Aldosterone Paradox: Differential Regulation of Ion Transport in Distal Nephron

The mechanisms through which aldosterone promotes apparently opposite effects like salt reabsorption and K⁺ secretion remain poorly understood. The identification, localization, and physiological analysis of ion transport systems in distal nephron have revealed an intricate network of interactions between several players, revealing the complex mechanism behind the aldosterone paradox. We review the mechanisms involved in differential regulation of ion transport that allow the fine tuning of salt and K⁺ balance.

The mineralocorticoid hormone aldosterone has traditionally been appreciated as the key hormone in the response to two apparently opposite physiological conditions: hypovolemia and hyperkalemia. Volume depletion leads to a Na⁺ retaining state in which salt transport mechanisms in the distal nephron are activated, at least in part, by the action of aldosterone. In this condition, while reabsorption of salt is increased, K⁺ secretion remains unchanged. Thus salt is retained without losing K⁺. On the other hand, if plasma K⁺ is increased, aldosterone is also released, favoring K⁺ secretion in the distal nephron, without affecting the salt reabsorption rate. Thus K⁺ is lost without retaining salt. This is commonly referred to as the aldosterone paradox. If aldosterone is elevated in both states but leads to two distinct physiological responses, how does the kidney know the difference between these opposite states? Since activation of the renin-angiotensin-aldosterone system (RAAS) is the hallmark of volume depletion and since angiotensin II is not affected by plasma K⁺ concentration, it is possible that angiotensin II plays an important role in making this distinction. Thus a major difference between volume depletion and hyperkalemia is the presence of angiotensin II. The discovery of several serine/threonine kinases differentially expressed along the distal nephron together with the increased tools and knowledge regarding the major ion transport proteins are beginning to reveal the existence of a complex network of interactions between kinases and transporters/channels that help unravel the aldosterone paradox. Here, we present an integrative view of the knowledge that has arisen in the last decade revealing that differential regulation of ion transport proteins by distinct segments of the distal nephron, with alternate hormone sensitivities, is the key behind the fine tuning of salt and K⁺ homeostasis.

Protein Expression Along the Distal Nephron

To understand how the differential modulations of ion transport proteins achieve the appropriate response to distinct physiological situations such as dehydration or hyperkalemia, it is imperative to understand the anatomy and expression of the different players in the distal nephron. The distal nephron is composed of the distal convoluted tubule (DCT), which is divided into the early (DCT1) and late (DCT2) segments, the connecting tubule (CNT), and the collecting duct (CD). It is important to clarify that CD receives the fluid from several nephrons, and as such it is not part of the classically defined nephron. Thus there are more DCTs than CDs. Each of these segments is characterized by differential expression of transport or regulatory proteins (FIGURE 1), suggesting intricate regulatory mechanisms behind the coordinated function of the different nephron segments (6, 62). In the distal nephron, Na⁺ reabsorption occurs through two pathways: the electroneutral thiazide-sensitive Na⁺:Cl⁻ cotransporter (NCC), which is expressed exclusively in the DCT with a robust expression in DCT1 that decreases gradually along DCT2 (19, 43, 44, 57), and the amiloride-sensitive epithelial Na⁺ channel (ENaC), whose expression increases gradually along DCT2 and is robust in the CNT and CD (9, 43). ENaC is not expressed in DCT1. The overlap of NCC and ENaC protein expression in DCT2 generates three distinctive segments (FIGURE 1): DCT1, where only NCC is expressed, DCT2 where NCC and ENaC are co-expressed, and CNT/CD where only ENaC is expressed (44). The Na⁺ reabsorption system in the distal nephron is coupled to a K⁺ secretion apparatus. Sodium entering through ENaC generates a lumen negative voltage that favors the secretion of K⁺ through a variety of K⁺ transport pathways in the apical membrane,
including the renal outer medullary potassium (K\(^+\)) channel (ROMK), the flow-dependent large Ca\(^{2+}\)-activated K\(^+\) channel (BK), and the K\(^+\)-Cl\(^-\) cotransporter, which are expressed along the DCT1, DCT2, CNT, and CD (5, 6, 28, 29, 31, 48, 65).

