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Proximal tubular NHEs: sodium, protons and calcium?

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Abstract

Na^+/H^+ exchange activity in the apical membrane of the proximal tubule is fundamental to the reabsorption of Na^+ and water from the filtrate. The role of this exchange process in bicarbonate reclamation and, consequently, the maintenance of acid-base homeostasis has been appreciated for at least half a century and remains a pillar of renal tubular physiology. More recently, apical Na^+/H^+ exchange, mediated by Na^+/H^+ exchanger isoform 3 (NHE3), has been implicated in proximal tubular reabsorption of Ca^{2+} and Ca^{2+} homeostasis in general. Overexpression of NHE3 increased paracellular Ca^{2+} flux in a proximal tubular cell model. Consistent with this observation, mice with genetic deletion of *Nhe3* have a noticable renal Ca^{2+} leak. These mice also display decreased intestinal Ca^{2+} uptake and osteopenia. This review highlights the traditional roles of proximal tubular Na^+/H^+ exchange and summarizes recent novel findings implicating the predominant isoform, NHE3, in Ca^{2+} homeostasis.

Keywords

calcium; sodium-hydrogen exchanger isoform 3; paracellular; proximal tubule; parathyroid hormone

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The Na^+/H^+ exchanger (NHE) family of proteins contains at least nine isoforms (23, 95). The family can be divided into plasma membrane isoforms (NHE1–NHE5) and endomembrane isoforms (NHE6–NHE9) (23). The plasma membrane isoforms function to exchange extracellular Na^+ for intracellular H^+, given typical physiological concentrations of substrates. Much less is known about the function of the endomembrane isoforms, although they likely secrete H^+ in exchange for Na^+, thereby acidifying the lumen of the endomembrane compartment in which they are expressed (29, 58, 89). NHE1 is ubiquitously expressed and serves a role in several housekeeping functions, including the maintenance of intracellular pH and cell volume regulation (95, 102). The expression pattern of the

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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remaining plasma membrane NHE isoforms is more restricted, and their functional roles are consequently more specialized (Table 1).

The proximal tubule expresses NHE1, NHE3, NHE4, and the so-called endomembrane isoforms (17, 18, 54, 99, 104). NHE3 is the predominant brush-border Na^+/H^+ exchanger in adults (14, 18, 53). NHE1 is expressed in the basolateral membrane of the proximal tubule, where it likely participates in the housekeeping functions mentioned above (104). NHE4 is also expressed basolaterally in this nephron segment, however, to a lesser extent than NHE1 (99). Its function in the proximal tubule remains unknown. The endomembrane NHEs (NHE6, NHE7, and NHE9) are expressed in the proximal tubule as well. The function of these isoforms in the proximal tubule remains to be determined. When expressed in yeast, COS-7, or HeLa cells, NHE8 predominantly localizes to the Golgi (14, 89), although in the proximal tubule it is situated in the apical plasma membrane (14, 53, 54). It may participate in Na^+ and bicarbonate reabsorption when expressed in the apical plasmalema, a role primarily served by NHE3 after development (12, 65, 77, 93, 109, 118, 120, 129). In fact, a recent study (12) using NHE3/NHE8 double-knockout mice has provided evidence consistent with NHE8, at least partially, compensating for the loss of luminal Na^+/H^+ exchange activity after genetic ablation of NHE3 (12). The apical exchange activity of NHEs in the proximal tubule serves multiple roles beyond simple reabsorption of Na^+ and acid/H^+ secretion (20). The purpose of this review is to highlight traditional functions and to discuss the recently described role for NHE3 in Ca^{2+} homeostasis (82, 97).

Luminal Na^+/H^+ Exchange Is Responsible for the Majority of Na^+ and Water Reabsorption From the Proximal Tubule

One of the primary functions of the proximal tubule is to reabsorb more than 2/3rd of the ~180 liters of water and ~27.5 mol Na^+ filtered by the glomerulus on a daily basis. In adults, NHE3 plays the predominant role in this. In exchange for a luminal H^+, NHE3 mediates the influx of Na^+ into the proximal tubular cell. This exchange is driven by a concentration gradient for Na^+, generated by basolateral Na^+-K^+-ATPase effluxing the apically absorbed Na^+ (Fig. 1). The massive reclamation of Na^+ from the proximal tubule via NHE3 plays a key role in preserving extracellular fluid volume. Given the importance of proximal tubular Na^+ transport in blood pressure maintenance, it is not surprising that the reduction of Na^+/H^+ exhange activity in $NHE3^{-/-}$ mice causes hypotension (109). In addition, a myriad of processes and hormones implicit to blood pressure regulation affect NHE3 localization, expression, and activity (80).

