Independent Regulation of Na\textsuperscript{+} and K\textsuperscript{+} Balance by the Kidney

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**Key Words**
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**Abstract**
The understanding of the independent regulation of sodium and potassium by the kidney has remained elusive. Recent evidence now points to dissimilar regulatory mechanisms in ion handling, dependent on the presence of either aldosterone alone or angiotensin II with aldosterone among other factors. This review summarizes past and present information in an attempt to reconcile the current concepts of differential regulation of sodium and potassium balance through the with-no-lysine (K) kinase (WNK) system and the previous knowledge regarding ion transport mechanisms in the distal nephron.

**Introduction**
Acute and chronic regulation of Na\textsuperscript{+} and K\textsuperscript{+} plasma concentrations is essential in maintaining homeostasis. Acutely, changes in plasma K\textsuperscript{+} can alter membrane voltage with the potential of causing life-threatening arrhythmias. Thus, the body’s rapid response involves shifting K\textsuperscript{+} in or out of K\textsuperscript{+}-rich cells in order to maintain a normal plasma K\textsuperscript{+} concentration. The triggers of this acute response (particularly in hyperkalemia) include stimulation of the β-adrenergic response, which will activate the Na\textsuperscript{+}/K\textsuperscript{+} ATPase pump and, thus, drive K\textsuperscript{+} into the cells. This is a relatively effective temporary mechanism. However, the total amount of K\textsuperscript{+} in the body remains unchanged. Thus, this is a transient response that buys time until a corrective (K\textsuperscript{+}-excreting) mechanism, i.e. the kidney, restores normal K\textsuperscript{+} levels. In addition to adrenergic stimulation, insulin can also promote activation of the Na\textsuperscript{+}/K\textsuperscript{+} ATPase, thus favoring K\textsuperscript{+} uptake. This mechanism is presumably important after eating.

Acute changes in Na\textsuperscript{+} can be divided in two ways: volume versus osmolarity. Volume deficit or overload implies a change in the amount of fluid in the extracellular compartment that generally does not change the salt-to-water ratio. Na\textsuperscript{+}-related osmolarity derangements on the other hand refer to changes in either Na\textsuperscript{+} or water, thus leading to changes in the salt-to-water ratio. There is, of course, considerable overlap of both these two entities in clinical practice, e.g. hypotonic diarrhea, which causes both volume and osmolarity derangements. However, in the interest of clarity, we will explain these concepts separately so as to understand the body’s response to each one. Volume deficit elicits a much more robust acute response than volume overload. During a volume-depleted state, blood pressure and thus tissue perfusion can become compromised. Thus, the acute mechanisms involved in regulation of volume are oriented towards
maintaining an adequate blood pressure in the presence of diminished extracellular fluid (ECF). These responses include the activation of the sympathetic nervous system and the pressor response of angiotensin II (Ang II), which will increase blood pressure without changing blood volume. Volume overload leads to a decreased sympathetic output, which prevents dangerous increases in blood pressure. Alterations in osmolarity can be caused by many factors, including changes in Na⁺ or water content. When ECF Na⁺ increases with no net change in water, or when ECF water decreases with no net change in Na⁺, the increased osmolarity will trigger the release of antidiuretic hormone (ADH) by the hypothalamus, thus leading to water retention by the kidney. Conversely, increased water content with no net change in total body Na⁺ leads to a decreased Na⁺ concentration and osmolarity, which will decrease ADH secretion and, thus, water diuresis.

With the exception of osmolarity derangements, the other acute responses to changes in Na⁺ and K⁺ concentration require adaptive mechanisms that are only temporary as the initial problem, i.e. increased/decreased K⁺ or increased/decreased volume, is not corrected. Chronic responses that do correct the initial problem are carried out by the kidney. Thus, the kidney is the major long-term regulator of Na⁺ and K⁺ homeostasis. The renal handling of both these ions involves aldosterone, hinting to common regulatory pathways. Nevertheless, the kidney is able to distinguish between these two contrasting situations. The way in which the kidney independently handles Na⁺ and K⁺ homeostasis is the focus of this review.