In addition to transport proteins, the expression of receptors and other regulatory proteins along the distal nephron is also important for the differential functions between the different segments. The effects of aldosterone on the distal nephron are restricted to a specific segment of the distal nephron that is known as the aldosterone-sensitive distal nephron (ASDN), which comprises the DCT2, the CNT, and the CD. It is in these regions that aldosterone’s action can take place due to the co-expression of the aldosterone receptor: the mineralocorticoid receptor (MR) (11), and the 11\(\beta\)-hydroxysteroid dehydrogenase type 2 (11\(\beta\)-HSD2), which is required to prevent promiscuous occupation of the MR by glucocorticoids (10, 11). The lack of 11\(\beta\)-HSD2 in DCT1 renders the early DCT insensitive to aldosterone. Interestingly, aldosterone has been shown to increase NCC total protein but not mRNA expression, suggesting that this mineralocorticoid modulates NCC expression by a posttranslation mechanism (1, 36, 50). This effect, however, would presumably only occur in the aldosterone-sensitive DCT2. In contrast, the expression of the angiotensin II type 1 receptor (AT1R) expands all along the distal nephron (49, 52) (FIGURE 1). Two other important regulatory proteins expressed all along the ASDN (45) that are involved in aldosterone’s actions are the neuronally expressed developmentally downregulated 4-2 (Nedd4-2) HECT E3 ubiquitin-ligase and the serum and glucocorticoid regulated kinase 1 (Sgk1) (43, 62) (FIGURE 1). Nedd4-2 has been shown to regulate multiple ion channels including ENaC (3). By interacting with PY motifs located in the carboxy-terminal domain of the ENaC’s \(\beta\)- and \(\gamma\)-subunits, Nedd4-2 induces the ubiquitylation of the channel, a signal known to promote its internalization and degradation (2, 78–80). Aldosterone-mediated regulation of ENaC is achieved by induction of Sgk1 expression (4) and Sgk1-mediated phosphorylation of Nedd4-2 on three Sgk1 phosphorylation motifs (RXRXXS/T), thus creating binding sites for the 14-3-3 protein (8), which consequently prevent the Nedd4-2 interaction with ENaC and decrease the ubiquitylation and degradation of the channel (16, 47);
Additionally, aldosterone may also control the abundance of Nedd4-2 (45). The PY motifs of ENaC are eliminated in Liddle’s syndrome-causing mutations (75, 78), thus preventing the interaction between Nedd4-2 and ENaC, leading to increased ENaC expression, with the consequent development of arterial hypertension and hypokalemia (12).

The activity and/or expression of the ion transporters and channels is modulated by members of two families of serine/threonine kinases whose expression, functional properties, and interactions have attracted the attention of several groups along the last decade. The with-no-lysine (K) kinases WNK1 and WNK4 (89) have been shown to play a critical role in the regulation of Na⁺ and K⁺ transport in the distal nephron. Indeed, mutations in the genes encoding these two kinases are found in families with an inherited hypertension and hyperkalemia disorder termed Gordon’s syndrome or Pseudohypoaldosteronism Type II (PHAII) (89). The WNK family is composed by four members designated as WNK1 to WNK4 (85). Three of these are expressed in the kidney: WNK1, WNK3, and WNK4 (FIGURE 1). The WNK1 gene produces several variants by alternative splicing mechanisms (17, 21, 56). The long isoform of WNK1 (L-WNK1) is expressed all along the distal nephron (89), whereas the short kidney-specific isoform (KS-WNK1) lacks the amino-terminal domain as well as the whole kinase domain. KS-WNK1 is present in the DCT, and its expression decreases gradually along the CNT (17, 54). WNK3 is expressed along the entire nephron (66). WNK4 is expressed only in the distal nephron, from DCT1 to CD (89); however, WNK4 expression along the TAL remains elusive. Aside from the KS-WNK1 variant, all WNKs are structurally similar, consisting of an NH₂ domain, a kinase domain, and a COOH-terminal domain containing several coil-coil domains (34, 70).

