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The regulation of proximal tubular salt transport in hypertension: an update

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Abstract

Purpose of review—Renal proximal tubular sodium reabsorption is regulated by sodium transporters, including the sodium glucose transporter, sodium amino acid transporter, sodium hydrogen exchanger isoform 3 and sodium phosphate cotransporter type 2 located at the luminal/apical membrane, and sodium bicarbonate cotransporter and Na⁺/K⁺ATPase located at the basolateral membrane. This review summarizes recent studies on sodium transporters that play a major role in the increase in blood pressure in essential/polygenic hypertension.

Recent findings—Sodium transporters and Na⁺/K⁺ATPase are segregated in membrane lipid and nonlipid raft microdomains that regulate their activities and trafficking via cytoskeletal proteins. The increase in renal proximal tubule ion transport in polygenic hypertension is primarily due to increased activity of NHE3 and Cl/HCO₃⁻ exchanger at the luminal/apical membrane and a primary or secondary increase in Na⁺/K⁺ATPase activity.

Summary—The increase in renal proximal tubule ion transport in hypertension is due to increased actions by prohypertensive factors that are unopposed by antihypertensive factors.

Keywords

hypertension; kidney; proximal tubule; sodium transporter

Introduction

The long-term regulation of blood pressure is accomplished by both renal and nonrenal mechanisms [1,2]. Abnormalities in renal epithelial ion transport play important roles in the pathogenesis of essential hypertension, especially in salt-sensitive hypertension [3]. The increase in blood pressure in response to an increase in sodium in the diet depends on the intake of sodium as halide salts and ethnicity. Sodium bicarbonate (NaHCO₃) and other nonchloride salts of sodium may not elevate blood pressure in humans and rodents [4]. However, in severely salt-sensitive blacks, sodium bicarbonate can increase blood pressure [5]. The renal proximal tubule, comprising the proximal convoluted tubule (S1 and S2 segments) and the proximal straight tubule (S3 segment), is responsible for 65–70% of filtered sodium and water reabsorption under normal conditions. The S1 and S2 segments have greater rates of solute and water reabsorption than the S3 segment. The reabsorption rate of HCO₃⁻ is higher in the first half whereas the reabsorption of chloride is higher in the later half of the proximal tubule. Tubular fluid osmolality falls along the tubule and becomes hypotonic, and the reabsorbate (in the peritubular capillary) becomes slightly hypertonic,

which increases water reabsorption. This is due to the preferential reabsorption of Na^+ with HCO_3^- and organic solutes in the first half of the proximal tubule.

A decrease or an increase in proximal tubular sodium transport can be compensated by changes in transport in more distal nephron segments, as well as by appropriate adjustments of glomerular filtration rate, via tubuloglomerular feedback. Nevertheless, changes in renal proximal sodium transport, independent of more distal nephron segments, can ultimately affect extracellular fluid volume and consequently blood pressure.

Sodium transport initially occurs at the apical membrane of the proximal tubule, therefore making apical sodium transport critical in the regulation of extracellular fluid volume and ultimately blood pressure. Indeed, in polygenic human essential hypertension, the major increase in sodium transport occurs at the proximal tubule and thick ascending limb of Henle [6,7,8*] rather than in more distal nephron segments, that is characteristic of monogenic hypertension [9*]. In some experimental models of essential hypertension, increased transport in distal convoluted tubule may also occur [10*].

The importance of proximal tubule sodium transport in the regulation of blood pressure has come from gene-silencing studies. The angiotensin type 1 receptor (AT_1R) increases sodium transport in the proximal tubule; silencing of the angiotensin type 1A receptor ($\text{AT}_{1\text{A}}\text{R}$) gene selectively in the proximal tubule in mice is associated with low basal blood pressure [11]. In contrast, silencing of the aromatic amino acid decarboxylase (AADC) gene in the renal proximal tubule in mice results in salt-sensitive hypertension [12]. AADC in the renal proximal tubule is rate limiting in the production of dopamine which decreases sodium transport [12].