The vectorial movement of Na^+ across the proximal tubule creates an osmotic gradient, which provides the driving force for water reabsorption (101). Consistent with this, microperfusion studies (109, 120) have demonstrate that fluid uptake from the proximal tubule of $NHE3^{-/-}$ mice is reduced by ~2/3. Similarly, a micropuncture study (77) found an ~50% reduction in proximal fluid reabsorption in the absence of NHE3. There is a significant amount of Na^+-coupled solute reabsorption across the proximal tubule, including that of phosphate, glucose, amino acids, etc. Given the relatively small concentration of these solutes in the filtrate, it is unlikely that these other Na^+-coupled processes account

entirely for the remaining water reabsorption from the proximal tubule of NHE3$^{-/-}$ mice. The residual Na^+/H^+ exchange activity may be attributable to NHE8.

NHE-dependent Na^+/H^+ exchange is coupled to apical Cl^-/base exchange, permitting some Cl^- reabsorption (9, 10), whereas the remainder of Cl^- is reabsorbed via the paracellular junction. Cl^- absorption, however, does not occur uniformly along the proximal tubule (101). The initial part of the proximal tubule supports significant bicarbonate reabsorption, such that the luminal Cl^- concentration rises in latter parts of this segment (76). This provides a significant driving force for paracellular Cl^- reabsorption from the latter part of the proximal tubule, where the majority of Cl^- reabsorption occurs (43, 101).

NHE3 and NHE8 Play a Role in Acid-Base Homeostasis

The luminal secretion of a H^+ in exchange for a Na^+ permits the reabsorption of bicarbonate from the proximal tubule (62, 68, 85, 100). This is evinced by the development of renal tubular acidosis in NHE3$^{-/-}$ mice (73, 109) and by microperfusion studies (109, 120) that demonstrated decreased bicarbonate reabsorption from the proximal tubule of these animals. Bicarbonate reclamation is not the only role that luminal NHEs play in acid-base homeostasis. H^+ excretion may serve to trap luminal NH_3 (44). In addition, the NHE3-dependent exchange of Na^+ for NH_4^+ would also facilitate the luminal excretion of NH_4^+ after its generation in the proximal tubule in response to acidosis (67, 87, 88). Furthermore, H^+ extruded by NHE_3 titrate citrate to its bivalent form, facilitating its reabsorption (22, 110).

Examination of proximal tubular H^+ transport in NHE3$^{-/-}$ mice revealed significant Na^+-dependent, amiloride-sensitive, H^+ extrusion, implying the presence of another NHE isoform in the brush-border membrane (26). This is likely due to NHE8, as a recent study (12) examining NHE3/NHE8 double-knockout mice found a more pronounced acidosis than in NHE3$^{-/-}$ mice and a near absence of amiloride-dependent H^+ extrusion in NHE3/NH8 double-knockout mice compared with significant residual activity in NHE3$^{-/-}$ mice. However, direct measurements of bicarbonate fluxes from perfused tubules of NHE3$^{-/-}$ mice argue against a role for NHE8 in bicarbonate reabsorption from the proximal tubule, as significant residual flux insensitive to the amiloride analog ethylisopropylamiloride has been demonstrated (NHE8 is amiloride sensitive) (126).

Proximal Tubule Ca^{2+} Reabsorption

There is extensive literature describing Ca^{2+} reabsorption from the proximal nephron in a number of species (2, 30). Fifty to sixty percent of total plasma Ca^{2+} is freely filtered by the glomerulus, whereas the remainder is complexed to plasma proteins and consequently retained in the plasma (41, 42, 55). Detailed physiological measurements using micropuncture have estimated that the convoluted part of the proximal tubule reabsorbs ~55–60% of Ca^{2+} from the filtrate (36, 111, 112). These studies suggested that an additional 10% of the filtered Ca^{2+} is reabsorbed from the straight proximal segment (pars recta). Therefore, 2/3rd of filtered Ca^{2+} or ~214 mmol Ca^{2+} are reabsorbed from the proximal tubule daily.

Not surprisingly, even a slight reduction in proximal tubular Ca^{2+} reabsorption can lead to increased urinary Ca^{2+} excretion.

