Sodium and potassium handling by the aldosterone-sensitive distal nephron: the pivotal role of the distal and connecting tubule

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1Unité 367, Institut National de la Santé et de la Recherche Médicale, 75005 Paris, France; 2Institut de Pharmacologie et de Toxicologie, Université de Lausanne, CH-1005 Lausanne, Switzerland; and 3Department of Medicine, Division of Nephrology, University of Alabama at Birmingham, Birmingham, Alabama 35294-0006

Meneton, Pierre, Johannes Loffing, and David G. Warnock. Sodium and potassium handling by the aldosterone-sensitive distal nephron: the pivotal role of the distal and connecting tubule. Am J Physiol Renal Physiol 287: F593–F601, 2004; 10.1152/ajprenal.00454.2003.—Sodium reabsorption and potassium secretion in the distal convoluted tubule and in the connecting tubule can maintain the homeostasis of the body, especially when dietary sodium intake is high and potassium intake is low. Under these conditions, a large proportion of the aldosterone-regulated sodium and potassium transport would occur in these nephron segments before the tubular fluid reaches the collecting duct. The differences between these two segments and the collecting duct would be more quantitative than qualitative. The collecting duct would come into play when the upstream segments are overloaded by a primary genetic defect that affects sodium and/or potassium transport or by a diet that is exceedingly poor in sodium and rich in potassium. It is likely that the homeostatic role of the distal convoluted and connecting tubules, which are technically difficult to study, has been underestimated, whereas the role of the more easily accessible collecting duct may have been overemphasized.

sodium reabsorption; potassium secretion; distal convoluted tubule; collecting duct

“IN EUVOLEMIC SUBJECTS, the collecting duct is the main nephron segment where sodium resorption is adjusted to maintain excretion at a level appropriate for dietary intake” (43). This statement, still found in some textbooks, reflects the emphasis that has been placed on the role of the collecting duct, which is sometimes considered as the final and main controller of urinary sodium and potassium excretion, matching the variations in dietary intakes. Such a view has been fostered during the past 20 years by a considerable number of studies performed in vivo and in vitro that analyzed the mechanisms and the regulation of sodium reabsorption and potassium secretion in this segment of the nephron. An incredible amount of data has been gained about the involvement of the Na-K-ATPase, the epithelial sodium channel (ENaC), and the inwardly rectifying potassium channel ROMK (21, 61, 79); regulatory proteins like the ubiquitin-protein ligase neural precursor cell-fying potassium channel ROMK (21, 61, 79); regulatory proteins have been localized in the intercalated cells (54). However, in rodents and humans, these systems are also highly abundant in the cells constituting

the upstream nephron segments, i.e., the connecting tubule (CNT) and the late part of the distal convoluted tubule (DCT) (4, 48). The cells forming the DCT are also characterized by the expression of the sodium-chloride cotransporter (NCC), which has been shown to be regulated by dietary sodium intake and aldosterone similarly to ENaC (42), although it remains elusive whether the entire DCT is sensitive to aldosterone given that mineralocorticoid receptor (MR) expression is rather low and 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is not detectable in the early part of the DCT (Fig. 1). Nevertheless, the epithelial cells of the DCT, CNT, and collecting duct, although morphologically distinct from each other, are capable of fulfilling similar functions in relation to sodium reabsorption and potassium secretion and form the aldosterone-sensitive distal nephron.

Several questions can be raised. Do the DCT and CNT play an active role in the regulation of urinary sodium and potassium excretion? Is their role comparable to that of the collecting duct? Do these nephron segments respond to specific environmental or physiological conditions or perturbations? This short review will consider recent findings, and some older observations, suggesting that the late DCT and the CNT, rather than the collecting duct, are the main physiological regulators of urinary sodium and potassium excretion and that the collecting duct intervenes only when these two segments are overwhelmed. As such, the late DCT and the CNT would represent the segments of the aldosterone-sensitive distal nephron that are responsible for regulating final salt balance on a day-to-day basis when dietary sodium intake is high and potassium intake is low.
APICAL ACCUMULATION OF ENaC AND ROMK INDUCED BY LOW DIETARY SODIUM INTAKE AND HIGH POTASSIUM INTAKE IS INITIATED IN THE LATE DCT AND THE CNT