About two-thirds of fluid transport across the proximal tubule occurs by active transport. The sodium transport in proximal tubules occurs via sodium glucose transporter (SGLT), sodium amino acid transporters, sodium hydrogen exchanger isoform 3 (NHE3, SLC9A3), sodium phosphate cotransporter type 2 (NaPi2, SLC34A3) at the apical membrane, as well as sodium–potassium–adenosine triphosphatase ($\text{Na}^+/\text{K}^+\text{ATPase}$, primary active) and sodium bicarbonate cotransporter (NBC, SLC4A4) at the basolateral membrane. The amount of transport is regulated by physical factors, including flow sensors and hormonal/humoral agents (see Tables 1 and 2). Renal cilia serve as sensors that respond to changes in tubular flow [13]. The activity of transporting proteins is regulated not only by their inherent activity (activity per transporter) but also by their abundance and subcellular distribution. In general, activity is greatest when the proteins are expressed in the body of the microvilli. Activity is decreased following their phosphorylation and redistribution from the body to the base of the microvilli that involves the cytoskeletal and other proteins, including sodium hydrogen exchanger regulatory factor-1 (NHERF-1) for NHE3 and NaPi2 and RhoGTPase for NHE3 [14]. Recent studies have highlighted the importance of plasma membrane microdomains in the regulation of the activity of receptors and transporters [15*].

In euolemia and hypovolemia, more than 50% of proximal tubular transport is directly regulated by angiotensin II, via the AT_1R , renal nerves/sympathetic activity and indirectly via tubuloglomerular feedback. In some types of volume contraction (e.g., proteinuria), distal tubular reabsorption may be more important than proximal reabsorption [16*].

Under normal conditions volume expansion is associated with a decrease in proximal tubular reabsorption, which may be mediated by an increase in local or systemic synthesis of natriuretic agents that decrease sodium transport (e.g., angiotensin 1–7, angiotensin 2–8, dopamine, nitric oxide, ouabain) or a decrease in antinatriuretic agents that increase sodium transport [e.g., angiotensin II]. The effect of volume expansion on ET-1 production is not consistent, as both increased and decreased production has been reported. The natriuresis of

volume expansion can also be the result of acute inhibition of AT₁R function by heterooligomerization with other G protein-coupled receptors (GPCRs) that inhibit ion transport, for example, D₁ (D₁R) and D₃ (D₃R) dopamine receptor or by stimulation of the natriuretic angiotensin type II receptor (i.e., AT₂R), the activity of which can be also influenced by heterooligomerization with other GPCRs. AT₁R expression may also be decreased chronically by a reduction in its transcription or subacutely by an increase in its degradation, for example, caused by the D₅ dopamine receptor (D₅R). Sodium taken orally also provokes the release of enteral hormones that aid in the renal elimination of sodium (e.g., guanylin/uroguanylin, gastrin, cholecystokinin). More than 50% of sodium excretion following the oral or parenteral increase in sodium intake can be attributed to activation of the renal dopaminergic system [17^{*}], independent of renal innervation. In this review, we summarize recent reports on the proximal sodium transport in the regulation of blood pressure in humans and rodents. The transport of sodium coupled to the reabsorption of solutes such as amino acids and glucose is not covered in this review.

NHE3

NHE3 (SLC9A3) is the major apical sodium transporter in the proximal tubule of the kidney, and flow-modulated NHE3 activity is the mechanism for glomerulotubular balance [13]. Renal NHE3 is important in blood pressure regulation. Blood pressure is lower in renal NHE3-deficient than in wild-type mice on a normal sodium chloride diet but is normalized when fed high sodium chloride diet [18]. NHE3 is expressed along the microvilli of the brush border of proximal tubule cells [19] but can be detected in the subapical, intracellular and vesicular compartments, consistent with the regulation of its activity by membrane trafficking [20^{*}]. It is also expressed in the apical membrane of the thick ascending limb of loop of Henle [21]. About 85% of NHE3 in renal plasma membranes is expressed in lipid rafts, disruption of which decreases NHE3 activity [22]. Lipid rafts are also important in the intracellular trafficking of NHE3. However, NHE3 activity can also be regulated without changing the surface expression of NHE3 (change in turnover number). Direct and indirect binding of NHE3 to ezrin is necessary for its intracellular trafficking [23^{*}]. NHE regulatory factor-1 (NERHF-1) links NHE3 to ezrin and the cytoskeleton, which in turn are regulated by RhoGTPase [15^{*}].