Micropuncture studies (36, 83, 115) on the rat, dog, and psammomys proximal tubule have consistently observed a proximal tubule fluid-to-ultrafiltrate Ca^{2+} ratio [$(TF/UF)_{Ca}$] between 1.0 and 1.2. The $(TF/UF)_{Ca}$ follows that of Na^+ during the administration of parathyroid hormone (PTH), acetazolamide, furosemide, hydrochlorothiazide, or acute and chronic metabolic acidosis (2, 13, 37, 115). Therefore, under the majority of situations studied, proximal tubular Ca^{2+} reabsorption parallels that of Na^+ reabsorption. This finding has been interpreted as Ca^{2+} reabsorption from the proximal tubule occurs predominantly via a passive paracellular process (32, 112, 115). The proximal tubule is highly permeable to Ca^{2+}, which would facilitate passive paracellular transport (84, 115). Moreover, a perfusion study (90) performed in the absence of a transepithelial potential difference and volume fluxes confirmed that the majority, but not all, Ca^{2+} transport across the proximal convoluted tubule was passive and likely paracellular.

Proximal tubular $(TF/UF)_{Ca}$ has been reported outside the range of 1.0–1.2. Induction of an osmotic diuresis via administration of saline or mannitol reduces $(TF/UF)_{Ca}$ to <1.0 (36, 72, 113). This finding can be interpreted as the proximal tubule has a capacity for active Ca^{2+} reabsorption. Consistent with this, a tubular perfusion study (103) performed on isolated pars recta from the rabbit found significant active Ca^{2+} flux, which was not inhibited by ouabain but was by a colder temperature. Together, the results of these reports suggest that the majority of Ca^{2+} transport is passive and paracellular in the proximal tubule. However, there may also be a small amount of active Ca^{2+} transport occurring via an as of yet poorly delineated mechanism.

Conversely, acute Ca^{2+} loading and immediately postparathyroidectomy are situations where proximal tubular $(TF/UF)_{Ca}$ have been reported to be above 1.2 (38, 71). Both of these experimental perturbations caused hypercalcemia and thus an increased proximal tubular load of Ca^{2+}. These results can be interpreted to mean that the significant capacity for paracellular Ca^{2+} flux across the proximal tubule is finite and potentially limiting to Ca^{2+} reabsorption under some circumstances.

What permits paracellular Ca^{2+} flux across the proximal tubule? Claudins are four membrane-spanning proteins that localize to the tight junction (8). The family consists of at least 24 isoforms in humans. Interactions between claudins in the same membrane and across the tight junction control the paracellular flux of ions (8, 39). For example, the unique paracellular permeability properties of the thick ascending limb of Henle’s loop (TAL) are conferred by a dynamic interplay between claudins. Claudin-16 and claudin-19 form a cationic pore in the TAL, which permits Ca^{2+} reabsorption and, importantly, Na^+ backflux (60, 61). This latter process contributes to the lumen-positive potential difference across the TAL, a driving force for Ca^{2+} reabsorption. In the presence of increased plasma Ca^{2+}, claudin-14 is expressed in the TAL, where it functions to block Ca^{2+} absorption, thereby inducing calciuresis (34, 52).

To date, there has been very little published on the molecules permitting Ca^{2+} flux across the proximal tubule. The proximal tubule expresses claudin-1, claudin-2, claudin-10a, and claudin-12 (1, 69). Claudin-11 has been reported in this nephron segment by immunohistochemistry (117), although this was later found to be nonspecific (86). The claudin-2 knockout mouse displays decreased proximal tubular paracellular Na^+, Cl^-, and water fluxes as well as an increase in paracellular shunt resistance, consistent with a role for claudin-2 in forming an integral part of the proximal tubular paracellular junction (86). Although the authors reported that these animals have hypercalciuria, extensive evaluation of Ca^{2+} homeostasis was not described. The role of claudins-1, claudin-10a, and claudin-12 in proximal tubular ion transport is not known.

NHE3 Plays a Role in Ca^{2+} Homeostasis

The large majority of proximal tubular Ca^{2+} reabsorption is passive and paracellular, driven by active transcellular Na^+ flux (112, 115). NHE3 is responsible for the majority of proximal tubular Na^+ and, consequently, for osmotically driven water reabsorption (77, 109). It follows, therefore, that NHE3 activity would drive the passive paracellular flux of Ca^{2+} (Fig. 1). We (97) recently reported a role for NHE3 in maintaining Ca^{2+} homeostasis using a proximal tubular cell culture model and $NHE3^{-/-}$ mice. Opossum kidney cells are a well-characterized proximal tubular cell culture model known to express NHE3 in the apical membrane (4, 7). By overexpressing NHE3 in this model system and measuring paracellular Ca^{2+} flux across confluent monolayers, we observed increased Ca^{2+} flux when NHE3 was overexpressed, an effect that was eliminated by the omission of Na^+ from the medium (97). Investigation of Ca^{2+} homeostasis in $NHE3^{-/-}$ mice revealed profound abnormalities (97). The fractional excretion of Ca^{2+} was double that of wild-type mice, consistent with significant urinary Ca^{2+} wasting. Plasma Ca^{2+} was not different between genotypes, nor was plasma PTH. However, $1,25[OH]_2D_3$ was dramatically elevated in $NHE3^{-/-}$ mice. Surprisingly, despite this, intestinal Ca^{2+} absorption was reduced in $NHE3^{-/-}$ animals. Ultimately, reduced intestinal Ca^{2+} absorption and increased urinary Ca^{2+} excretion occur at the expense of bone health. $NHE3^{-/-}$ mice were found to have significantly reduced cortical and trabecular bone mass relative to wild-type animals of the same age, sex, and blood pH.