The adaptations of the aldosterone-sensitive distal nephron to variations in dietary sodium and potassium intakes include short-term regulation that typically consists of posttranslational modifications and trafficking of the ion transport systems between intracellular compartments and the plasma membrane, as well as long-term regulation involving changes in the abundance of these systems (21, 42, 77, 88). The activity of ENaC in the apical membrane largely determines the rate of transepithelial sodium reabsorption in the late DCT, the CNT and the cortical collecting duct (CCD). The activity of the channel is positively correlated with plasma levels of aldosterone and inversely correlated with dietary sodium intake (3, 25, 27, 65). Control of the number of functional channels present in the apical membrane appears to be the principal mechanism by which aldosterone (or dietary sodium intake) influences ENaC-mediated sodium transport (5, 9, 32, 67). The abundance of the α-subunit is controlled by both changes in its synthesis rate and its insertion or retrieval to or from the apical membrane, whereas the abundance of the β- and γ-subunits is mainly regulated by their shifts between intracellular compartments and the apical membrane without substantial change in their synthesis rates (49, 58). The retrieval of ENaC from the apical membrane is mediated by Nedd4–2, which can interact with the PY domains of the β- and γ-subunits (38). The phosphorylation of Nedd4–2 by Sgg1, whose expression is rapidly and strongly induced by aldosterone (12, 62), prevents this interaction and increases ENaC cell-surface expression (38, 81). Thus when rodents are switched from high to low dietary sodium intake, the increase in plasma aldosterone level triggers a marked accumulation of ENaC in the apical membrane of the late DCT, the CNT, and the CCD, which, together with an upregulation of Na-K-ATPase activity (21), greatly raises the capacity of these nephron segments to reabsorb sodium (58). Low sodium intake and high plasma aldosterone levels also provoke a marked increase in the abundance of NCC that further enhances the sodium reabsorption capacity in the DCT (42).

An important observation is that when mice are chronically fed a moderately low-sodium diet (0.05%), the apical accumulation of ENaC is very strong in the CNT and is much less pronounced in the CCD (49). This latter segment becomes involved only when the mice are challenged with very low sodium intake (0.001% or less). Apparently, the apical recruitment of ENaC is initiated in the late DCT and the CNT, and these two segments are able to reabsorb enough sodium to compensate for a moderately low-sodium diet (Fig. 2). Similarly, in adrenalectomized rats, aldosterone infusion induces, within a few hours, a shift of ENaC to the apical membrane in the late DCT and the CNT but not in to the CCD (51).

Analogously, in NCC-deficient mice, constitutively elevated plasma aldosterone levels due to defective sodium reabsorption in the early portion of the DCT are associated with an increased apical localization of ENaC in the CNT but not in the CCD (50). The important role of the CNT in the final adjustment of urinary sodium excretion is also suggested by the presence of a decreasing gradient in the magnitude of ENaC-mediated currents between the CNT, the initial part of the collecting duct, and the CCD in aldosterone-treated rats (26).