Renal Mechanisms for K⁺ and Na⁺ Handling

Potassium

The kidney normally excretes between 90 and 95% of our daily K⁺ intake. The rest is excreted through the colon. Potassium is freely filtered in the glomerulus and it is both, reabsorbed and secreted across the nephron in a regulated manner in order to achieve the correct level of urinary excretion according to the level of ingestion. Potassium handling in the proximal nephron (before the macula densa) usually does not vary with K⁺ intake. The bulk of filtered K⁺ is reabsorbed in the proximal tubule (about 80%) and another 10% is reabsorbed in the thick ascending limb of Henle’s loop. Thus, only about 10% of the filtered K⁺ remains in the lumen fluid by the time it gets to the distal tubule [1–4]. Beyond the macula densa, K⁺ handling is modulated by plasma K⁺ level. When it is low (as in low K⁺ intake), distal K⁺ reabsorption is stimulated and the final urinary K⁺ excretion may represent only 1–3% of the filtered load [4, 5]. On the other hand, when K⁺ intake is normal to high, renal retention is not warranted, hence it is secreted along the distal nephron, in which case urinary output can represent from 10 to 150% of the filtered load [4]. Normal K⁺ intake in a modern diet is approximately 80–120 mmol [6]. With a normal glomerular filtration rate (GFR) of approximately 180 liters/day and a plasma K⁺ concentration of 4 mm, around 720 mmol of K⁺ are filtered per day. Thus, under low K⁺ intake and maximal distal K⁺ reabsorption, the 2% of the filtered load that is excreted, represents about 14 mmol. However, with high plasma K⁺, distal nephron secretion of K⁺ is stimulated, and excretion can go from 72 to 1,080 mmol (10–150% of the filtered load, respectively). Thus, the system allows important variations in dietary intake, i.e. the kidney possesses the capacity to adjust K⁺ excretion and maintain a balance in the face of intakes 10 times lower or 10 times higher than normal modern dietary intake values. Intakes higher than these values are very rare so that hyperkalemia more commonly occurs due to impaired output that may result from renal disease.

The reabsorption and secretion of K⁺ involve cellular ion transport mechanisms. Reabsorption takes place within α intercalated cells (IC) of the distal convoluted tubules (DCT), connecting tubules (CNT) and the initial and cortical collecting ducts (ICD and CCD). ICs express an apical H⁺/K⁺ pump, whose activity is driven by ATP hydrolysis, which is necessary for transporting K⁺ against its electrochemical gradient. K⁺ then exits the cell through K⁺ channels present in the basolateral membrane [5, 7].

Regarding K⁺ secretion, initial studies with micropuncture and microcatheterization, in which secretion and reabsorption were estimated by comparing K⁺ amounts found in fluid that was collected from different nephron segments and urine, demonstrated that secretion takes place mainly within the late portion of the classical distal tubule, i.e. in the CNT and ICD. It was also shown that K⁺ excretion also takes place in the CCD but in less important levels [4, 8]. Further studies focused on demonstrating that principal cells of the collecting ducts (CDs) are capable of secreting K⁺ and that this activity can be modulated by factors which are known to modulate K⁺ excretion in vivo, e.g. aldosterone [1, 9–11]. Thus, principal cells were long considered to be the major site for regulation of K⁺ excretion and their activity was thought to be crucial for maintenance of K⁺ balance.
More recently, the importance for K\(^+\) balance of more proximal nephron segments (late DCT and CNT) has been highlighted. Reilly and Ellison [3] showed that a large percentage of K\(^+\) secretion occurs between 20 and 80% of superficial distal tubule length which comprises mainly DCT2 and CNT. Different cell types in charge of K\(^+\) secretion are found in each of these nephron segments, DCT cells in DCT2, CNT cells in CNT and principal cells in ICD and CCD. These diverse cell types share mechanisms for K\(^+\) secretion. The basolateral Na\(^+\)/K\(^+\) pump mediates K\(^+\) entry and Na\(^+\) exit. This promotes the increase in intracellular K\(^+\) and the generation of an electrochemical gradient necessary for K\(^+\) exit through the apical membrane which occurs mainly through the small-conductance renal outer medullary K\(^+\) (ROMK) channel [1, 12]. Other exit routes through the apical membrane are the large Ca\(^{2+}\)-activated K\(^+\) channel (MaxiK or BK channel) [1, 15 –17], which normally does not contribute to secretion, but that becomes activated by enhanced flow through the tubule [18] and a K\(^+\)-Cl\(^-\) cotransport pathway which has also been proposed to participate in the DCT [13, 14]. In addition to the K\(^+\)-secreting channels, the presence of an epithelial Na\(^+\) channel (ENaC) is necessary for an adequate adaptation to K\(^+\) loading. ENaC mediates Na\(^+\) movement from the tubule lumen to the cell down a favorable concentration gradient generated by the Na\(^+\)/K\(^+\) ATPase [19, 20]. This flux of positive charges generates a lumen negative potential which drives K\(^+\) secretion. Both, Na\(^+\)/K\(^+\) pump activity and Na\(^+\) reabsorption through ENaC are regulated during changes in plasma K\(^+\) and, consequently, K\(^+\) secretion through apical channels is indirectly affected [1].

In humans, impaired ENaC activity presents as pseudohypoaldosteronism type I (PHAI), a syndrome characterized by hypotension due to urinary Na\(^+\) loss and hyperkalemia due to impaired renal K\(^+\) secretion [21]. Genetic mouse models for this syndrome have been generated by disruption of ENaC activity in specific nephron segments. Interestingly, mice with specific disruption of ENaC in the CDs do not display a PHAI-like phenotype [22], while mice lacking ENaC activity in the CNT as well as the CDs present a mild PHAI phenotype, with hyperkalemia and renal salt loss, as compared to the severe phenotype observed in humans [23]. These results clearly demonstrate an important role for CNT K\(^+\) secretion in the maintenance of K\(^+\) balance. That the phenotype is not as severe as in humans leaves the possibility of an essential role for DCT2 in K\(^+\) balance regulation. Alternatively, the difference could be due to variations between species.