Other NHE isoforms, for example, NHE1 (SLC9A1), NHE2 (SLC9A2), NHE4 (SLC9A4) and NHE8 (SLC9A8) [19,24] are expressed in the adult kidney but are of lesser abundance relative to NHE3 [24]. NHE1 is present in the basolateral membrane of most segments of the renal tubule. NHE8 is expressed in the apical membrane of renal proximal tubules in neonates [25] and aged rats [26^{*}] and has a similar function to NHE3 [26^{*},27]. However, it is mostly intracellular in adults [28^{*}].

Regulation of NHE3

Activation of the renin–angiotensin system (RAS) is associated with increased sodium transport in the renal proximal tubule, and RAS inhibition produces the opposite effect though volume depletion may negate the inhibitory effect of angiotensin-converting enzyme (ACE) inhibition on renal proximal sodium transport [29^{*}]. Angiotensin II increases NHE3 activity via AT₁R because it does not affect NHE3 activity in AT₁A_R knockout mice and renal proximal tubule cells in which the AT₁R is blocked or silenced [30]. Activation of AT₁R increases NHE3 activity by several mechanisms that include an increase in NHE3 expression in the apical membranes, which is partly related to an increase in NHE3 transcription [31] and protein trafficking. ACE inhibition, which causes a full retraction of NHE3 to the base of the microvilli, and redistribution to high-density, endosome-enriched membranes, provokes the retraction of NHERF-1 and decreases the expression of proteins needed for the apical distribution of the transporter [32^{*}]. There are tissue-specific

differences in the regulation of NHE3. In the proximal tubule, cAMP-mediated inhibition of NHE3 requires NHERF-1 whereas this is not required in the ileum [33].

Besides angiotensin II, other humoral agents can increase NHE3 expression and activity. Androgens may increase the expression of NHE3 by upregulating the proximal tubule RAS [34*]. The sympathetic nervous system, thyroid hormone [24] and insulin also increase NHE3 expression. The chronic effect of the latter is mediated by the phosphatidylinositol-3 kinase and serum-dependent and glucocorticoid-dependent kinase 1 pathway [35]. Recent studies show that thyroid hormone is important in the developmental change from NHE8 to NHE3 [36*] that is accelerated by glucocorticoids [37–39]. Aldosterone, which regulates sodium reabsorption in the distal nephron, also stimulates NHE3 activity in part by increasing its cell surface expression in human proximal tubule cells [40*]. Aldosterone also increases NHE1 activity in the renal proximal tubule cells of spontaneously hypertensive rats (SHRs) [40*].

NHE3 activity can be decreased by decreasing total cellular expression or apical membrane distribution or both. Short-term exposure of renal proximal tubules to parathyroid hormone (PTH) decreases NHE3 activity by decreasing its apical surface expression [41], whereas long-term exposure reduces NHE3 activity by decreasing NHE3 mRNA transcript levels. Chronic ouabain treatment decreases NHE3 expression in apical membranes by inhibition of transcription. However, basolateral but not apical ouabain application inhibits NHE3 activity by increasing the intracellular trafficking of NHE3 that is dependent on integrity of lipid rafts, an increase in intracellular calcium and endocytosis of Na⁺/K⁺ATPase [42*]. In contrast, increased expression of Na⁺/K⁺ATPase activates NHE3 [43].