Aside from its involvement in the maintenance of sodium balance, the aldosterone-sensitive distal nephron is also the primary site of renal potassium secretion. The activity of ROMK in the apical membrane of the DCT, CNT, and CCD is thought to determine the rate of transepithelial potassium secretion, depending on dietary potassium intake. High potassium intake has been shown to increase apical potassium conductance (66, 67, 90) and ROMK activity (68, 87). The main mechanism by which high potassium intake increases the activity of ROMK is the control of the number of functional channels in the apical membrane (88). This is achieved by a shift of the channel between intracellular compartments and the apical cell membrane, with no significant changes in its synthesis rate (28, 60). The effect of low potassium intake is less clear, as it reduces the abundance of ROMK by increasing...
endocytosis and degradation of the channel (13, 60) without affecting significantly the number of functional units in the apical membrane (70, 92). Although high potassium intake increases plasma aldosterone levels and stimulates the activity of the Na-K-ATPase (30, 82), it is unclear whether aldosterone regulates the activity of ROMK in the apical membrane. Neither the infusion of aldosterone nor low sodium intake increases the number of channels in the apical membrane of the late DCT, the CNT, and the CCD (69, 92). However, high potassium intake increases ROMK activity to a lesser extent in adrenalectomized rats than in intact rats, suggesting that aldosterone may exert a permissive effect on the activation of the channel (67). Moreover, some but not all experiments in the Xenopus laevis oocyte expression system suggest that aldosterone-induced Sgk1 can stimulate ROMK activity by increasing the cell-surface abundance of the channel (97, 98). Nevertheless, the disturbed adaptation of Sgk1-deficient mice to high potassium intake appears to be mainly due to a diminished Sgk1-dependent activation of ENaC rather than to a reduced activity of ROMK, whose apical abundance in the collecting system is actually increased compared with wild-type mice (33). A clearer mechanism underlying the retrieval and translocation of ROMK from and to the apical membrane seems to involve the phosphorylation state of its COOH terminus, which is controlled by protein tyrosine phosphatases and by protein tyrosine kinases such as c-Src and c-Yes, the abundance of the latter being modulated by dietary potassium intake (47, 88, 89). ROMK trafficking is also regulated by protein kinase C, which can phosphorylate the channel and influence its export from the endoplasmic reticulum to the cell membrane (46). However, the physiological significance of this latter pathway is still unclear as neither aldosterone nor dietary potassium intake has been shown to regulate the activity of protein kinase C. The overall result of these regulatory pathways is a marked increase in the abundance of ROMK in the apical membrane of the late DCT, the CNT, and the CCD when mice are subjected to high potassium intake. In association with aldosterone-dependent stimulation of Na-K-ATPase activity and ENaC-mediated electrogenic and NCC-mediated electroneutral sodium reabsorption (80), the accumulation of ROMK in the apical membrane greatly increases the capacity of these nephron segments to secrete potassium into urine. It should be mentioned that potassium secretion in these segments depends on the driving force across the apical membrane, which can be significantly increased by the activation of ENaC and the resulting apical membrane depolarization, without requiring any change in the apical potassium conductance (80). This can be related to the fact that high potassium intake triggers the apical translocation of both ROMK and ENaC in contrast to low sodium intake, which increases the apical abundance of ENaC but does not affect the subcellular localization of ROMK (52). As with ENaC, an important observation is that when the mice are fed a moderately high-potassium diet (3%), the apical accumulation of ROMK is seen predominantly in the late DCT and the CNT, the CCD becoming strongly involved only if the mice are subjected to a very-high-potassium diet (5% or more) (52). This is consistent with previous micropuncture experiments showing that increased renal potassium secretion in rats fed a moderately high-potassium diet (2%) is mainly observed along the DCT, with little contribution from the collecting duct (95).

Altogether, these results suggest that the late DCT and the CNT are the first nephron segments to be mobilized when dietary sodium or potassium intakes are modified and that they can sustain sufficiently sodium reabsorption or potassium secretion rates to compensate for moderate changes in dietary sodium or potassium intake (Fig. 2).

THE LACK OF ENaC IN THE COLLECTING DUCT DOES NOT IMPAIR ADAPTATION OF MICE TO LOW SODIUM INTAKE

A selective inactivation of the gene encoding the α-ENaC subunit in the collecting duct has been recently achieved in the mouse by using Cre-loxP technology and a tissue-specific promoter (Hoxb7) expressed along the collecting duct but not in the DCT and CNT (78). In these mice, the α-ENaC subunit is completely absent from the collecting duct, and its activity is abolished as shown by immunodetection of the α-, β-, and γ-subunits and by measurement of amiloride-sensitive current at the single-cell level. In these conditions, when the mice are subjected to very low sodium intake (<0.001%), the apical accumulation of ENaC is strictly limited to the late DCT and the CNT (Fig. 3). Despite the lack of ENaC recruitment in the CCD, the mice are still able to adapt to this very low sodium intake as shown by the absence of the salt-losing syndrome.
This is in sharp contrast to another mouse model, in which the α-ENaC subunit level is decreased to 1% of that of the wild-type along the entire aldosterone-sensitive distal nephron. These mice grow normally on a high-sodium diet (0.3%) but cannot tolerate a very-low-sodium diet (0.01%), which triggers a rapid and marked salt-losing syndrome (72). These results show that even in the absence of any ENaC activity in the CCD, mice can still appropriately increase renal sodium reabsorption, which stresses the importance of the late DCT and the CNT and the relatively negligible role of the collecting duct for achieving sodium balance. However, additional studies will be needed to determine whether the selective inactivation of the α-ENaC subunit in the collecting duct does not modify the minimum urinary sodium concentration (and maximum potassium concentration) that can be reached in mice.