On WNK4, most of the PHAII mutations are localized to a specific negatively charged and highly conserved stretch of 10–15 amino acid residues located downstream of the kinase domain. Interestingly, missense mutations in this region affect charged amino acids (34). In addition to the WNK kinases, the Ste20p-related proline-alanine rich kinase (SPAK) and the oxidative stress response 1 (OSR1) have also been shown to play a critical role in NCC regulation (18). Several groups have shown that WNKs lie upstream of SPAK/OSR1, at least in their effects toward the cation-coupled chloride cotransporters (24, 51, 59, 63, 64, 86). Immunohistochemical staining of microdissected mouse renal tubules recently demonstrated that SPAK is expressed in the TAL and DCT, whereas its expression in CNT or CD is minimal to none (61, 87). Its expression in TAL and DCT was also shown by immunohistochemistry of human kidneys (87). The expression of OSR1, in contrast, has not been carefully analyzed along the nephron (FIGURE 1).

**Sodium and Potassium Handling in the Distal Nephron is Interdependent**

There is a clear relationship between Na⁺ reabsorption and K⁺ secretion in the distal nephron. Potassium secretion is favored by an increased distal delivery of Na⁺. Additionally, the presence of the BK channels in the CNT (60) also favors an elevated K⁺ secretion when distal delivery of intratubular fluid is increased. The high distal delivery of Na⁺ favors Na⁺ reabsorption via ENaC with subsequent secretion of K⁺ via ROMK and/or BK. Clinically, the association between distal fluid and/or Na⁺ delivery and K⁺ secretion is clearly supported by the phenotype of patients with either gain-of-function or loss-of-function mutations in Na⁺ transport pathways. NKCC2 or NCC loss-of-function mutations are the cause of type I Bartter’s or Gitelman’s syndromes, respectively (7, 26, 76, 77), which feature hypotension with hypokalemic metabolic alkalosis. Conversely, ENaC loss-of-function mutations in pseudohypoaldosteronism type I (PHAII) are associated with hypotension and hyperkalemia due to a failure in exchanging Na⁺ for K⁺ (74). In contrast, increased activity of NCC in patients with PHAII is associated with hypertension and a reduced distal delivery of salt, with the consequent hyperkalemia (46), whereas increased Na⁺ transport by gain-of-function mutations of ENaC in patients with Liddle’s syndrome result in hypertension with hypokalemia (12, 41). Thus one could think of the distal nephron as having two opposite states of function: 1) a salt-retaining state with minimal K⁺ secretion and 2) a K⁺-secreting state in which salt reabsorption is not increased. Both states can be achieved by activation of RAAS components. The first scenario is what occurs during hypovolemia when both angiotensin II and aldosterone are secreted. The second scenario is what occurs during hyperkalemia when only aldosterone, and not angiotensin II, is increased. To reach these opposite states of function in the distal nephron, the transporters and channels are subjected to a differential regulation by the kinases described above.