$NHE3^{-/-}$ mice have increased $1,25[OH]_2D_3$ levels, a hormonal response that should increase intestinal Ca^{2+} absorption. However, contrary to this expectation, they do not. Why is this the case? NHE3 is expressed throughout the small intestine (96) and is responsible for a large amount of Na^+ and osmotically driven water reabsorption (46). Ca^{2+} absorption from the intestine largely occurs in a passive paracellular fashion similar to the proximal tubule. One could hypothesize that the same mechanism is at play in the bowel as in the kidney. Further research will be needed to support this.

The localization of NHE3 in the proximal tubule, the experimental data described above, and the route of Ca^{2+} absorption from the proximal tubule strongly support that NHE3 drives paracellular proximal tubular Ca^{2+} absorption (18, 97, 112). It is worth considering the mechanistic details of this process briefly. The transepithelial movement of Na^+ provides an osmotic driving force for the reabsorption of water. The movement of water, in turn, drives paracellular Ca^{2+} flux (Fig. 1). There are at least two potential mechanisms we can envisage

whereby water movement causes Ca^{2+} flux. There is a significant amount of water flux across the proximal tubule, 25% of which is estimated to move via the paracellular pathway (106). This may be sufficient to drive Ca^{2+} flux by convection, a process referred to as solvent drag. Alternatively, the removal of water will increase the concentration of solutes, including Ca^{2+}, in the proximal tubular lumen, even more so in unstirred layers at the tight junction. This Ca^{2+} gradient may be sufficient to provide the driving force for diffusive Ca^{2+} reabsorption. Current experimental approaches are not capable of distinguishing between these possibilities, and, consequently, more sophisticated techniques will be required to differentiate between them.

The amount of Na^{+} ingested alters urinary Ca^{2+} excretion (70). Consistent with this, volume depletion decreases urinary Ca^{2+} excretion (114), and the hypocalciuria induced by thiazide diuretics has been attributed to mild volume contraction and increased proximal tubular transport (91). Such changes are likely dependent on increased NHE activity in the proximal segment. In fact, given the role of NHE3 in maintaining proximal tubular transport, it is likely that increased NHE activity contributes importantly to both Na^{+} and Ca^{2+} reabsorption in volume-contracted states. Volume expansion decreases Ca^{2+} reabsorption from the proximal tubule (114) and causes redistribution of NHE3 from the brush-border membrane to the base of the microvilli (80). However, whether decreased NHE3 activity causes the decrease in Ca^{2+} reabsorption during volume expansion remains to be determined.

PTH Inhibits NHE3

PTH is a calciophosphoregulatory hormone released by the parathyroid gland in response to a reduction in ionized Ca^{2+} levels in the blood. Its ability to reduce urinary Ca^{2+} excretion has been appreciated for decades (31). This effect is largely mediated by increasing active transcellular Ca^{2+} reabsorption from the distal nephron (2). PTH also induces natriuresis (2, 3). This is the result of decreased proximal tubular Na^{+} reabsorption. PTH acutely and chronically inhibits NHE3 activity via a variety of mechanisms (15, 27, 51, 74, 122, 127, 130). Given the above discussion implicating NHE3 in proximal tubular Ca^{2+} reabsorption, it seems contradictory that PTH, a calciotropic hormone that decreases urinary Ca^{2+} excretion, decreases NHE3 activity. The reasons for this are unclear. A micropuncture study (75) found that the acute administration of PTH increases the distal delivery of bicarbonate, most likely via inhibition of NHE3. An alkaline lumen in the distal nephron increases active transcellular Ca^{2+} absorption (79, 116). Consistent with this, the transient receptor potential V5 channel, the major influx pathway for Ca^{2+} in the distal nephron, is activated by an alkaline pH (128). Together, these data have led some authors to speculate that PTH inhibits NHE3 to increase the distal delivery of bicarbonate, which alkalinizes the lumen of the distal nephron, in turn increasing active distal Ca^{2+} uptake (27, 51).