**Sodium**

The average intake of Na\(^+\) in a Western diet is about 120 mmol/day. In order to maintain an adequate ECF volume, the kidneys must excrete the same amount. This means that from the about 25,500 mmol of Na\(^+\) that are filtered daily in the glomerulus (Na\(^+\) plasma concentration of 140 mmol/l × 180 liters/day) only a small fraction must be excreted in the urine (approximately 0.4% of the filtered load, i.e. 100 mmol). Thus, the majority of filtered sodium is reabsorbed. As with K\(^+\), the bulk reabsorption takes place in the proximal nephron (before the macula densa): 60–70% in the proximal tubule and 25% in the thick ascending limb of Henle’s loop. Of the remaining 8%, about 5% is reabsorbed in the DCT, CNT and ICD and about 3% in the medullary collecting duct. The current knowledge of several genetic diseases that result from altered renal Na\(^+\) handling has contributed to a better understanding of the role of each transport protein and nephron segment in tubular Na\(^+\) reabsorption. Several reviews on this subject have been written by others [24–26] and they present an alternative way of describing renal Na\(^+\) handling.

The macula densa, a group of specialized epithelial cells located precisely in the site where the ascending loop of Henle passes between the afferent and efferent arterioles, is an important center for regulation of kidney function. For instance, it orchestrates a regulatory mechanism called tubuloglomerular feedback (TGF) which functions in maintaining relatively constant levels of GFR. Changes in GFR are sensed as changes in NaCl delivery to the macula densa through the Na\(^+\)/K\(^+\)/2Cl\(^-\) cotransporter (NKCC2), expressed in these cells [27, 28]. An increase in delivery produces a response that affects renal arteriolar tone, causing a decrease in GFR. The opposite occurs with decreased distal NaCl delivery [29]. This mechanism has implications for renal Na\(^+\) handling because it limits the possibility of altering urinary Na\(^+\) excretion by affecting GFR or proximal tubular reabsorption since these alterations would be sensed as changes in NaCl delivery to the macula densa and, therefore, would exert a compensatory modulation of GFR. A very clear demonstration of this is the fact that inhibitors of Na\(^+\) reabsorption mechanisms in proximal tubule, e.g. acetazolamide, do not have an important diuretic effect in contrast to that produced by inhibitors of distal Na\(^+\) reabsorption, e.g. thiazides and amiloride. Loop diuretics are an exception to the rule because, even when they block reabsorption in the thick ascending limb of Henle’s loop, its target is precisely NKCC2, the macula densa sensor, so that, although salt delivery to the macula densa is in-
creased, it is not detected because the sensor is blocked by the loop diuretic, impairing TGF [30]. This implies that physiologic responses which regulate renal Na⁺ excretion would not be able to produce a response by altering filtration or proximal reabsorption unless they alter the TGF mechanism.

Distal reabsorption, however, is not subjected to a feedback mechanism of this type. Thus, as demonstrated by the use of thiazide diuretics, modulation of distal reabsorption can be readily reflected in urinary Na⁺ excretion. This idea is reinforced by the fact that all the monogenic genetic disorders characterized to date with altered blood pressure are caused by mutations in genes coding for proteins affecting renal distal salt handling [25, 31]. In spite of the low level of Na⁺ reabsorption that takes place in this segment as compared to that occurring in the proximal nephron, if altered, important changes in urinary excretion can be produced, suggesting that this site is perhaps more adequate for exerting the fine tuning of renal Na⁺ excretion.

Na⁺ reabsorption in the distal nephron is exclusively an active transcellular process driven by the activity of the basolateral Na⁺/K⁺ ATPase, which extrudes Na⁺ to the extracellular space generating a concentration gradient which favors Na⁺ entry across the apical membrane. Two different pathways are involved. In the DCT (early and late), the thiazide-sensitive, electroneutral Na⁺/Cl⁻ co-transporter (NCC) mediates apical Na⁺ and Cl⁻ entry thanks to the electrochemical Na⁺ gradient [32, 33]. Re-absorption of Na⁺ in the late DCT, the CNT, and CD is mediated by the amiloride-sensitive ENaC [3, 34]. In both situations, maintenance of the Na⁺/K⁺ ATPase activity requires potassium extrusion to the extracellular space. The electroneutral Na⁺ uptake through NCC is coupled to both, apical and basolateral K⁺ exit. The importance of this K⁺ recycling for NCC activity has been recently highlighted by the demonstration that inactivating mutations in the DCT basolateral K⁺ channel KCNJ10 are the cause of SeSAME/EAST syndrome. This syndrome is characterized by a pattern of alterations similar to those developed in Gitelman’s syndrome, which is caused by inactivating mutations in NCC (see below) [35, 36]. However, no net reabsorption or secretion of K⁺ takes place in this segment. In contrast, ENaC activity is tightly coupled to K⁺ secretion since the apical exit of the K⁺ is greatly favored by the lumen-negative transepithelial potential established by the electrogenic Na⁺ uptake through ENaC [21].

