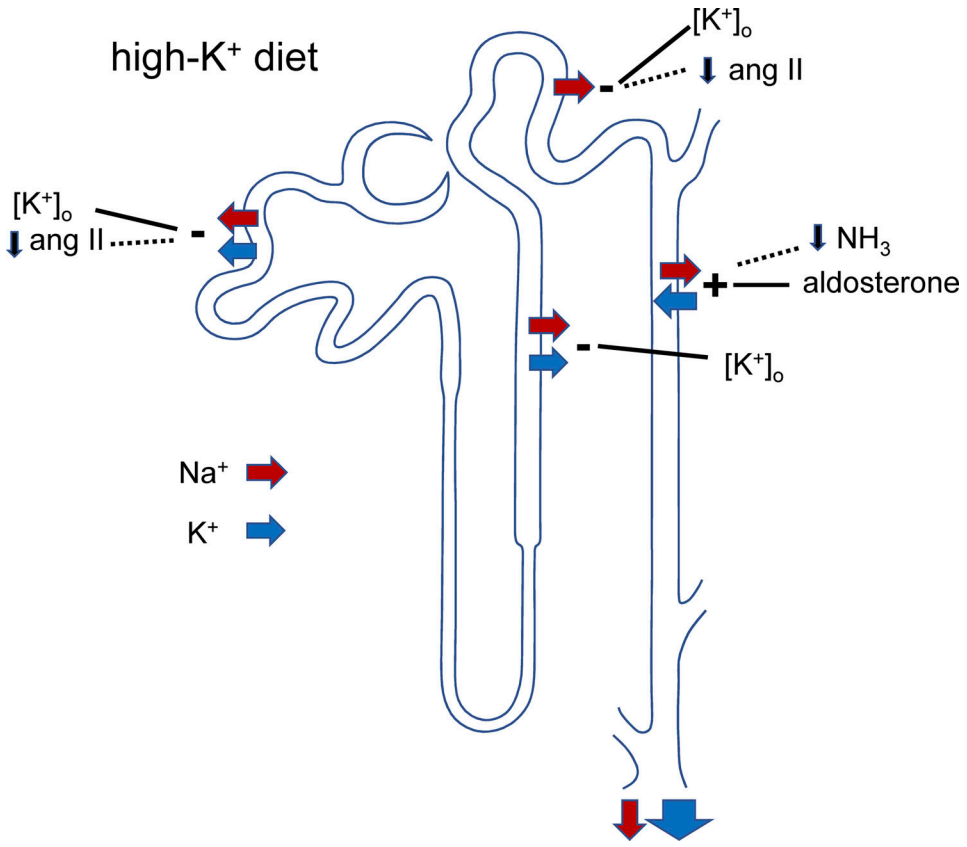

Figure 3. **Changes in Na^+ and K^+ transport by the kidney when dietary K^+ intake is high.** + and – symbols indicate increased and decreased transepithelial movement of ions, respectively. Solid lines represent well-established signaling systems for regulating transport under these conditions. Dashed lines represent pathways that regulate transport but have not been shown to be involved in the response to increased K^+ intake. The net result is that urinary K^+ excretion is enhanced while Na^+ excretion remains constant.

et al., 2013; Rengarajan et al., 2014). The mechanism involves a direct response of the DCT cell to elevations in plasma K^+ (Penton et al., 2016; Terker et al., 2016). NCC dephosphorylation can occur within 30 min of ingestion of a K^+-rich meal (Sorensen et al., 2013), suggesting that it can help maintain Na^+ and K^+ balance over short time periods.

Under more chronic conditions, the overall as well as surface expression of NCC in the kidney varies inversely with K^+ intake (Vallon et al., 2009; Frindt and Palmer, 2010; van der Lubbe et al., 2013; Vitzthum et al., 2014; Terker et al., 2015; Wade et al., 2015). The chronic K^+-loaded condition is also associated with decreased NCC function, assessed in mice as the response to the NCC-blocker hydrochlorothiazide in vivo (Li et al., 2019). Furthermore, when rats were fed a diet deficient in both Na^+ and K^+, ENaC activation was reduced relative to depletion of Na^+ alone, and NCC expression was strongly upregulated (Frindt et al., 2011). This indicates a redistribution of Na^+ transport from K^+-secreting segments to the DCT.