**THE LATE DCT AND CNT HAVE VERY LARGE SODIUM AND POTASSIUM TRANSEPITHELIAL TRANSPORT CAPACITIES COMPARED WITH THE COLLECTING DUCT**

Several lines of evidence point to the fact that, compared with the DCT and CNT, the collecting duct may play a minor role in sodium conservation or potassium secretion. First, Na-K-ATPase activity measured in isolated nephron segments and expressed as picomoles $[^{32}\text{P}]\text{Pi}$ released per millimeter tubule length per hour has been demonstrated to be several-fold higher in the DCT and CNT than in the collecting duct (26). Accordingly, the rate of sodium transport measured in isolated, perfused nephron segments and expressed as picomoles $^{22}\text{Na}$ per millimeter tubule length per hour has been found to be much higher (at least a 10-fold}

**Fig. 3.** α-ENaC location along the aldosterone-sensitive distal nephron in sodium-depleted mice with a selective inactivation of the α-ENaC gene in the collecting duct. After 1 wk with very low sodium intake (< 0.001%), the apical accumulation of α-ENaC is observed in the late DCT and the CNT but ceases abruptly at the transition from the CNT to the CCD (arrows). The presence of the CCD is confirmed by aquaporin-2 (AQP2) immunostaining. AQP2-negative cells in the CNT and CCD are intercalated cells. The data have been obtained by immunofluorescence on consecutive cryosections with rabbit antibodies against α-ENaC or AQP2. P, proximal tubule. Scale bar = 20 μm. Adapted from Ref. 75.

**Fig. 4.** Na-K-ATPase activity profile in rabbit, rat, and mouse nephron. The activity has been determined in isolated nephron segments with a method that measures labeled inorganic phosphate released by the hydrolysis of $[^{32}\text{P}]\text{ATP}$ (expressed as pmol $[^{32}\text{P}]\text{Pi}$ released $\times h^{-1}$). In these experiments, the DCT and CNT have not been separated and are designated together as DCT. PCT, proximal convoluted tubule; PR, pars recta; TDL, thin descending limb; TAL, thin ascending limb; MAL, medullary thick ascending limb; CAL, cortical thick ascending limb; CCT, cortical collecting tubule; MCT, medullary collecting tubule. Adapted from Ref. 37.

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SEVERAL REGULATORY PROTEINS LINKED TO HYPERTENSIVE STATES ARE LOCALIZED IN THE DCT AND CNT RATHER THAN IN THE COLLECTING DUCT

Long-term regulation of blood pressure has been shown to be critically dependent on the control of renal sodium excretion and extracellular fluid volume (29, 45). In this context, it is noteworthy that several regulatory proteins causing hypertension when they are defective, or being abnormally expressed in hypertensive states, are mainly localized in the DCT and CNT with no or little expression in the collecting duct (Fig. 1). This is the case of the recently described serine-threonine kinases termed “with no lysine” (WNK) due to their lack of a lysine residue usually conserved in the catalytic domain of serine-threonine kinases (85). Mutations in the genes encoding WNK1 and WNK4, two members of the human WNK family, are responsible for an autosomal dominant form of low-renin hypertension associated with hyperkalemia, metabolic acidosis, hypercalciuria (in some, but not all pedigrees), and an enhanced sensitivity to thiazide diuretics (93). These features, which are the opposite of those resulting from the presence of inactivating mutations in the gene encoding NCC, suggest that the primary defect is an increased NCC-mediated sodium reabsorption in the DCT. Although genetic analyses have excluded NCC itself as being directly involved in the cases studied so far, this hypothesis is corroborated by in vitro experiments showing that the kinase domain of WNK4 decreases the surface expression and the activity of NCC and that WNK1 prevents WNK4 inhibition of NCC via an auto-inhibitory domain (94, 96). The hypothesis is also consistent with the nature of the mutations described in the WNK4 and WNK1 genes. The missense mutations that are clustered in highly conserved domains of WNK4, close to coiled-coil domains usually involved in interactions with other protein partners, would preclude the inhibitory action of the kinase on NCC, whereas the large deletions in the first intron of the WNK1 gene seem to result in higher levels of expression of the kinase, thus also preventing the inhibitory action of WNK4 on NCC (93, 94, 96).