**The WNK4 Conundrum**

Growing evidence points to WNK4 as the “molecular switch” that alternates between different functional states of Na⁺ and K⁺ handling in the distal nephron. Since PHAII is treated with low doses of thiazides (46) and it is the mirror image of Gitelman’s disease, it was expected that increased NCC
activity was involved in the pathophysiology of PHAII. Supporting this hypothesis, it was shown that WNK4 inhibits the activity of NCC (90, 92) and that this effect is prevented by either eliminating the catalytic activity of WNK4 (13, 27, 72, 90) or by introducing one of the PHAII-type mutations in WNK4 (13, 90). This suggests that in certain circumstances WNK4 is an inhibitor of NCC, whereas in other situations (i.e., PHAII-type mutations) WNK4 behaves as an activator of the cotransporter (35). A similar situation occurs with ENaC: wild-type WNK4 is an inhibitor of ENaC, whereas this effect is lost in disease-causing PHAII-WNK4 mutations (67). In contrast, the opposite occurs with ROMK and the tight junction paracellular Cl– transport proteins, the claudins. Wild-type WNK4 inhibits ROMK activity in a kinase-independent fashion, and the inhibition is further increased by PHAII mutations (35). Similarly, wild-type WNK4 increases claudins’ activity and phosphorylation, and this effect is further increased by PHAII mutations (32, 91). Thus the consequences of PHAII mutations in WNK4 toward NCC or ENaC resemble a loss-of-function mutation, whereas toward ROMK and claudins they resemble a gain-of-function mutation (FIGURE 2). The consequences of PHAII mutations in WNK4 have been corroborated in vivo by reproducing the disease in different transgenic mouse models. In one study, a WNK4-D561A knock-in mouse model reproduced PHAII and was associated with increased phosphorylation of SPAK and NCC (97). In another study, Lalioti et al. (37) made two opposite transgenic mouse models. One model contains four wild-type WNK4 alleles (two endogenous alleles and two extra copies of wild-type WNK4). The second model contains the two endogenous wild-type alleles and two exogenous PHAII-mutant WNK4 alleles. Interestingly, the mice with the four wild-type WNK4 alleles developed a Gitelman’s-like syndrome, with hypoplasia and hypotrophy of DCT. In contrast, the PHAII allele’s model reproduced the PHAII disease with a remarkable hyperplasia and hypertherphy of DCT. Thus, despite the presence of two wild-type WNK4 alleles, the additional expression of two WNK4 alleles with PHAII mutations resulted in increased NCC activity. These results suggest that PHAII is not due to loss-of-function mutations in WNK4. Instead, because PHAII is an autosomal dominant disease, it is very likely that the phenotype results from a gain-of-function mutation that modifies the behavior of WNK4 toward a variety of transport systems (FIGURE 2). Finally, reducing the activity of NCC either by thiazides, as observed in humans (46), or by crossing the PHAII mice with NCC-null mice completely corrected the full syndrome, including the hyperkalemia under high K+ diet (37). These results highlight the importance of NCC activity in modulating the K+ secretion in ASDN.

FIGURE 2. WNK4-PHAII: gain-of-function or loss-of-function mutations? The autosomal dominant PHAII-WNK4 mutations would act 1) as gain-of-function mutations with regard to ROMK (PHAII-WNK4 further inhibit the channel) but 2) as loss-of-function mutations with regard to NCC and ENaC (PHAII-WNK4 activate NCC and ENaC). Recent evidence strongly suggests that PHAII-WNK4 is a gain-of-function mutation that mimics the angiotensin II-mediated activation of NCC via the WNK4-SPAK pathway, during which NCC and ENaC are activated and ROMK is inhibited. Thus, during volume depletion, Na+ reabsorption is maximal, whereas K+ loss is minimal, corresponding to the hypertensive and hyperkalemic PHAII patient phenotype.
surface and is dependent on its catalytic activity. In fact, elimination of WNK3’s catalytic activity, obtained by the substitution of the aspartic acid 294 for alanine, not only prevents the activation of NCC but turns WNK3 into a powerful inhibitor of NCC (and NKCC1 or NKCC2) (33, 66). Thus WNK3 is an activator of NCC, whereas WNK4 is an inhibitor. Interestingly, by using two different polyclonal antibodies against WNK3, it has been demonstrated that WNK3 is heavily expressed in DCT and co-localized with NCC (66, 93). Chimeric analysis between WNK3 and WNK4 suggested that the aminoterminus domain of each kinase contains the key information to define the type of effect toward NCC (72). On the other hand, evidence also suggests that interactions between WNK3 and WNK4 could define the NCC activation/inactivation mechanism as well (94). Interestingly, WNK3 has been shown to be a powerful inhibitor of ROMK (40) and of the K⁺:Cl⁻ cotransporters (15). These results show that WNK3, which is present in DCT1 and ASDN, can at the same time activate NCC and inhibit K⁺ secretory pathways, making this kinase ideally suited to take part in the differential regulation of ion transport pathways during hypovolemia. However, the RAAS effects on WNK3 expression and/or activity remain unknown.

### Differential Regulation of Na⁺ and K⁺ Transport Between DCT1 and ASDN: Integration of the Renin-Angiotensin-Aldosterone System

The fact that PHAII-type mutations in WNK4 represent the pathophysiological version of what would be expected to occur during hypovolemia (salt reabsorption leading to hypertension with reduced K⁺ secretion and thereby hyperkalemia) (FIGURE 4), it is possible that these mutations could be mimicking the effects of angiotensin II on WNK4, as shown in FIGURE 2. Several lines of evidence support this hypothesis. Indeed, angiotensin II modulates the trafficking of NCC toward the apical membrane of DCT cells (73). In addition, chronic angiotensin II infusion in mice increases salt reabsorption by an aldosterone-independent mechanism that is thiazide-sensitive, suggesting that salt reabsorption is mediated by NCC (99).