Inhibition of NKCC2 transport in the medullary TALH may also contribute to shifting of Na^+ reabsorption from proximal to distal segments. This segment is a good candidate for responding to changes in K^+ intake because increases in extracellular K^+ are amplified in the medullary interstitium by K^+ recycling, reaching concentrations >30 mM (Battilana et al., 1978). Stokes showed that variations in this range can impact Na^+ transport by the perfused TALH, with higher concentrations inhibiting NaCl reabsorption (Stokes, 1982). This could reflect depolarization of the basolateral membrane, slowing Cl^- exit from the cell through Cl^- channels.

Hyperkalemia can also inhibit Na^+ reabsorption in the PT. Micropuncture studies in rats showed inhibition of transport when plasma K^+ was acutely raised from 4.3 to 6 mM by infusing KCl in vivo (Brandis et al., 1972). This may result from depolarization of the basolateral membrane, slowing HCO_3^- efflux, alkalinizing the cell, and inhibiting NHE3 (Weinstein, 2017). Under more chronic conditions, dietary K^+ loading of mice for 1 wk decreased the abundance of NHE3 in mice (Yang et al., 2018). However, similar results were not observed in rats (unpublished data), raising questions about the generalizability of this effect.

Any of the above mechanisms may contribute to rebalancing Na^+ reabsorption when distal K^+ secretion is altered. The PT and the TALH handle larger fractions of filtered Na^+ than does the DCT and are therefore potentially more powerful sites of inhibition. Reducing transport in the PT has the additional advantage of increasing fluid flow rates in the K^+-secreting segments. This will limit the accumulation of K^+ in luminal fluids, maintaining a cell-to-lumen driving force for K^+ secretion. It can also activate luminal BK channels through flow-dependent increases in cell Ca^{2+} (Woda et al., 2001).

