Vasopressin regulates the renal Na\textsuperscript{+}-Cl\textsuperscript{−} cotransporter

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The renal thiazide-sensitive Na\textsuperscript{+}-Cl\textsuperscript{−} cotransporter (NCC) is the major salt reabsorption pathway in the distal convoluted tubule (DCT), a region of the nephron that is located beyond the macula densa. Because of this location, salt reabsorption in DCT is not subjected to the tubular-glomerular balance mechanism, affecting the final concentration of salt in urine and, thus, arterial blood pressure. Additionally, salt reabsorption in DCT is essential to define the amount of salt delivery to the collecting duct, which is required for the Na\textsuperscript{+}/K\textsuperscript{+} exchange between the epithelial Na\textsuperscript{+} channel (ENaC) and the apical K\textsuperscript{+} channels ROMK and BK to promote K\textsuperscript{+} secretion regulation. These roles of NCC in blood pressure and K\textsuperscript{+} secretion regulation have been demonstrated extensively. On one hand, inactivating mutations of the SLC12A3 gene encoding NCC produce Gitelman’s disease that features arterial hypotension and hypokalemia. On the other hand, dysregulation of NCC by mutations in the with-no-lysine serine/threonine kinases WNK1 and WNK4 is the major mechanism producing arterial hypertension and hyperkalemia in pseudohypoaldosteronism type II (10). Thus NCC activity is critical to define arterial blood pressure levels and K\textsuperscript{+} secretion; therefore, a lot of attention has been given in the last years to regulatory mechanisms of this cotransporter. It is widely accepted that NCC is regulated by both aldosterone and ANG II. Aldosterone modulates NCC activity by increasing its expression (9). This is an effect that is likely to be more important for DCT2, rather than DCT1, since the early DCT lacks expression of 11β-hydroxysteroid dehydrogenase type 2 (11HSD2). ANG II, in contrast, regulates NCC activity by increasing its expression (9). This is an effect that is likely to be more important for DCT2, rather than DCT1, since the early DCT lacks expression of 11β-hydroxysteroid dehydrogenase type 2 (11HSD2).

Aldosterone, atrial natriuretic peptide, catecholamines, etc., vasopressin does it by modulating both vascular smooth muscle contraction and urinary salt/water reabsorption. These effects are traduced in the smooth muscle and renal tubular cells through the G\textsubscript{a} coupled receptors V\textsubscript{1} and V\textsubscript{2}, respectively. In the kidney, vasopressin is known to modulate the activity of NKCC2, ENaC, and aquaporin 2. Its effects in DCT, however, have not been clearly demonstrated. Studies from Elalouf et al. (5) using micropuncture in homozygous diabetes insipidus (DI) Brattleboro rats strongly suggested that vasopressin increases salt reabsorption in DCT. Mutig et al. (11) demonstrated by in situ hybridization and immunohistochemistry of human, mouse, and rat kidney the presence of the V\textsubscript{2} mRNA and protein in DCT1. The study of vasopressin on the NCC, however, has been limited by the absence of reliable cultured cell lines from DCT.

In the American Journal of Physiology-Renal Physiology, the study of Mutig et al. (12) for the first time provides direct evidence of NCC regulation by vasopressin, taking advantage of the molecular tools that have been developed to study NCC regulation/phosphorylation. Short-term stimulation of NCC by vasopressin in physiological or pharmacological doses was assessed in DI Brattleboro rats 30 min after intraperitoneal injection of desmopressin (dDAVP). Using confocal microscopy, immunogold staining of NCC in electron microscopy analysis, and Western blot of vesicle-enriched fraction, the authors observed that dDAVP administration was associated with significant trafficking of NCC toward DCT apical plasma membrane. With the aid of phosphospecific antibodies recognizing phosphorylation of NCC threonine-53 or serine-71, it was demonstrated that dDAVP administration resulted in increased phosphorylation of these residues. Next, the authors observed that dDAVP administration resulted in increased phosphorylation of these residues. Next, the authors observed that dDAVP administration resulted in increased phosphorylation of these residues. Finally, consistent with the previous observation that V\textsubscript{2} receptors are more abundant in DCT1 than in DCT2 (11), it was observed that dDAVP-induced phosphorylation of NCC serine-71 was confined to DCT1, since 11HSD2-positive DCT2 cells showed no major change in pS71 NCC after dDAVP administration. Thus, although aldosterone seems to be a regulator of NCC in DCT2, vasopressin probably affects NCC activity only in

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DCT1, suggesting a fine tune of regulation of NCC in two different cells.

The observations presented in the American Journal of Physiology-Renal Physiology by Mutig et al. (12) resolve with reasonable degree of certainty the question of the vasopressin effect on NCC activity. With these observations, it is now known that vasopressin modulates renal salt/urea/water transport all the way from the loop of Henle to the inner medullary collecting duct. Several issues rise with these observations that will be testable in the future. One is to find out if the vasopressin effect on NCC phosphorylation/trafficking also involves modulation of the WNKs-SPAK/OSR1 pathway. Phosphorylation of NCC and NKCCs in the conserved NH2-terminal threonines seems to be a common final pathway of several stimuli, including, for instance, intracellular Cl− depletion (2, 13, 14), WNKs (8, 16, 19, 21), SPAK (15), growth hormone (3), salt depletion/ANG II (1, 17), and vasopressin (7, 12). It is going to be interesting to find out if activation of a Gs-coupled receptor, like V2, can eventually modulate WNKs/SPAK interaction to phosphorylate NCC or if NH2-terminal threonines of NCC can be a target of another kinase. Another interesting issue to be resolved is to what extent the effect of vasopressin on NCC is solely by activation of the V2 receptor or if activation of other hormonal systems (perhaps ANG II, aldosterone, cortisol, catecholamines) is also involved. Finally, a third type of studies will be required to integrate the vasopressin effect on NCC to define the hierarchy of each of the components within the redundancy of the modulator mechanism.

REFERENCES


