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Renal Sodium Transporters and Water Channels

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▌ABSTRACT▌

Hypertension is closely related to salt and water retention. The kidney plays an important role in the blood pressure regulation primarily to modulating tubular sodium and water reabsorption. The regulation of the salt and water balance depends upon an array of solute and water channels in the renal tubules. An altered regulation of sodium and water channels in the kidney may be related to various pathological conditions associated with altered salt and water retention. This review will discuss renal handling of sodium and water, with particular emphasis on aquaporins and renal sodium transporters and channels.

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Key Words: Aquaporins; Sodium; Membrane transport proteins; Kidney

Introduction

The kidney plays a central role in the regulation of the salt and water balance, which depends upon an array of solute and water channels in the various regions of the kidney. Between 90% and 99% of filtered sodium is reabsorbed along the renal tubules. Approximately 60% to 70% of the filtered load of sodium is absorbed in the proximal tubules. The remaining 30% to 40% is delivered to the thick ascending limb, where, as much as 20% to 30% of delivered sodium is absorbed in the absence of water reabsorption. The distal convoluted tubule and the collecting duct are each responsible for 5% to 10% of sodium reabsorption.[1,2)]

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Aquaporins facilitate the transport of water and, in some cases, other small uncharged solutes, such as glycerol, CO_2, ammonia, and urea, across the membrane depending on the size of the pore. Seven aquaporins are known to be expressed in the kidney where they not only facilitate osmotic water transport across water-permeable epithelia, but also play critical roles in the urinary concentration and dilution process.[2,3)]

Renal sodium transporters

Renal sodium absorption is mediated by membrane-transport proteins, which facilitate sodium movement across the plasma membranes of renal epithelial cells. The major apical sodium transporters are as follows: in the proximal tubule, the type 3 Na-H exchanger (NHE-3), Na-glucose cotransporters, and the type 2 sodium-phosphate cotransporter (NaPi2); in the thick ascending limb, the sodium-potassium chloride co-

Table 1. Renal sodium transporters and channels

Protein	Localization	Transport	Physiology
Sodium-protein exchanger type 3 (NHE-3)	PT	Na^+, H^+	ECFV, BP, acid-base regulation
Sodium-phosphate cotransporter type 2 (NaPi-2)	PT	Na^+, P^+	ECFV, BP, P+ metabolism
Sodium-potassium chloride cotransporter-2 (NKCC2)	TAL	Na^+, K^+, Cl^-	ECFV, BP
Sodium chloride cotransporter (NCC)	DT	Na^+, Cl^-	ECFV, BP
Epithelial sodium channel (ENac)	CD	Na^+	ECFV, BP

PT, proximal tubule; TAL, thick ascending limb; DT, distal tubule; CD, collecting duct; ECFV, extracellular fluid volume, BP, blood pressure.

transporter-2 (NKCC2); in the distal tubule, the sodium chloride cotransporter (NCC); and in the collecting duct, the epithelial sodium channel (ENaC) (Table 1).[1,2]

1. Proximal tubules

The NHE-3 and NaPi2 transporters are primarily located in the apical membrane of proximal tubular epithelial cells. This tubule segment plays a critical role in sodium absorption since it reabsorbs two-thirds of the glomerular filtrate. It is well known that the tubuloglomerular feedback and increased distal sodium reabsorption will compensate for any potential defects in any one component of these sodium transports.[4]

Recent studies on sodium transporters that play a major role in the increase in blood pressure in essential/polygenic hypertension.[5-6] The increase in renal proximal tubule ion transport in polygenic hypertension is primarily due to increased activity of NHE-3 and Cl/HCO_3 exchanger at the luminal/apical membrane.[5] There are persistent changes in NHE-3 and NaPi2 distributions and activity in response to chronic hypertension in spontaneous hypertensive rat.[6]