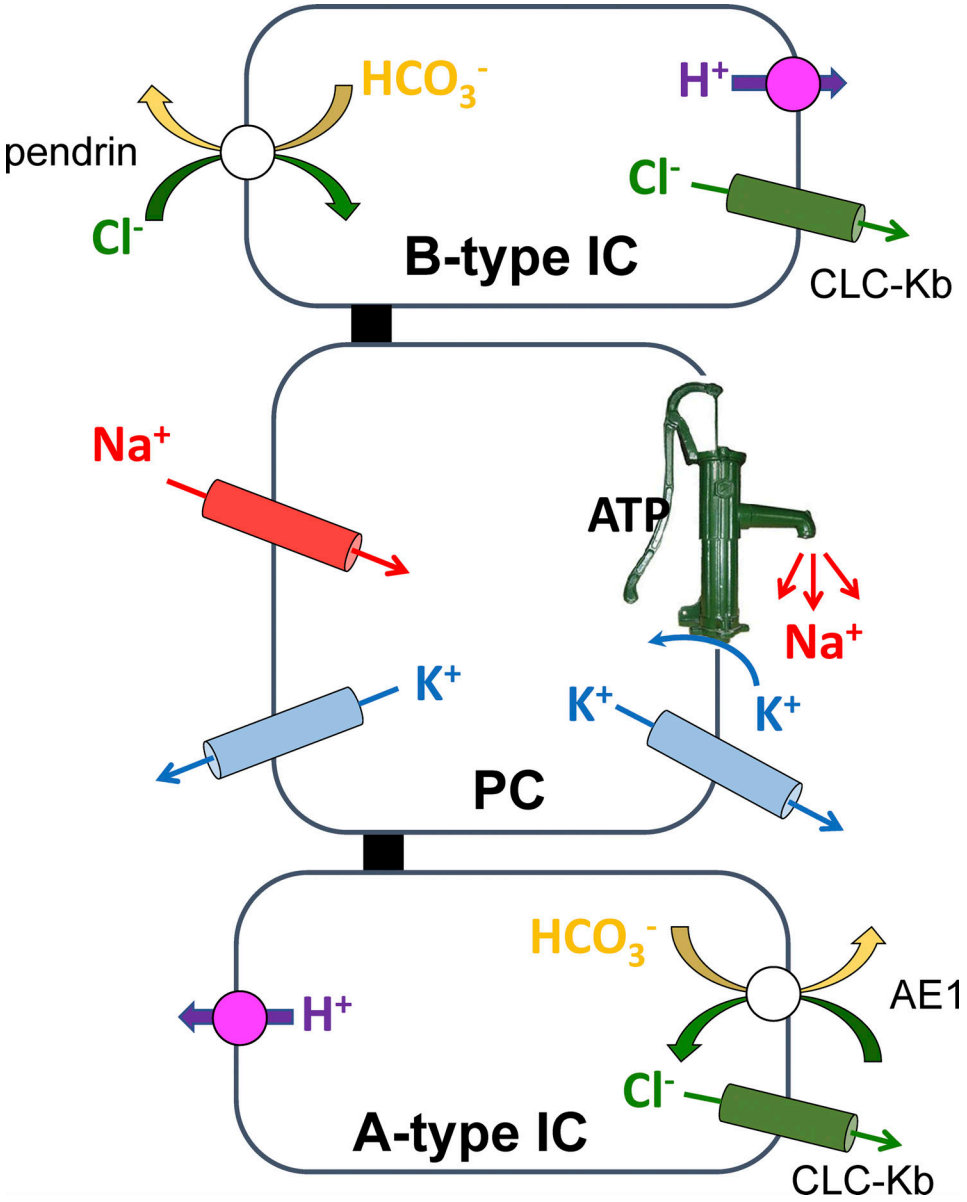

Figure 4. **Transcellular Cl^- reabsorption in the CD.** Type A ICs secrete H^+ while type B ICs secrete HCO_3^-. Transport is powered by H^+-ATPase on the apical and basolateral sides of the cell, respectively. When both are active, the net result is the reabsorption of Cl^- through apical pendrin and basolateral Cl^- channels. Transepithelial Na^+ reabsorption by the principal cells (PC) can be balanced either by K^+ secretion of Cl^- reabsorption.

However, these effects will be blunted by enhanced Na^+ reabsorption in downstream segments (Palmer and Schnermann, 2015). Furthermore, increased delivery of NaCl to the macula densa region just beyond the TALH will also trigger a decrease in glomerular filtration rate through the process of tubuloglomerular feedback (Schnermann and Briggs, 2008). This will diminish the effects of transport inhibition in proximal segments (Weinstein, 2022). Increased NaCl at the macula densa can also inhibit renin release, suppressing aldosterone and compromising the ability of the distal segments to secrete K^+ (Schweda, 2015).

In contrast, Na^+ remaining in the tubular fluid following inhibition of NCC in the DCT will be directly transmitted to the K^+-secreting segments (CNT and CD). Furthermore, effects on NCC can be profound, with decreases in phosphorylated protein of up to 80% in Sorensen et al. (2013); Castaneda-Bueno et al. (2014); and Yang et al. (2018). Since the DCT handles only 5–10% of filtered Na^+, this is more than enough to balance even very large changes in rates of K^+ secretion.

Inhibition of transport in more proximal segments can, in principle, drive K^+ secretion by pushing additional Na^+ to the CNT and CD. This is thought to underlie, at least in part, urinary K^+ wasting and hypokalemia resulting from diuretic treatment. However, acute pharmacological inhibition of NCC-mediated transport using thiazide diuretics does not enhance K^+ secretion to levels seen with dietary K^+ loads (Yang et al., 2021) and in some cases does not acutely increase K^+ excretion at all (Hunter et al., 2014). However, proximal inhibition of Na^+ transport will

ensure that adequate Na^+ is delivered to the distal segments to participate in K^+ secretion. More fundamentally, it will help maintain Na^+ balance by compensating for increased downstream Na^+ reabsorption coupled to K^+ secretion.

Signaling factors

Regulation of Na^+ and K^+ transporters in the kidney involves many signaling pathways and a complete discussion is beyond the scope of this Perspective. I will instead focus on what is known about signals that arise directly from challenges to the maintenance of Na^+ and K^+ balance, especially those that mediate responses to reduced Na^+ intake (Fig. 2) and enhanced K^+ intake (Fig. 3).

Consideration of signaling factors that control these events starts with the adrenal cortical steroid aldosterone. By activating ENaC, aldosterone enhances both Na^+ reabsorption and K^+ secretion in the CNT and CD. Its production is stimulated by low salt intake through the renin–angiotensin–aldosterone axis, with increased circulating levels of both angiotensin II (ang II) and aldosterone. Aldosterone secretion is also enhanced independent of the renin–angiotensin–aldosterone axis by increased plasma (K^+; Spat and Hunyady, 2004). Administration of aldosterone mimics the effects of reduced Na^+ intake or increased K^+ intake on the channels (Pácha et al., 1993; Palmer et al., 1994).