**Integration of Sodium and Potassium Handling by the Kidney**

As we have seen, the distal nephron is the site where the fine tuning of Na⁺ and K⁺ balance takes place. As such, ion transport proteins along this segment have a very specific distribution (fig. 1). This in turn will generate three different distal nephron segments: the early DCT or DCT1, in which NCC and ROMK are expressed, the late DCT or DCT2 where NCC, ENaC and ROMK are expressed, and the CNT/CD where ENaC, ROMK and BK channels are expressed [3, 37–40]. This differential protein expression will render these nephron segments specific for different functions. These are: (1) DCT1 – sodium reabsorption, (2) DCT2 – sodium reabsorption > potassium secretion, and (3) CNT/CD – potassium secretion > sodium reabsorption.

Sodium reabsorption can be either electroneutral (via NCC) or coupled to K⁺ secretion (via ENaC) (see above). Electroneutral reabsorption of Na⁺ via NCC inhibits K⁺ secretion since it competes with ENaC-mediated reabsorption. The more Na⁺ that is reabsorbed by NCC, the less to be transported by ENaC and thus no potassium secretion takes place. Similarly, increased availability of Na⁺ favors reabsorption via ENaC and thus promotes K⁺ secretion. Additionally, increased flow to the distal nephron will stimulate the BK channels, favoring K⁺ secretion [18, 40]. Analyzed in this light, the clinical consequences of the different classes of diuretics become readily apparent. In addition to the Na⁺ wasting they provoke, diuretics can be classified into two families depending on their effect on potassium, i.e. K⁺-wasting or K⁺-sparing diuretics. Loop diuretics (which inhibit NKCC2) and thiazide diuretics (which inhibit NCC) increase the distal delivery of Na⁺ and, through the Na⁺/K⁺ exchange and flow-dependent mechanisms (see above), favor K⁺ secretion [41]. The site of action of potassium-sparing diuretics is limited to the region of the distal nephron specialized in K⁺ secretion, and through the inhibition of ENaC, amiloride and triamterene block the ENaC/ROMK-mediated Na⁺/K⁺ exchange, which leads to increased plasma levels of K⁺ [41].

**Regulation of Renal K⁺ Excretion: High-K⁺ versus Low-K⁺ Diet**

Variations in plasma K⁺ must elicit adequate compensatory mechanisms in order to maintain adequate neuromuscular function, which is dependent on ECF K⁺ levels. These in turn are a direct result of IC K⁺ levels, where 95%
of the total body K⁺ is stored. With variations in daily K⁺ intake, the kidney must adjust accordingly. An in-depth discussion of hyper- and hypokalemia is beyond the scope of this review; however, the renal adaptation to high- or low-K⁺ diet elicits the same molecular response as hyper/hypokalemia, respectively, albeit dietary variations elicit a more discrete response in contrast to life-threatening variations in K⁺.

A high-K⁺ diet will favor increased K⁺ secretion, with minimal impact on Na⁺ balance. When faced with an increased K⁺ intake, the kidney must adjust K⁺ excretion rapidly in order to prevent life-threatening increases of plasma K⁺. This response is carried out through both the mineralocorticoid hormone aldosterone and aldosterone-independent mechanisms [42]. Expression of the inward-rectifying pore channels in the glomerulosa cells of adrenal glands, TWIK and, more specifically, TASK, maintains the membrane potential close to the equilibrium potential for K⁺, thus making the glomerulosa cells sensitive to changes in plasma K⁺ [43–45]. Therefore, changes in plasma K⁺ will depolarize the glomerulosa cells, favoring Ca²⁺ entry which will stimulate aldosterone synthesis [43, 44]. The increased levels of aldosterone will in turn stimulate the mineralocorticoid receptor in the aldosterone-sensitive distal nephron (ASDN) favoring K⁺ secretion. The clinical relevance of this mechanism is emphasized in patients treated with spironolactone (mineralocorticoid receptor antagonist) in which plasma K⁺ concentration increases, sometimes dangerously. Increased aldosterone stimulation in the ASDN will lead to an increase in both ENaC and ROMK activity [46]. The increase in the Na⁺/K⁺ exchange mechanism, however, is dependent on an increased distal delivery of Na⁺. This would require inhibition of Na⁺ reabsorption upstream of the ASDN. Nonetheless, any variations in Na⁺ handling by the proximal tubule and the loop of Henle would be offset by a TGF feedback mechanism rendering variations in these nephron segments relatively ineffective to regulate adequate Na⁺ delivery. However, downregulation of NCC would result in an adequate increased distal delivery of Na⁺ that could be coupled to K⁺ secretion (fig. 2). Indeed, Frindt and Palmer [47] have recently shown that in rats under a high-K⁺ diet, the surface expression of NCC is decreased while Vallon et al. [48] have shown that a high-K⁺ diet in mice has a negative effect upon NCC N-terminal phosphorylation (which is related to its level of activity). A parallel can be drawn here to the mechanism of action of thiazide-type diuretics.
Thiazides specifically inhibit NCC, thus increasing distal Na⁺ delivery; accordingly, patients with chronic thiazide treatment may develop low plasma K⁺ concentration unless adequate dietary corrections are made. This mechanism explains why diets with high potassium are associated with lower blood pressure levels because in order to excrete the excess of potassium, NCC is inhibited. In other words, high potassium diets exert a ‘thiazide-like effect’ [49]. Likewise, diuretics that inhibit ENaC, e.g. amiloride and triamterene, and impair the Na⁺/K⁺ exchange favor increased plasma K⁺ concentration in patients, thus, the term ‘potassium-sparing diuretics’. In addition to the ENaC/ROMK exchange mechanism, the increased distal delivery of Na⁺ favors increased flow in the distal nephron where the flow-sensitive BK channels are expressed [50, 51]. The flow-stimulated BK-mediated K⁺ secretion is also increased when distal delivery of Na⁺ is increased [52]. The specific role of the flow dependence of BK channels was studied by Grimm et al. [18] by generating a BK channel β1-subunit knockout, with impaired BK channel function, which displayed hyperkalemia, hyperaldosteronism and hypertension. Thus, BK channel expression and regulation are critical in the maintenance of normal K⁺ concentrations under high K⁺ intake. Taken together, the stimulation of the ENaC/ROMK exchange mechanism and the BK channel stimulation serve as the kidney’s primary response mechanisms to an increased K⁺ load.