2. Henle's loop

The NKCC2 transporter is located in the apical membrane of epithelial cells of the thick ascending limb of Henle's loop and in macula densa cells. The transport of sodium in the basolateral plasma membrane along the renal tubules is facilitated by sodium potassium adenosine triphosphase. Approximately 30% of the sodium filtered in the glomerulus is reabsorbed in this segment.[1,4] Angiotensin-II, vasopressin, and parathyroid hormone increase sodium reabsorption while prostaglandin E2, endothelin-1, and nitric oxide decrease it. There exists a family of with no lysine (K) (WNK) serine-threonine kinases that play a critical role in regulating sodium transport not only in the thick ascending limb, but also in the distal tubule and collecting duct.[7]

NKCC2 knockout mice manifest severe polyuria and die of dehydration shortly after birth. There are several described mutations in the NKCC2 gene that can result in a loss of protein function, thereby causing Bartter syndrome, which is characterized by a large loss of salt in the urine, hypotension, hypokalemia, and hypercalciuria.[8] Several studies have suggested an association between increased activity of the NKCC2 transporter and hypertension. Pseudohypoaldosteronism (PHA) type II, also known as Gordon syndrome, stems from mutations in WNKs and results in an inherited form of salt sensitive hypertension.[9]

3. Distal tubule

The NCC is located in the apical membrane of distal tubule cells. Approximately 5% to 10% of the sodium filtered in the glomerulus is reabsorbed in this segment. NCC is regulated by WNK. Plasma membrane abundance

and phosphorylation of NCC are increased by aldosterone, angiotensin-II, estradiol, and vasopressin.[1] NKC knockout mice manifest a Gitelman syndrome, which is characterized by hypotension, hypokalemic alkalosis, hypocalciuria, and magnesium wasting.[10] Mutations in the WNK kinases that result in hyperactivity of the NCC, which is characterized by hypertension, hyperkalemia, metabolic acidosis and normal renal function, Gordon syndrome, or PHA type II.[7,11]

4. Collecting tubule

ENaC is constitutively expressed in the apical membranes of connecting and collecting tubule epithelial cells. The collecting duct is responsible for the reabsorption of nearly 3% to 5% of the sodium filtered.[1] Aldosterone is the principal hormone regulating ENaC. Angiotensin-II, vasopressin, insulin, and insulin-like growth factor I appear to regulate ENaC.[12,13] Serum and glucocorticoid-induced kinase 1 (SGK1) activates the ENaC in tubules. The aldosterone-activated mineralocorticoid receptor increases SGK1 gene transcription in the cortical collecting ducts (CCD), and SGK1, in turn, strongly stimulates the activity and expression of the ENaC and NHE-3.[14-16] The abundance of SGK1 in rat kidney may play a role in salt adaptation and the pathogenesis of hypertension.[17]

Increased ENaC activity of mutations in the β- and γ -subunits of ENaC causes Liddle syndrome, an autosomal dominant disease characterized by hypertension, metabolic alkalosis, low renin, low aldosterone, and volume expansion.[18]

ENaC plays a role in the development of hypertension, particularly in salt-sensitive hypertension.[12,13] High-salt intake in the salt-sensitive population induces oxidative stress in the kidney, which enhances the apical membrane expression of ENaC and ENaC activity with an unknown mechanism. This increased activity eventually causes sodium overreabsorption in CCD followed by water retention and elevation of blood pressure (BP). The volume expansion in the vascular compartment alters blood flow (shear stress) and directly affects endothelial function by reducing the synthesis of nitric oxide.[19]

Renal water channels (aquaporins)

The chief regulator of water excretion is the peptide hormone vasopressin, whereas the chief molecular target for regulation is the water channel aquaporin-2. Aquaporin-1, -2, -3, -4, -6, -7, and -11 are known to be expressed in the kidney where they not only facilitate osmotic water transport across water-permeable epithelia, but also play