**FIGURE 3.** The WNK4 conundrum

Under basal conditions, WNK4 acts as an inhibitor of NCC, ENaC, and ROMK all along the distal nephron. During hypovolemia (high angiotensin II and aldosterone levels) and PHAII mutations, WNK4 inhibits ROMK all along the distal nephron but upregulates NCC in DCT1 and DCT2 and ENaC function in the ASDN. During hyperkalemia, however, WNK4 inhibits both NCC and ROMK in DCT1 (favoring an increased distal delivery of Na⁺) and activates ENaC and ROMK in the ASDN, favoring the Na⁺ and K⁺ exchange, as well as BK channel activation. The exact effect of aldosterone on NCC in DCT2 is still debated. However, evidence points toward an aldosterone-mediated increase in NCC.
Finally, overexpression of several players (AT1R, NCC, WNK4, and SPAK) in *Xenopus laevis* oocytes showed that angiotensin II stimulates NCC, but only in the presence of WNK4, by switching WNK4 from an inhibitor to an activator of NCC (71). Since angiotensin II had no effect on PHAII-WNK4, it was suggested that PHAII mutations reconstitute the effect of angiotensin II on WNK4. Additionally, independent studies using *Xenopus* oocytes and mpkDCT cells demonstrated that angiotensin II induces phosphorylation of SPAK and NCC, suggesting that the effects of angiotensin II on NCC are mediated by the WNK4-SPAK pathway (71, 82). Genetically altered mice showed that elimination of SPAK activity in the kidney, either by a SPAK knock-in (61) or by a SPAK knockout (96), decreases NCC expression and phosphorylation and induces a Gitelman’s like syndrome, indicating the importance of SPAK in modulating NCC activity. Adrenalectomized rats treated with either angiotensin II or aldosterone showed increased expression and phosphorylation of NCC amino-terminal threonines, suggesting that both angiotensin II and aldosterone are able to induce NCC activation independently of each other (84). Thus angiotensin II should be able to activate NCC in both DCT1 and DCT2, whereas aldosterone by itself would promote NCC activation only in DCT2, where the 11β-HSD2 is expressed (11). On the other hand, angiotensin II inhibits ROMK activity in renal cortical CD (88), and preliminary data suggest that the inhibitory effect of angiotensin II on ROMK is due to both WNK4-dependent and WNK4-independent mechanisms (98). Finally, assessment of apical NCC and ENaC abundance in rat kidney during variations in Na⁺ intake, using in situ biotinylation and immunoblotting, revealed that low Na⁺ diet increases NCC and ENaC β- and γ-subunits at the cell surface (22). The effect on ENaC subunits, but not on NCC, was reproduced by administration of aldosterone. These data suggest that the effects of the low Na⁺ diet on NCC were mediated by angiotensin II rather than by aldosterone, whereas the low Na⁺ diet effects on ENaC expression were transduced by the aldosterone-Sgk1-Nedd4-2 pathway. Taken together, these observations suggest that angiotensin II-mediated activation of the WNK4-SPAK pathway is responsible for the switch between the salt-retaining/K⁺ conservation mode, characteristic of hypovolemia, and the K⁺-secreting state, characteristic of hyperkalemia.

Hyperkalemia is also a major stimulus that favors aldosterone secretion to increase net K⁺ loss without increasing volume retention. As discussed above, this is achieved by increasing distal Na⁺ delivery, favoring ENaC-mediated Na⁺ reabsorption, which is coupled to ROMK-mediated K⁺ secretion (FIGURE 4). Aldosterone, presumably by increasing Sgk1 expression, promotes the phosphorylation of WNK4 on S1169 that switches WNK4 to the K⁺ secretory mode by preventing the WNK4-induced inhibition of ENaC and ROMK (68), whereas NCC remains inhibited (70, 71). If WNK4 becomes phosphorylated on two sites (S1169 and S1196), NCC inhibition might be released (69). However, this can occur only in DCT2 where the aldosterone response can be achieved via MR activation, leaving NCC inhibited in DCT1, thus increasing distal salt delivery. What determines that WNK4 becomes phosphorylated at one (S1169) or two (S1169/S1196) canonical Sgk1 phosphorylation sites remains to be elucidated. However, it...