In turn, during K⁺ depletion, the kidney must adjust accordingly and switch from a K⁺-secreting organ to a K⁺-retaining organ (fig. 2). As discussed previously, the major site for K⁺ regulation in the nephron is the ASDN. Accordingly, under a low-K⁺ diet, the previously discussed ENaC/ROMK exchange mechanism and the BK channel-mediated K⁺ secretion must be downregulated (fig. 2). Observations by Frindt and Palmer [47] have shown that during low-K⁺ supplementation there was a decrease in the surface expression of ENaC and ROMK. Although there were not differences in the surface expression of NCC, increased activity of NCC is not ruled out.
Regulation of Renal Na\(^+\) Excretion: High-Na\(^+\) versus Low-Na\(^+\) Diet

The plasma concentration of Na\(^+\) generally does not vary under different dietary intakes. This is achieved by the coming together of the two mechanisms mentioned in the introduction: volume and osmolarity regulation. That is, in the face of changes in Na\(^+\) dietary intake, water intake and excretion, through induction of thirst drive and variations in ADH secretion, respectively, are immediately modified so that plasma osmolarity remains close to 290 mosm/kg. This leads to changes in ECF volume and circulating volume, which in turn are detected by different mechanisms and activate several responses that stimulate or decrease renal Na\(^+\) excretion. Renal Na\(^+\) handling is, thus, intimately related to ECF volume regulation which in turn affects blood pressure levels by mechanisms that have been thoroughly reviewed elsewhere [25]. Indeed, in all pathophysiological conditions characterized to date with altered blood pressure, renal Na\(^+\) handling is affected [25].

When an individual is subjected to a high-NaCl diet, an acute increase in circulating volume takes place which is sensed by the low-pressure sensors located on the right side of the heart. This promotes the secretion of atrial natriuretic peptide and renal vasodilation, which promotes an increase in renal plasma flow, both responses leading to increased Na\(^+\) excretion (fig. 3) [53, 54].

On the other hand, when an individual is subjected to a low-NaCl diet, the decrease in circulating volume is sensed acutely and in turn promotes three different responses: the stimulation of sympathetic activity of the autonomic nervous system, the activation of the renin-angiotensin-aldosterone system (RAAS), and the secretion of ADH (fig. 3). In addition to these neurohumoral responses, the kidney by itself can modulate urinary Na\(^+\) excretion in response to changes in blood pressure, a phenomenon called pressure natriuresis [54, 55].

Renal sympathetic nerve activity influences renal sodium handling by altering renal hemodynamics (increased renal vascular resistance, decreased renal blood flow), by stimulating tubular Na\(^+\) reabsorption, and by stimulating activation of RAAS.

RAAS is activated in three ways: by sympathetic stimulation, by sensing low renal perfusion pressure through a specialized groups of cells, the granular cells, located in the juxtaglomerular apparatus, and by sensing a decrease in NaCl concentration of the fluid delivered to the mac-