Table 2. Renal water channels

Protein	Localization	Transport	Physiology
Aquaporin-1	Apical and basolateral plasma membrane of PT, thin limb of Henle's loop cells and descending vasa recta	Water	Urine concentration, cell migration
Aquaporin-7	Apical plasma membrane of PT (S3)	Water, anion, glicerol	Water reabsorption, glycerol reabsorption
Aquaporin-11	Endoplasmic reticulum of PT	Water	Organelle maintenance
Aquaporin-2	Apical plasma membrane and intracellular vesicle of CD principal cell	Water	Urine concentration
Aquaporin-3	Basolateral plasma membrane and intracellular vesicle of CD principal cell	Water and urea	Urine concentration
Aquaporin-4	Basolateral plasma membrane and intracellular vesicle of CD principal cell	Water	Urine concentration
Aquaporin-6	Intracellular vesicles of CD intercalated cells	Water, anion, glicerol	Urine concentration, acid secretion

PT, proximal tubule; CD, collecting duct.

critical roles in the urinary concentration and dilution process.[2,3] The water permeability of renal tubules is mainly dependent upon the amount of aquaporins located at the membrane of the epithelial tubular cells. There are no water channels at the thick ascending limb and the distal tubule which are impermeable to water.(Table 2)

1. Proximal tubule

Aquaporin-1 is a constitutive water channel localized in the apical and basolateral membranes of the proximal tubules, in the descending limb of Henle's loop cells, and in the descending vasa recta. As aquaporin-1 facilitates the reabsorption of water in these tubule sections, it plays an important role in the countercurrent multiplication process needed to concentrate urine.[3,20,21] Aquaporin-7 is expressed in the brush borders of proximal straight tubules, where it facilitates glycerol and water transport. Aquaporin-11 is expressed in the endoplasmic reticulum of proximal tubule cells.[2,3]

2. Collecting tubule

Aquaporin-2 is found exclusively in collecting duct principal cells, specifically in the apical membrane and in intracytoplasmic vesicles.[22] Vasopressin is the main hormonal regulator of aquaporin-2. Binding of vasopressin to V2 receptors in the basolateral membrane stimulates adenylate cyclase producing cyclic adenosine monophosphate and protein kinase A. Short-term vasopressin exposure results in trafficking of subapical vesicles containing aquaporin-2 to the apical plasma membrane, whereas long-term exposure causes a marked increase in the aquaporin-2 whole-cell abundance via regulation of aquaporin-2 gene transcription and protein degradation.[22-24]

Mutations in aquaporin-2 cause congenital diabetes insipidus, which is characterized by an inability to concentrate urine despite normal or elevated vasopressin plasma levels, thus leading to polyuria and polydipsia.[25] Several situations have been linked to altered aquaporin-2 trafficking or with the downregulation of protein expression; these include lithium treatment, hypokalemia, hypercalcemia, ureteral obstruction, nephritic syndrome, liver cirrhosis, and congestive heart failure.[26-31]

Aquaporin-3 is constitutively localized in the basolateral membrane of the principal cells of the collecting ducts. Aquaporin-4 is constitutively localized in the basolateral plasma membrane of principal cells and inner medullary collecting duct cells. Aquaporin-6 is localized in the intracellular vesicles of acid-secreting a-intercalated cells in the collecting ducts. As this water channel has low water permeability, acting mainly as an anion transporter, it is thought to be involved in urinary acid secretion.[2,3]

Dysregulation of the expression/shuttling of the renal ENaC and the aquaporin-2 has been suggested to play a role in the pathogenesis of essential hypertension. An increased expression of ENaC subunits and an increased expression and apical targeting of aquaporin-2 (AQP2) has been reported in spontaneous hypertensive rats, an experimental model of hypertension.[32] The urinary aquaporin-2 excretion was abnormally increased in response to hypertonic saline in essential hypertension.[33] These results suggest that an abnormal regulation of the expression/shuttling of AQP2 and/or ENaC could be involved in the pathogenesis of essential hypertension. Several studies suggest excessive vasopressin-dependent ENaC stimulation could be a risk factor for sodium and water retention and resulting increase in BP.[34]

Conclusion

The kidney plays an important role in the BP regulation primarily to modulating tubular sodium and water reabsorption. The regulation of the salt and water balance

is complex and depends upon an array of sodium and water channels in renal tubules. An altered regulation of sodium and water channels in the kidney may be related to various pathological conditions associated with altered salt and water retention. Understanding the physiologic regulation of sodium and water channel in the kidney will provide insights into the sodium and water balance.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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