The effect of some hormones on NHE3 can be variable depending upon the duration of exposure. Acute exposure of opossum kidney cells to ET-1, via ETB receptor, increases whereas chronic exposure decreases NHE3 activity [44]. Glucagon has opposite effects; acutely it inhibits but chronically it activates NHE3 activity in opossum kidney cells [45].

The role of nitric oxide (NO) in the regulation of NHE3 activity is difficult to decipher. The NO synthase inhibitor, NG-nitro-L-arginine methyl ester (L-NAME), abolishes the increase in NHE3 protein abundance in rats treated with aldosterone and fed high salt diet. However, L-NAME increases proximal tubular reabsorption and NHE3 protein levels in a rat model of cirrhosis [46]. The cyclooxygenase/prostaglandin pathway may also be involved in the regulation of NHE3 protein or function. Certain eicosanoids [e.g., 20-hydroxyeicosatetraenoic acid and 5,6-epoxyeicosatrienoic acid (EETs)] can modulate sodium transport in the proximal tubule. Cytochrome P450 (CYP)2J5, which is important in the production of EETs, has been shown to be involved in the regulation of blood pressure and proximal tubular transport; deletion of CYP2J5 produces sex-specific hypertension [47*].

Role of NHE3 in hypertension

Genetic and acquired hypertension is associated with increased NHE3 activity [47*,48–50]. Mutations or polymorphisms of NHE3 have not been reported to be associated with essential hypertension [9*]. The increased activity of NHE3 in hypertension may be due to excess activation or to failure of appropriate inhibition. In normotensive rats, in the basal state, NHE3 and NaPi2 are located at the body of the micro-villi. Acute or chronic elevation (as is the case in SHRs) of blood pressure results in partial retraction of NHE3 to the base of microvilli [51] which is a compensatory response rather than contributory to the development of hypertension [52]. Hypertension provokes differential trafficking of the proximal tubule NHE3 (to the base of the apical microvilli) and NaPi2 (to endosomes). As stated above, NHE3 is expressed mainly in lipid rafts. In contrast, NaPi2 is expressed mainly

in non-lipid rafts [20*]. These domain properties may play a role in the distinct trafficking patterns observed during elevated pressure [53].

Stimulation of dopamine receptors inhibits proximal sodium reabsorption by decreasing NHE3 activity and protein abundance in the apical membrane without changing total cellular NHE3. Although D₁-like receptor agonist alone can decrease renal proximal tubule apical membrane NHE3 expression, D₂-like receptor agonists synergistically enhance the effect of D₁-like receptors [54]. Dopamine-stimulated NHE3 endocytosis can be blocked by protein kinase A (PKA) inhibition or by mutation of two PKA target serines (Ser-560 and Ser-613) suggesting that PKA-mediated phosphorylation of proximal tubule NHE3 leads to endocytosis of the transporter via clathrin-coated vesicles [55]. D₁-like receptors (D₁R and D₅R) inhibit NHE3 activity via PKA in rat renal proximal tubule cells. In contrast, the D₁-like receptor-mediated inhibition of NHE3 in opossum kidney cells involves both PKA and protein kinase C (PKC) [56–59]. However, the D₃R inhibits renal NHE3 activity via a PLC–PKC-mediated event, modulated by intra-cellular Ca²⁺ [60]. Interestingly, mice with disruption of any of the D₂-like receptors (D₂R, D₃R, D₄R) have increased blood pressure and increased renal protein abundance of NHE3 [17*], whereas D₅R-deficient mice develop hypertension without an increase in NHE3 protein abundance (unpublished data).