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**Fig. 3.** A loss in circulating volume will activate both Na\(^+\)- and water-retaining pathways in order to gain volume without changing the osmolarity. This is achieved through the activation of both the RAAS and the secretion of ADH. The initial secretion of catecholamines and Ang II will maintain blood pressure (through vasoconstriction) in spite of the volume deficit. However, the increased reabsorption of both Na\(^+\) and water will eventually correct the underlying problem without affecting osmolarity or plasma K\(^+\) concentration (a). An increase in circulating volume, however, will have the opposite effect. It will inhibit the RAAS and the sympathetic nervous system (SNS), thus favoring Na\(^+\) and water secretion. In addition, atrial natriuretic peptide secretion will be stimulated, which will favor Na\(^+\) and water wasting by the kidney. This response will not alter plasma osmolarity or plasma K\(^+\) concentration (b).
ATPase, the K⁺ channel ROMK and the Na⁺ channel mentioned above, aldosterone stimulates the Na⁺/K⁺ excretion, given that changes in reabsorption at aldosterone could be a more effective way of altering urinary sodium excretion by the adrenal cortex which will in turn increase filtration fraction [57], stimulates proximal Na⁺ reabsorption by promoting activity of the apical Na⁺/H⁺ exchanger and the basolateral Na⁺ bicarbonate cotransporter [58–60], and also stimulates distal Na⁺ reabsorption through the actions of Ang II and aldosterone on membrane transport proteins (see below). All these actions promote Na⁺ retention. As mentioned before, the kidney possesses a mechanism called TGF through which NaCl delivery to the macula densa is sensed and GFR is modulated accordingly. As we have seen, this mechanism normally prevents changes in GFR and can also prevent changes in distal NaCl delivery caused by changes in proximal reabsorption, i.e. decreased proximal reabsorption would be compensated with a decrease in GFR, which will in turn correct distal delivery. Thus, given the existence of this mechanism, can the RAAS really exert an effect upon urinary sodium excretion through its effects on renal hemodynamics and proximal reabsorption? The explanation that has been given to support the idea that indeed it can, is that Ang II can increase the sensitivity of the TGF mechanism by stimulating macula densa NaCl transport. That is, in the presence of high Ang II, a decrease in NaCl delivery to this site can occur without compensatory changes in GFR [55, 61]. In any case, modulation of distal Na⁺ transport by Ang II and aldosterone could be a more effective way of altering urinary Na⁺ excretion, given that changes in reabsorption at this point are not subjected to the scrutiny of the TGF mechanisms. Additionally, at this nephron site, a much smaller proportion of Na⁺ reabsorption takes place, which, nevertheless, if affected, can have a high impact on final urinary excretion. This is the reason why distal nephron has been seen as the site at which the fine tuning of urinary Na⁺ excretion takes place [3].

An interesting observation concerning Na⁺ and K⁺ balance can be made regarding aldosterone action. As mentioned above, aldosterone stimulates the Na⁺/K⁺ ATPase, the K⁺ channel ROMK and the Na⁺ channel ENaC expressed in the ASDN [46]. When K⁺ levels vary, the modulation of these proteins affects urinary K⁺ excretion, leading to correction of plasma K⁺ levels. In contrast, when aldosterone is secreted in response to a low-salt diet, the purpose of stimulating these proteins is to increase distal Na⁺ reabsorption while K⁺ excretion should remain unchanged. That is, even when the system for K⁺ secretion is predicted to be activated, only Na⁺ reabsorption must occur. This phenomenon has been described under the name of ‘aldosterone paradox’ [62, 63]. The clue must be that the system for K⁺ excretion is not really activated. The reason must lie in a condition that differs between both situations in which aldosterone is stimulated, high plasma K⁺ or hypovolemia.

It is well known that distal Na⁺ delivery can affect K⁺ secretion by the ROMK/ENaC system (see above) because when less Na⁺ is available for reabsorption through ENaC, the electrical driving force for K⁺ secretion is not generated [4, 64]. In addition, Na⁺ delivery is related to flow delivery to the distal nephron and, under low Na⁺/flow delivery, flow-sensitive K⁺ channels (BK channels) are inhibited [18]. Thus, reduced distal delivery during low Na⁺ intake may contribute to inhibition of K⁺ excretion under high aldosterone levels. This reduced Na⁺ delivery may be due to the actions of sympathetic activity and Ang II on renal hemodynamics and proximal reabsorption. Moreover, recent evidence suggests that Ang II can induce activation of the DCT-specific NCC [65–67] (fig. 2). Indeed, NCC surface expression is stimulated in rats on a low-salt diet [68]. Activation of this cotransporter in the first two segments of the distal nephron (DCT1 and DCT) promotes Na⁺ reabsorption and has a negative effect upon K⁺ secretion: the opposite picture of what happens with the administration of thiazide-type diuretics which block NCC (see above). That activation of NCC can lead to a reduced K⁺ secretion and inactivation has the opposite effect is also demonstrated by genetic disorders in which NCC activity is affected. Patients with pseudohypoaldosteronism type II (PHAII) develop high blood pressure with hyperkalemia and these alterations are thought to be mainly caused by increased NCC activity [69–72]. On the other hand, patients with Gitelman’s syndrome, caused by inactivating mutations in the gene SLC12A3 that encodes for NCC, present with hypotension and hypokalemia [73, 74] and one of the known secondary effects of antihypertensive therapy with thiazide-type diuretics is precisely hypokalemia [74].

Nevertheless, decreased distal Na⁺ delivery for ENaC-mediated reabsorption and decreased distal flow probably do not completely explain the different effects of aldosterone under hypovolemia and hyperkalemia or, in other words, the independence of regulation of Na⁺ and
K⁺ balance. The reason is that prevention of K⁺ secretion by diminished distal Na⁺ delivery has to involve a negative effect upon ENaC-mediated reabsorption, questioning the idea that ENaC activation during hypovolemia is important for achieving Na⁺ retention. Therefore, ENaC activity during hypovolemia must be at some level enhanced but uncoupled to K⁺ secretion. The relatively recent description of a group of kinases that differentially regulate the activity of several renal epithelial transport proteins has shed light in this direction (see next section).