ROMK channels are regulated by K^+ intake independent of aldosterone as administration of the hormone does not activate the channels (Palmer et al., 1994; Wei et al., 2005). The factors that modulate ROMK when dietary K^+ intake changes are incompletely understood, although tyrosine kinase pathways are involved at least in the suppression of the channels with dietary K^+ restriction (Wei et al., 2001).

In addition to activating aldosterone secretion, ang II can itself stimulate Na^+ reabsorption in several different segments. Ang II acutely increases Na/H exchange in the proximal tubule (Harris and Navar, 1985; Cogan, 1990) and in the DCT (Wang and Giebisch, 1996). The hormone also induces a rapid translocation of NCC to the apical membrane from intracellular sites, mimicking the effects of dietary Na^+ restriction on the transporter (Sandberg et al., 2006; Sandberg et al., 2007). Chronic administration of ang II increases the abundance of NHE3 in the proximal tubule (Nguyen et al., 2015) and the abundance and phosphorylation of NCC in the DCT (van der Lubbe et al., 2010; Castaneda-Bueno et al., 2014; Nguyen et al., 2015). In the setting of a low-Na^+ diet, it therefore contributes to increased Na^+ reabsorption proximal to the CNT/CD. It can also contribute to the upregulation of ENaC in the CNT and CCD (Mamenko et al., 2012; Wu et al., 2020) under these conditions.

Ang II may also change the coupling of K^+ and Na^+ transport in the CNT/CCD. It stimulates pendrin (Pech et al., 2007), enhancing Cl^- reabsorption. It can also inhibit ROMK channels in K-depleted animals (Wei et al., 2007), diminishing K^+ secretion. In contrast, the hormone can stimulate ROMK when dietary K^+ intake is high (Wei et al., 2007). These divergent effects are thought to be mediated by different receptors—AT1R for inhibition and AT2R for stimulation. However, the identification of the receptors is uncertain as neither type was found in RNA sequencing assays of the distal nephron segments (Ransick et al., 2019; Chen et al., 2021).

Plasma renin activity is reduced by elevated K^+ intake in rats (Sealey et al., 1970), implying lowered ang II. This could come about because aldosterone secretion by the adrenals is already stimulated by extracellular K^+, obviating the need for ang II. Reduced ang II could enhance K^+ excretion both by promoting distal secretion and inhibiting Na^+ reabsorption in more proximal segments. However, the role of the suppression of ang II in promoting K^+ excretion has not been directly demonstrated.

Shibata et al. (2013) proposed a mechanism of ang II in the CCD in which the hormone leads to dephosphorylation and activation of mineralocorticoid receptors in type-B intercalated cells, ultimately stimulating pendrin. In contrast, hyperkalemia leads to phosphorylation and inactivation of the receptors. This elegant system for controlling Na^+/K^+ coupling was demonstrated in a heterologous expression system. Using intercalated cell (IC)–specific mineralocorticoid receptor knockout mice, Pham et al. (2020) confirmed regulation of pendrin by these receptors in vivo, although they did not observe a dependence of this effect on K^+ intake.

Antidiuretic hormone stimulates ENaC in the CCD (Frindt and Burg, 1972; Reif et al., 1986; Tomita et al., 1986; Mironova et al., 2012) and NKCC2 in the TALH (Ares et al., 2011; Bachmann and Mutig, 2017). In the CCD, its effects are synergistic with those of aldosterone (Tomita et al., 1985; Reif et al., 1986). The main role of antidiuretic hormone is to control water balance, where the stimulus for secretion is plasma hyperosmolarity. It can also be released in response to decreased plasma volume, but only when such decreases are large (>10%; Dunn et al., 1973). Thus, its relevance to the day-to-day management of Na^+ or K^+ balance is unclear.