Although WNK4 is present all along the aldosterone-sensitive nephron segment, the kinase localizes with the tight junctions in the DCT, whereas it is cytoplasmic in the CCD, suggesting that it plays different roles in the two segments or that its recruitment is limited to the DCT in the environmental conditions prevailing in these studies. In addition to regulating NCC, in vitro experiments indicate that WNK4 inhibits ROMK-mediated potassium currents by decreasing the surface expression of the channel (37). Interestingly, the mutations described in the WNK4 gene increase the kinase-mediated inhibition of ROMK activity, at least in the X. laevis oocyte expression system (37). The resulting higher ROMK activity may contribute to the hyperkalemia associated with the inhibition of NCC. However, the hyperkalemia might also be secondary to a decrease in potassium secretion in the CNT and CCD, where ENaC-mediated sodium reabsorption is diminished as a result of the lowered plasma aldosterone levels and the reduced sodium delivery to the tubular segments downstream of the DCT. Nevertheless, these results suggest that WNK4 is a regulator that can directly or indirectly vary the balance between sodium reabsorption and potassium secretion in the aldosterone-sensitive distal nephron. The case of WNK1 is also revealing: the gene comprises three promoters generating two isoforms with a complete kinase domain and a short isoform lacking the kinase domain but still able to prevent WNK4 inhibition of NCC via its auto-inhibitory domain (14, 63). The short kinase-defective isoform is kidney specific like WNK4, but it localizes exclusively in the DCT, where its expression level is highly preponderant compared with the other WNK1 isoforms (63; and Jeunemaitre X, personal communication). Thus it appears that this kidney-specific isoform is the major product of the WNK1 gene that would be upregulated by the large deletions in the first intron, with a resulting increased inhibition of WNK4 limited to the DCT.

Tissue kallikrein is another example of a regulatory protein whose expression in the aldosterone-sensitive distal nephron is mostly restricted to the late DCT and the CNT (22, 23, 64), with very low levels in the collecting duct (73). Although tissue kallikrein is probably not a primary controller of blood pressure (59), low synthesis rate and urinary excretion of the enzyme have been repeatedly and consistently linked to elevated blood pressure in animals and humans (6, 56, 57), indicating that the late DCT and the CNT are highly reactive to the renal defects associated with or causing hypertension. In addition, the synthesis of tissue kallikrein is strongly induced by elevated dietary potassium intake, suggesting that the enzyme may play a role in the adaptive response of these nephron segments to increasing potassium secretion into urine (34, 35, 86). Interestingly, it has been recently shown that the epithelial cells that synthesize tissue kallikrein also express renin as part of a paracrine tubular renin-angiotensin system operating downstream of the macula densa (75, 76). The expression of renin in the CNT, which is modulated by dietary sodium intake and can affect ENaC activity via the generation of angiotensin II (7, 44, 71), emphasizes again the central role of this segment in the coordinated regulation of sodium reabsorption and potassium secretion.

Concerning the aldosterone signaling pathway, which has been linked to blood pressure disorders (45), the expression of the MR and 11β-HSD2 is not limited to the DCT and CNT and...
extends to the collecting duct. However, the important role of the DCT is underlined by micropuncture and expression-profiling experiments showing that NCC is a target for aldosterone-mediated transport regulation (40, 84) and is critically involved in mineralocorticoid escape and pressure-natriuresis (91).

Although the presence of several regulatory proteins linked to hypertensive states in the DCT and CNT, sometimes exclusively, clearly suggests a pivotal role of these nephron segments in blood pressure disorders, it does not rule out the involvement of the collecting duct. Indeed, this latter segment may also participate in the increase in systemic sodium and blood pressure levels induced by a gain of function in the sodium transport systems or regulatory proteins whose expression extends to the collecting duct (ENaC, Na-K-ATPase, MR, 11β-HSD2, Sgk1, WNK4).

CURRENT DIETARY SODIUM AND POTASSIUM INTAKES IN WESTERNIZED SOCIETIES ARE LIKELY TO MOBILIZE ONLY THE DCT AND CNT

All the regulatory mechanisms may not be identical among rats, mice, and humans, but the general structure of the aldosterone-sensitive distal nephron is very similar in these different species (8). It is therefore possible, based on the observations reported above, that the high sodium and low potassium intakes currently observed in Westernized populations are handled almost entirely by the DCT and CNT, with little involvement of the collecting duct. Indeed, the current sodium and potassium intakes are very different from the physiological intakes that have prevailed during mammalian evolution. The food consumed by terrestrial mammals, including primates, never contained a lot of sodium. Except in rare cases, plants contain only traces of sodium and the consumption of very large amounts of fruits, roots, leaves, and seeds did not present much sodium to the organism. For omnivorous and carnivorous species, the occasional or regular absorption of meat increases sodium intake but in limited proportions, because the consumed meat corresponds most often to the sodium-poor intracellular medium and not to the sodium-rich extracellular medium that is generally lost when the animal is killed or cooked. For example, a chimpanzee in Gabon or a Yanomamo Indian in the Amazon, who almost exclusively eats plants, ingests 1–10 meq sodium/day. The diet of a Bushman in Botswana or an Eskimo in Alaska, which usually used to feed them is relatively rich in sodium (0.3%) and poor in potassium (0.9%) and does not favor the recruitment of the collecting duct for reabsorbing sodium and secreting potassium.