The activity of NHE3 can be affected by other transporters at the apical membrane. For example, SLC26A6 (PAT1, CFEX), the major chloride/base exchanger, located at the apical membrane of the renal proximal tubule, can regulate NHE3. The multifunctional anion exchanger family (SLC26) encompasses 11 identified genes, all of which except SLC26C10 encode proteins and function primarily as anion (sulfate, iodide, formate, oxalate, hydroxyl ion and bicarbonate anions) exchangers, whereas other SLC26 proteins function as chloride ion channels or anion-gated molecular motors. Members of this family may play important roles in the pathogenesis of hypertension (SLC26A4 and SLC26A6). In renal proximal tubules, SLC26A6 mediates anion exchange at the apical membrane to facilitate transcellular sodium chloride absorption [61]. Formate-induced intracellular alkalinization, which is mediated by NHE3, is impaired but not angiotensin-II-stimulated NHE3 activity in SLC26A6 knockout mice [62*]. The increased activity of NHE3 in renal proximal tubule cells from SHR is associated with an increased activity of SLC26A6 [63*]. This may explain the slight but significant increase in serum sodium chloride concentration in essential hypertension [64].

NaPi2

Several sodium phosphate (NaPi) cotransporters have been identified in the mammalian kidney [65–67]. NaPi cotransporter type I (Npt1, SLC17A1) and type IIa (Npt2a, SLC34A1) are expressed in the renal proximal tubule. NaPi2 is expressed to a greater extent than NHE3 in nonlipid rafts [20*].

Endocrine, paracrine and autocrine regulators of NHE3 expression and activity also regulate Npt2 expression and activity (Tables 1 and 2). Thus, angiotensin II also increases the expression of Npt2a in both the proximal tubular cell and the brush border membrane [68]. Dopamine, via D₁R, also decreases phosphate transport via activation of PKA [69–72]. In opossum kidney cells, the D₁-like receptor agonist, fenoldopam, induces the accumulation of Npt2a and membrane-associated 17 kDa protein (MAP17) in the trans-Golgi network [73].

Role of NaPi2 in hypertension

Sodium phosphate cotransport seems to be only mildly, if, at all, impaired in hypertension. The fractional excretion of phosphate on a low-phosphate diet is actually higher in SHRs

than in normotensive Wistar–Kyoto rats (WKY) rats indicating a defect in renal Pi reabsorption in hypertension [74]. Patients with hypertension and SHRs are hypophosphatemic though this has been ascribed to decreased Pi reabsorption in the intestine [75]. Furthermore, the inhibitory effect of endogenous dopamine on Pi reabsorption is maintained in SHR kidneys [76]. Acute hypertension in rats provokes a decrease in renal proximal tubule salt and fluid reabsorption along with the redistribution of Npt2a from the brush border to higher-density membranes (internalization), a response similar to the cellular response to PTH, and is mediated by similar pathways [51,77]. In SHRs, Npt2a is localized to subapical vesicles rather than to brush border membranes. Lowering of blood pressure does not change the distribution or abundance of the transporter, though treatment with an ACE inhibitor results in the redistribution of the transporters from transport-relevant domains of apical membranes to endosome-enriched membranes, as well as a decrease in its abundance [78]. In contrast, chronic renal injury-induced hypertension produces a shift of Npt2a to apical brush border membranes [79] that should result in an increased Pi reabsorption.

Sodium bicarbonate cotransporter

Sodium bicarbonate ($\text{Na}^+/\text{HCO}_3^-$) cotransporters (NBC) belong to the family of solute carrier 4 (SLC4) anion transporters that maintain intracellular pH and extra-cellular pH within a narrow physiological range [61,80]. kNBC1 (SLC4A4), a variant of the electrogenic NBC, located at the basolateral membrane, is essential for the majority (~80%) of reabsorption of filtered HCO_3^- in renal proximal tubules [81]. Angiotensin II and dopamine are also important in the regulation of kNBC1 activity and expression (Tables 1 and 2).