**FIGURE 4.** Sodium and potassium transport in DCT1 and ASDN under hypovolemia vs. hyperkalemia: an explanation for the aldosterone paradox

A: during hypovolemia, angiotensin II stimulates NCC activity via WNK4-SPAK and inhibits ROMK, presumably via both a WNK4-dependent and -independent mechanisms, in both DCT1 and DCT2. In DCT2, angiotensin II releases ENaC inhibition. In addition, ENaC is further activated by aldosterone-mediated stimulation of the Sgk1-Nedd4-2 pathway, together with an L-WNK4-mediated inhibition of ROMK in both DCT2 and CNT/CD, such that volume retention is favored by increasing NCC and ENaC activity and K⁺ loss is minimized through ROMK inhibition. B: in contrast, hyperkalemia will only elicit a response by aldosterone. Since DCT1 is insensitive to aldosterone regulation, WNK4-mediated inhibition of NCC and ROMK favored by a K⁺-induced overexpression of K₅-WNK1 will be maintained. DCT2, however, will respond to aldosterone by increasing ENaC activity via activation of the Sgk1-Nedd4-2 pathway. Sgk1-mediated phosphorylation of WNK4 will release the WNK4-mediated inhibition of both ROMK and NCC. In a similar fashion, ENaC and ROMK will be upregulated in the CNT/CD, thus favoring ENaC/Romk-mediated Na⁺ and K⁺ exchange.
would not be surprising if this is modulated by angiotensin II.

Another important player in the switch of the distal nephron to promote \( K^+ \) secretion without salt reabsorption is WNK1. The effect of WNK1 on NCC regulation is, however, less understood. WNK1 does not seem to have a direct effect on NCC (92) but prevents the WNK4-induced inhibition of NCC, presumably by direct interaction with WNK4 (92, 95). Thus the more L-WNK1 is expressed, the less NCC is inhibited by WNK4. This is illustrated in PHAII patients who carry a WNK1 intronic deletion and consequently overexpress L-WNK1 (46). As shown in FIGURE 1, KS-WNK1 expression is restricted to DCT and to a part of the CNT. KS-WNK1, by interacting with L-WNK1, prevents L-WNK1-mediated inhibitory effect on WNK4 (81). Thus, as KS-WNK1 increases, NCC activity decreases. On the other hand, L-WNK1 reduces ROMK activity in a kinase-independent fashion, in part by promoting a dynamin-dependent channel internalization and degradation (14, 39).

This mechanism requires the presence and interaction of ROMK with the autosomal recessive hypercholesterolemia (ARH) adaptor (20). Interestingly, this effect of WNK1 is completely prevented by NCC expression in DCT1, DCT2, or both (25, 53, 58).

Conclusions

Taken together, studies show that the differential regulation of ion transport proteins along the ASDN is possible thanks to a complex expression and interaction of several kinases, of which WNK4 seems to be the central regulator. In addition, it has been shown that NCC and ROMK expressed in DCT1 are insensitive to aldosterone but sensitive to angiotensin II, whereas in DCT2 they are sensitive to both hormones (FIGURE 4). This is not the case for ENaC because it is not expressed in DCT1. Thus ENaC can be regulated by aldosterone, even in the absence of angiotensin II, but not by angiotensin II alone (FIGURE 4). The difference in hormone sensitivities between DCT1 and ASDN can thus be attributed to the absence of the 11β-HSD2 in DCT1 but its presence in ASDN. This would explain the differential regulation of Na\(^+\) and \( K^+ \) transport between the two nephron segments and is suggested to be the key mechanism behind the aldosterone paradox. It is important to note that the role of other neuro-hormonal systems in the differential regulation between sodium retention and preferential kaliuresis remains to be clarified. For instance, it has been recently shown that vasopressin can also stimulate the activity of NCC, but it is not clear whether the effect is present in DCT1, DCT2, or both (25, 53, 58).

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