This dietary shift, which is unique to the human species, was rapid in evolutionary terms and therefore unlikely to have been accompanied by a corresponding genetic adaptation. Indeed, given the low spontaneous mutation rate of nuclear DNA in mammals, no significant accumulation of mutations or polymorphisms can arise in such a short period of time for adapting a species to a new environment (17, 19). Therefore, our genetic makeup is probably still adapted to a diet poor in sodium and rich in potassium that has been the rule for the dozen million years during which mammalian evolution took place. During this evolution, species, including the human species, have accumulated mutations and polymorphisms to survive on this diet. The discrepancy between our genes and our present-time diet may explain the detrimental effect of high sodium and low potassium intakes on the development of hypertension and cardiovascular diseases (31, 53). In this context, it is particularly revealing that most of the genes identified in humans and mice as controllers of blood pressure are precisely the genes involved in renal sodium and potassium handling (45).

CONCLUDING REMARKS

The data presented in this review suggest that sodium reabsorption and potassium secretion in the DCT and CNT are populations to a present range of 1–4 (10- to 400-fold increase) in Westernized societies (18, 24) (Fig. 5). In this new environment, the kidneys have a minimal need to reabsorb sodium and to secrete potassium, which can be easily fulfilled by the DCT and CNT, in contrast to the ancient environment, in which the collecting duct was perhaps necessary to achieve high sodium reabsorption and high potassium secretion rates. It should be also mentioned that the physiological needs of the mammalian species studied in the laboratory (rodents, pigs, primates) are probably similar to human requirements (15) and that the diet usually used to feed them is relatively rich in sodium (0.3%) and poor in potassium (0.9%) and does not favor the recruitment of the collecting duct for reabsorbing sodium and secreting potassium.

Fig. 5. Exchange of potassium for sodium in the diet of Westernized societies. The transition from hunter-gatherer populations to modern societies was accompanied by a large reduction in potassium intake from 230–300 to 70–80 meq/day. As a result, the sodium/potassium ratio in the diet changed from a range of 0.01–0.1 in the hunter-gatherer populations to a range of 1–4 (10- to 400-fold increase) in Westernized societies. Adapted from Ref. 23.
sufficient to maintain sodium and potassium balance, with little or no contribution of the collecting duct. The homeostatic role of the sodium and potassium transport systems in the collecting duct can be questioned, especially in conditions where dietary sodium intake is high and potassium intake is low compared with the physiological needs of the organism. In these conditions that prevail in our current environment, it is possible that a large proportion of the aldosterone-regulated sodium reabsorption and potassium secretion occurs in the DCT and CNT before the tubular fluid reaches the collecting duct. The main difference between the functions of the late DCT and the CNT compared with those of the collecting duct is more quantitative than qualitative, the latter nephron segment coming into play when the upstream segments become overloaded by a primary genetic defect or by a diet poor in sodium and rich in potassium. It is probable that the physiological and pathological roles of the DCT and CNT, which are technically difficult to study, have been underestimated whereas the role of the more easily accessible collecting duct has been overemphasized. Nevertheless, the important role of the collecting duct in the control of acid-base balance, urea excretion, and vasopressin-mediated regulation of water balance and systemic toxicity should not be neglected (10). In fact, the ion transport capacity of the collecting duct may depend on the state of hydration of the body. Isolated, perfused studies in rats have demonstrated that the collecting duct does not transport a large quantity of sodium and potassium, even with long-term mineralocorticoid exposure, but that its transport capacity is strongly stimulated by vasopressin (74, 83). These considerations suggest that the collecting duct may have little physiological role except when circulating vasopressin levels are elevated, i.e., when the body is partially dehydrated. As such, the role of the collecting duct would be revealed when the requirement for sodium and water conservation is maximal.

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