Role of sodium bicarbonate cotransporter in hypertension

In some salt-sensitive, but not in salt-resistant patients, oral loading with NaHCO_3 increases blood pressure, but the pressor effect of NaHCO_3 is half that of NaCl [5]. In SHRs, dopamine or dopamine D_1 -like receptors agonists fail to inhibit kNBC1 though the effects of PTH are similar to those in WKY rats [82]. kNBC1 activity and the expression of kNBC1 mRNA are lower in proximal tubule cells from SHR than in those from WKY rats. However, kNBC1 in SHR cells is more resistant to 4,4'-diisothiocyanatodihydrostilbene-2,2'-disulphonic acid and responds better to acidosis [83]. In addition, Na^+ -independent HCO_3^- transport system activity ($\text{Cl}^-/\text{HCO}_3^-$ exchanger, SLC26A6) is stimulated by oxidative stress and $\alpha 1$ -adrenoceptor in immortalized proximal tubular epithelial cells of SHRs [84]. Angiotensin II also increases $\text{Cl}^-/\text{HCO}_3^-$ exchanger activity to a greater extent in immortalized renal proximal tubules from SHRs than in those from WKY rats. The greater sensitivity to angiotensin II in SHR cells may be related to increased generation of H_2O_2 , which increases the expression of AT_1Rs in lipid rafts [85].

Na^+/K^+ ATPase

Na^+/K^+ ATPase, present at the basolateral membrane of the tubular cells, is critical in the primary active transport across the membrane. Na^+/K^+ ATPase expression is low in the macula densa and thin descending limb of loop of Henle and minimally or not at all present in the thin ascending limb of Henle [86,87]. It is composed of α and β subunits, each having at least four isoforms [88] and γ subunit. The α subunit contains an ouabain-binding site that is the receptor for cardiotonic steroids. The $\alpha 1$ isoform, expressed in the kidney, is relatively resistant to ouabain in rodents but not in humans; conferring ouabain sensitivity to the $\alpha 1$ isoform in mice augments the natriuretic response to an acute salt load. The sodium excretion rate in mice made to express ouabain-sensitive $\alpha 1$ isoform is similar to that in mice expressing ouabain-resistant α when endogenous Na^+/K^+ ATPase inhibitors are

sequestered with an antidigoxin antibody. These studies suggest that the ouabain-binding site of $\alpha 1$ Na^+/K^+ ATPase can participate in the natriuretic response to a salt load [89*]. Renal Na^+/K^+ ATPase is associated with the γ -subunit (FXYD2), a single-span membrane protein that modifies ATPase properties. There are two splice variants with different amino termini: $\gamma(a)$ and $\gamma(b)$. $\gamma(a)$ is predominantly expressed in isolated proximal tubule cells and regulates Na^+/K^+ ATPase activity [90].

As with other membrane proteins, Na^+/K^+ ATPase subunits are also found in lipid and nonlipid rafts [91]. However, the relative distribution of the subunits in lipid and nonlipid rafts has not been reported. The recruitment of $\alpha 1$ subunit of Na^+/K^+ ATPase into lipid rafts in a renal tubular epithelial cell line increases its activity [92*]. In addition, the inhibitory effect of hydrostatic pressure on Na^+/K^+ ATPase is attenuated in a model lipid raft mixture of dioleoyl phosphatidyl choline, shingomyelin and cholesterol [93].

Role of Na^+/K^+ ATPase in hypertension

Abnormalities of tubular Na^+/K^+ ATPase activity have been observed in essential hypertension. Several mechanisms are involved in determining the abnormalities among which the participation of increased circulating levels of endogenous ouabain has been demonstrated recently. Chronic administration of exogenous ouabain induces hypertension in rodents. Ouabain inhibits Na^+/K^+ ATPase activity primarily by acting on the $\alpha 2$ isoform (mainly expressed in vascular smooth muscle cells) than the $\alpha 1$ isoform, which is relatively ouabain-resistant, and expressed in rodent renal tubules [94]. The inhibition of $\alpha 2$ Na^+/K^+ ATPase in vascular smooth muscle cells increases intracellular sodium which activates the sodium calcium exchanger 1 (NCE1). NCE1 increases intracellular calcium and, therefore, vasoconstriction and, hence, hypertension [95,96*]. NCE1 makes an important contribution to the pathogenesis of sodium-chloride-dependent hypertension but not to sodium-chloride-independent hypertension [97].