Extracellular K^+ serves as a signal to differentially affect Na^+ and K^+ transport along the nephron. As discussed above, hyperkalemia per se can directly inhibit Na^+ reabsorption in the PT and the TALH, likely through changes in cell membrane voltage. In the DCT, extracellular K^+ can also promote the dephosphorylation of NCC through direct effects on the tubular cells (Penton et al., 2016; Terker et al., 2016). This response is mediated at least in part by increased cell Cl^-, driven by membrane depolarization. Cl^- inhibits the with no lysine (WNK) kinases, which in turn control SPAK, the kinase that activates NCC through phosphorylation (for reviews see Subramanya et al. [2006]; Gamba [2009]; Hoorn et al. [2020]). Engineering mice with a Cl^--insensitive WNK4 abolished the effects of K^+ depletion and acute but not chronic K^+ loading on NCC (Chen et al., 2019). However, other mechanisms likely also contribute to the effect. Penton et al. (2016) showed K^+-dependent dephosphorylation of NCC in vitro that was independent of Cl^-. Frindt et al. (2017) reported K^+-dependent dephosphorylation of NCC in vivo that could not be explained by increased cell Cl^-. In any case, this response will enhance excretion of an acute K^+ load, where increases in plasma K^+ of ∼1 mM are sufficient to drive acute increases in excretion in response to a K^+-rich meal (Rengarajan et al., 2014).

To effectively promote K^+ secretion, these changes must be accompanied by upregulation of ENaC and/or ROMK channels in the downstream segments. Such changes have been documented (Palmer and Frindt, 1999). When they occur over several

hours, as with the ingestion of a K^+-rich meal, activation of ENaC may be mediated by aldosterone whose secretion is stimulated by extracellular K^+. More acute changes can occur independent of aldosterone, perhaps also as direct effects of K^+ on the secreting cells (Sorensen et al., 2019; Yang et al., 2020).

It is less clear whether extracellular K^+ mediates the more chronic effects of K^+ intake on NCC and other transporters. After adaptation to different diets for 1 wk or more, large increases or decreases in K^+ excretion are observed without detectable changes in plasma K^+ (Chen et al., 2006; Frindt and Palmer, 2009; Wang et al., 2010), and is some cases it can even decrease (Chen et al., 2019). The drivers of altered NCC expression under these conditions have yet to be identified. They may be related to the factors that control ROMK.

Paracellular mediators may also be involved. In response to volume depletion, PT cells secrete α-ketoglutarate, which can activate pendrin-dependent Cl^- reabsorption in the distal nephron (Grimm and Welling, 2017). Chronic increases in K^+ intake inhibit NH_4^+ production by the proximal tubule (Tannen and McGill, 1976). Weinstein (2022) proposed that decreased interstitial NH_4^+ levels result in alkalinization of the cytoplasm of the CNT/CD, increasing the activity of both ENaC and ROMK channels.

Rabinowitz posited a "feed-forward" mechanism in which K^+ secretion could be regulated through sensing of ingested K^+ in the GI tract (Rabinowitz et al., 1984). The concept is attractive as it can explain changes in K^+ excretion in the absence of parallel changes in plasma K^+. Insulin is one possible candidate. This hormone is secreted in response to increased extracellular K^+ as well as glucose (Hiatt et al., 1972; Santeusanio et al., 1973), and helps maintain constant plasma K^+ after a meal by promoting cellular uptake of the ion (Youn, 2013). Exogenous insulin may also stimulate renal K^+ excretion (Rossetti et al., 1987), possibly by activating ENaC (Pavlov et al., 2013) or ROMK (Frindt and Palmer, 2012). However, a role of insulin in controlling K^+ excretion under conditions of elevated K^+ intake has not been directly demonstrated. Other kaliuretic factors may be released in the stomach, but they have not been identified (Youn, 2013).

Summary and perspectives

We have made considerable progress in understanding how the kidneys keep track of multiple solutes such as Na^+ and K^+ and regulate their excretion independently. This involves both changes in the ratio of K^+ to Na^+ transported within individual nephron segments and switching of Na^+ reabsorption from K^+-reabsorbing to K^+-secreting segments. Two major challenges remain. One is to assign quantitative roles to each nephron segment participating in Na^+ and K^+ homeostasis under different conditions. This is a daunting task. Although it is possible to assess levels of mRNA and protein for many different channels and transporters in the same kidney, these measurements will not necessarily reflect function. A second challenge is to identify additional signaling pathways, particularly those affecting K^+ secretion under chronic conditions. In particular, the roles of hormones such as ang II, and putative gut and paracrine factors need to be elucidated. Answering these questions will require combining studies at the cellular and whole-organism levels with mathematical models of the system.

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