The WNK System in the Independent Regulation of Na⁺ and K⁺ Balance

So far, we have seen that regulation of Na⁺ and K⁺ balance is orchestrated by the differential action of various epithelial transport proteins under distinct physiological conditions. However, a more detailed description of the specific regulatory mechanisms is warranted. A family of serine/threonine kinases which lack a highly conserved catalytic lysine residue and are thus named the with-no-lysine (K) or WNK kinases have been shown to be key players in the regulation of NCC, ENaC and ROMK. The WNK family in mammals is composed of four different proteins named WNK 1–4, which consist of an N-terminal domain, a highly conserved catalytic domain, and a C-terminal domain [75, 76]. Interestingly, a splice variant of WNK1 produces a kidney-specific variant of WNK1 (KS-WNK1). This KS-WNK1 lacks the N-terminus and most of the kinase domain of WNK1. Three of the four members of the WNK family (WNK1, 3 and 4) are expressed in the distal nephron and are capable of modulating the function of transport proteins [62, 70, 76–78]. The role of the WNKs as regulators of ion transport in the distal nephron became evident when Lifton’s group [70] discovered that mutations in the genes that encode either WNK1 or WNK4 are the cause of PHAII also known as familial hyperkalemic hypertension (FHHt). As mentioned above, patients with PHAII, which have a blunted expression of KS-WNK1 have an increased level of NCC phosphorylation (fig. 5) [86]. Conversely, KS-WNK1 expression is reduced in rats placed on a low salt diet. Accordingly, this may lead to an increase in NCC activity, as further supported by the observation that mice which have a blunted expression of KS-WNK1 have an increased level of NCC phosphorylation (fig. 5) [86, 87]. Additionally, it has been shown that Ang II stimulates NCC membrane translocation [66] and it has been shown in vitro that Ang II activates NCC through a WNK4-dependent pathway [65] (fig. 5). This effect has been paralleled with the activation mediated by the

Regulation of NCC by the WNK Kinase System

The discovery of the WNK system has begun to shed light on how the regulation of NCC takes place. WNK4 is coexpressed with NCC [70] and it has been shown in vitro that it functions as a negative regulator of NCC activity [79], apparently, at least in part, through lysosomal-mediated endocytosis [80]. This inhibitory effect is lost in the WNK4 harboring a PHAII-type mutation, leading to activation of NCC [79]. Additionally, WNK4 mouse models generated by Lalioti et al. [72] corroborated these findings as the mice which carried two extra alleles of wild-type WNK4 were hypotensive and the mice that carried two extra alleles of WNK4 with a PHAII mutation were hypertensive.

WNK1, in which mutations causing PHAII have also been found, can also modify NCC function. WNK1 serves as an indirect upregulator of NCC by inhibiting WNK4 [81]. Evidence shows that WNK1 is able to inhibit the WNK4-mediated inhibition of NCC, thus activating NCC [81]. All PHAII-type mutations in WNK1 gene consist of deletions in intron 1 which lead to overexpression of the kinase, thus providing a plausible molecular mechanism behind the WNK1 mutations that generate PHAII [70]. Interestingly, another indirect regulator of NCC function is KS-WNK1. KS-WNK1 inhibits WNK1 and therefore abrogates the WNK1-mediated inhibition of WNK4. Thus, KS-WNK1 functions as an indirect inhibitor of NCC [82].

As discussed previously, regulation of NCC is crucial for both Na⁺ and K⁺ handling by the kidney. The WNK system is one of the mechanisms that allow the differential regulation of NCC and, thus, Na⁺ and K⁺ ions. The presence of aldosterone without Ang II, i.e. hyperkalemia, leads to an upregulation of KS-WNK1 [83–85]. KS-WNK1 is presumed to inhibit NCC, thereby increasing the distal delivery of Na⁺ and favoring the ENaC-ROMK Na⁺ and K⁺ exchange mechanism (fig. 4). Indeed, NCC N-terminal phosphorylation, which has been clearly positively correlated with its level of activation, is inhibited in mice that overexpress KS-WNK1 [86]. Conversely, KS-WNK1 expression is reduced in rats placed on a low salt diet. Accordingly, this may lead to an increase in NCC activity, as further supported by the observation that mice which have a blunted expression of KS-WNK1 have an increased level of NCC phosphorylation (fig. 5) [86, 87]. Additionally, it has been shown that Ang II stimulates NCC membrane translocation [66] and it has been shown in vitro that Ang II activates NCC through a WNK4-dependent pathway [65] (fig. 5). This effect has been paralleled with the activation mediated by the
WNK4-PHAII mutations, in that mutations in WNK4 which activate NCC mimic Ang II-mediated stimulation of the WNK4-NCC pathway [65]. Phosphorylation and thus activation of NCC by Ang II in vivo has been corroborated in adrenalectomized rats, eliminating the possibility that Ang II effects are transduced by aldosterone [67]. This upregulation of NCC in the scenario of hypovolemia may be important for promoting Na⁺ retention and also for competing with the ENaC-ROMK Na⁺ and K⁺ exchange mechanism, thereby preventing K⁺ wasting in the context of high aldosterone.