Approximately 33% of humans with untreated essential hypertension have significantly elevated plasma ouabain; moreover, blood pressure (BP) correlates directly with plasma endogenous ouabain [98]. Rostafuroxin which antagonizes the pressor effect of ouabain and normalizes ouabain-dependent upregulation of the renal Na^+/K^+ ATPase also lowers BP in Milan hypertensive rats [98].

The decrease in Na^+/K^+ ATPase activity with salt loading has been attributed, in part, to an increase in renal tubular dopamine synthesis; dopamine, probably via D_1R decreases renal tubular basolateral expression caused by endocytosis [99]. Milan hypertensive rats carrying a genetic variation in α -adducin cytoskeletal protein have a higher renal tubule Na^+/K^+ ATPase activity, and their Na^+/K^+ ATPase α subunits do not undergo endocytosis in response to dopamine as do those renal tubules from a normotensive strain. Thus, increased renal Na^+/K^+ ATPase activity and altered renal tubular sodium reabsorption in certain forms of hypertension could be attributed to a mutant form of α -adducin that impairs the dynamic regulation of renal Na^+/K^+ ATPase endocytosis in response to natriuretic signals [100].

Angiotensin II regulates renal tubular sodium absorption, in part, through its effects on Na^+/K^+ ATPase. At low concentrations, angiotensin II stimulates Na^+/K^+ ATPase; higher concentrations inhibit the enzyme, this effect is mediated by AT_1R -nitric oxide signaling. However, in rats treated with L-buthionine sulfoximine, an oxidant, and exhibiting increased oxidative stress, angiotensin II stimulates Na^+/K^+ ATPase activity at low and high concentrations. This is associated with oxidative stress-mediated AT_1R upregulation [101*]. The role of increased activity of Na^+/K^+ ATPase in the proximal tubule, independent of other nephron segments, in hypertension remains to be determined.

Conclusion

In summary, renal proximal tubule transport is increased in human and rodent models of essential hypertension. The increased transport predominantly involves sodium chloride because of increased activity of NHE3 and Cl/HCO₃ exchanger at the luminal membrane and Na⁺/K⁺ATPase at the basolateral membrane. Because water follows sodium chloride transport in the proximal tubule, the serum concentration of sodium chloride is slightly increased in essential hypertension [64]. The contribution of other sodium transporters in the increased sodium and anion transport in the renal proximal tubule in the pathogenesis of essential hypertension remains to be determined.

Acknowledgments

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 456–457).

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Table 1

Humoral/hormonal agents that increase ion transport in the proximal tubule

Agent	Transporter/pump
Angiotensin II	NHE3
	Npt2a
	kNBC1 (at low concentrations of angiotensin II)
	Na ⁺ /K ⁺ ATPase (at low concentrations of angiotensin II)
Aldosterone	NHE1
	NHE3
Androgens	NHE3
Endothelin-1	NHE3 (acute effect)
Glucocorticoids	NHE3
	kNBC1
Glucagon	NHE3 (acute effect)
Nitric oxide	kNBC1
Norepinephrine	NHE3
	kNBC1
	Na ⁺ /K ⁺ ATPase
Phosphate deprivation	Npt2a
Thyroid hormone	NHE3

Table 2

Humoral/hormonal agents that decrease ion transport in the proximal tubule

Agent	Transporter/pump
Angiotensin 1–7	Na ⁺ /K ⁺ ATPase (at high concentrations of angiotensin II) Npt2a
Angiotensin 2–8	Na ⁺ /K ⁺ ATPase
Dopamine	Cl/HCO ₃ NHE3 Npt2a and c Na ⁺ /K ⁺ ATPase NBC
Endothelin-1 (chronic)	NHE3
Glucagon (chronic)	NHE3
High dietary phosphate	Npt2a and c
Nitric oxide	NHE3 Na ⁺ /K ⁺ ATPase
Ouabain	NHE3 Na ⁺ /K ⁺ ATPase
Parathyroid hormone	Npt2a and c
Phosphatonins (FGF-23 sFRP-4)	Npt2a