**Regulation of ENaC by the WNK Kinase System**

In addition to the well-known aldosterone-mediated regulation of ENaC through the serum-glucocorticoid-induced kinase 1 (SGK1)-neural precursor cell expressed, developmentally down-regulated 4-2 (Nedd4-2) (SGK1-Nedd4-2) pathway [88], ENaC is also regulated by the WNK kinase system. In vitro studies suggest that WNK4, which functions as a negative regulator of ENaC, can be inhibited by aldosterone-induced SGK1 through phosphorylation of serine 1169 in the C-terminal region (fig. 4) [46, 89]. Thus, the WNK4-mediated inhibition of ENaC would be abrogated during high-aldosterone states, i.e. hypovolemia and hyperkalemia (fig. 4, 5). This, however, is different from the regulation of NCC in that KS-WNK1, which functions as an inhibitor of NCC [81], activates ENaC (fig. 4). Indeed, transfection of KS-WNK1 increases amiloride-sensitive currents in mineralocorticoid receptor-transfected, M1 cells [83]. The increased expression of KS-WNK1 and activation of ENaC during high-aldosterone states would be warranted, albeit different to the regulation of NCC. KS-WNK1 induced by high K⁺ or aldosterone would inhibit NCC but would disinhibit ENaC, thus favoring K⁺ secretion aided with distal delivery of Na⁺. The role of WNK1 as a regulator of ENaC is apparently through the SGK1 pathway, as WNK1 phosphorylates SGK1 and thus activates ENaC [90], although there is still no evidence demonstrating the modulation of this kinase in high-aldosterone states. The exact role of the interaction between WNK1-KS, WNK1 and WNK4 with regard to the regulation of ENaC still remains to be elucidated.

**Regulation of ROMK by the WNK Kinase System**

In addition to NCC, ROMK is another protein that is 'switch' regulated by the WNK kinase system. WNK4 functions as an inhibitor of ROMK under steady-state conditions. However, the phosphorylation of WNK4 on serine 1169 by SGK1 inhibits WNK4 and thus releases the WNK4-mediated inhibition of ROMK [46]. This effect would be important when the induction of SGK1 by aldosterone is necessary to promote K⁺ secretion (fig. 4). In the presence of hypovolemia, this would prove counter-intuitive. However, Ang II is capable of restoring inhibition in the presence of SGK1 [91] (fig. 5). Although this pathway has been elucidated in an in vitro system, there is also in vivo evidence of the negative effect of Ang II
Upon ROMK [92]. Thus, in the presence of Ang II, K⁺ would no longer be excreted. Additionally, it has been shown in vitro that PHAII-type mutations in WNK4 potentiate the inhibitory effect of WNK4 upon ROMK [93]. This effect fits perfectly with the proposal mentioned above of PHAII-WNK4 functioning as an Ang II-induced state of WNK4 which promotes Na⁺ retention and K⁺ excretion (fig. 5).

WNK1 also exerts a negative effect on ROMK [94]. However, KS-WNK1 has a positive effect upon ROMK, by opposing the negative effect exerted by WNK1 [85]. As mentioned above, KS-WNK1 protein expression levels increase in the context of high aldosterone [83–85], thus it could be an important mediator of ROMK activation and increased K⁺ secretion under this condition (fig. 4). Indeed, transgenic mice overexpressing KS-WNK1 present higher ROMK immunostaining and renal K⁺ wasting. Interestingly, however, when aldosterone is accompanied by Ang II, this effect is apparently lost since it has been observed that KS-WNK1 expression is reduced in rats subjected to a low-salt diet [84]. This reduction could be important for promoting ROMK inhibition during hypovolemia and for preventing K⁺ wasting (fig. 5).

In summary, a large body of evidence now supports the notion that a regulatory network conformed by WNK and other kinases plays a central role in modulating distal tubule function in order to achieve Na⁺ and K⁺ homeostasis in the face of challenges to the body.

Conclusions

The objective of this review was to reconcile both old and new information concerning the role of the kidneys as major players in the long-term regulation of sodium and potassium balance.

We have described the general handling of Na⁺ and K⁺ by the kidney, emphasizing the fact that regulation of Na⁺ and K⁺ balance takes place specifically within the distal nephron. The distal nephron, in turn, comprises several sections, each with a very specific and important role for the achievement of the adequate modulation of Na⁺ and K⁺ excretion. We have also seen that, within this nephron segment, a specialized network of protein kinases, the WNK kinase system, is in charge of regulating the activity of the transepithelial transport mechanisms and that now much research is being focused on trying to understand the regulation of this system by well-known hormonal axes which maintain Na⁺ and K⁺ homeostasis.

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