Other explanations are worth considering. High doses of PTH decrease the glomerular filtration rate (74, 107). This may conserve whole body Ca^{2+} as less Ca^{2+} will be filtered and therefore need to be reabsorbed. However, lower doses of PTH fail to alter the glomerular filtration rate and still inhibit NHE3 (74). PTH administration can induce hypercalcemia and increase Ca^{2+}-sensing receptor (CaSR) expression (51, 122), although hypercalcemia and/or

CaSR activation are insufficient to alter NHE3 expression (Ref. 121; R. T. Alexander, H. Dimke, and E. Cordat, unpublished observations). Instead, PTH-induced hypercalcemia promotes urinary water loss, leading to volume contraction. This effect, coupled to PTH-mediated decreased Ca^{2+} excretion, may serve to increase the free plasma Ca^{2+} concentration. This explanation implies that the maintenance of plasma Ca^{2+} levels is of greater importance than safeguarding intravascular volume, a huge assumption with little supporting evidence. Further research using novel model systems will be required to understand the role of PTH-mediated NHE3 inhibition in the maintenance of Ca^{2+} homeostasis.

Administration of PTH or a PTH-related peptide to humans does not lower blood pressure, as one might predict based on the above studies. Instead, an increase in blood pressure has been reported, especially with higher doses (40, 63). This is consistent with the frequent association of hypertension in persons with hyperparathyroidism. PTH administration causes natriuresis in humans, similar to rodents (56, 59), although the effect of PTH on NHE3 activity in humans remains to be determined.

The effect of active vitamin D on NHE3 activity is less clear. A renal cell culture study (19) found an increase in NHE3 activity, whereas intestinal cell culture and brush-border membrane preparation experiments found an inhibition (50, 119). The intestinal effect was attributed to decreased NHE3 expression (50), although the expression of NHE3 is unaltered in the kidneys of vitamin D-treated rats (121). Further studies will be required to clarify these seemingly contradictory effects.

Other Roles for Luminal Na^+/H^+ Exchange

NHE3 has been implicated in other transport processes. It associates with megalin and participates in receptor-mediated endocytosis and, consequently, the reabsorption of filtered proteins (16, 47–49). The extrusion of a H^+ across the brush-border membrane also permits H^+-coupled amino acid and oligopeptide influx from the proximal tubular lumen (123). Given the number of transport processes that NHE3 activity is required for, it is not surprising that there is a myriad of factors that regulate NHE3 activity, both acutely and chronically. Many of these have been described in detail and include hormones, posttranslational modifications, altered membrane recycling, protein-protein interactions, and, more recently, protein-lipid interactions (6, 20, 35, 57, 64, 80). Given the important role of NHE activity in secondary reabsorption of Ca^{2+}, it will be important to test whether some of these factors are regulated by extracellular Ca^{2+} or calciotropic hormones.

Future Directions

NHE3 participates in the reabsorption of Na^+, bicarbonate, and water from the proximal tubule, contributing to the maintenance of intravascular volume, blood pressure, and acid-base homeostasis. Emerging work has also implicated NHE3 in proximal tubular Ca^{2+} reabsorption. The extent to which NHE8 participates in these processes remains to be fully elucidated. Given these findings, several questions arise. For instance, do calciotropic hormones such as PTH and $1,25[OH]_2D_3$ alter NHE8 expression or activity, and could this

be a possible mechanism altering renal Ca^{2+} transport? Moreover, can the divergent developmental expression of NHE3 and NHE8 help explain the increased fractional excretion of Ca^{2+} observed in neonates and infants (66)? Tubular perfusion and micropuncture studies have indicated significant paracellular permeability of the proximal tubule to Ca^{2+}. It will be critical to establish which components determine the permeability characteristics of the proximal tubule. Following this line of inquiry, it will be important to elucidate whether permeation of Ca^{2+} in the proximal tubule is regulated as has been observed in the TAL, where the permeability of the paracellular junction is modulated by PTH and Ca^{2+} itself (34, 52, 78, 124). An elegant translational study (125) on individuals with hypercalciuria and kidney stones has pointed to a defect in proximal tubular Ca^{2+} absorption. This fact emphasizes the need to dissect out these molecular pathways to better understand the causative factors and improve therapy for the large number of people with kidney stones. The use of genetically modified animals in combination with detailed physiological characterization techniques such as micropuncture and tubular perfusion will hopefully provide a platform to answer the above questions and many more.

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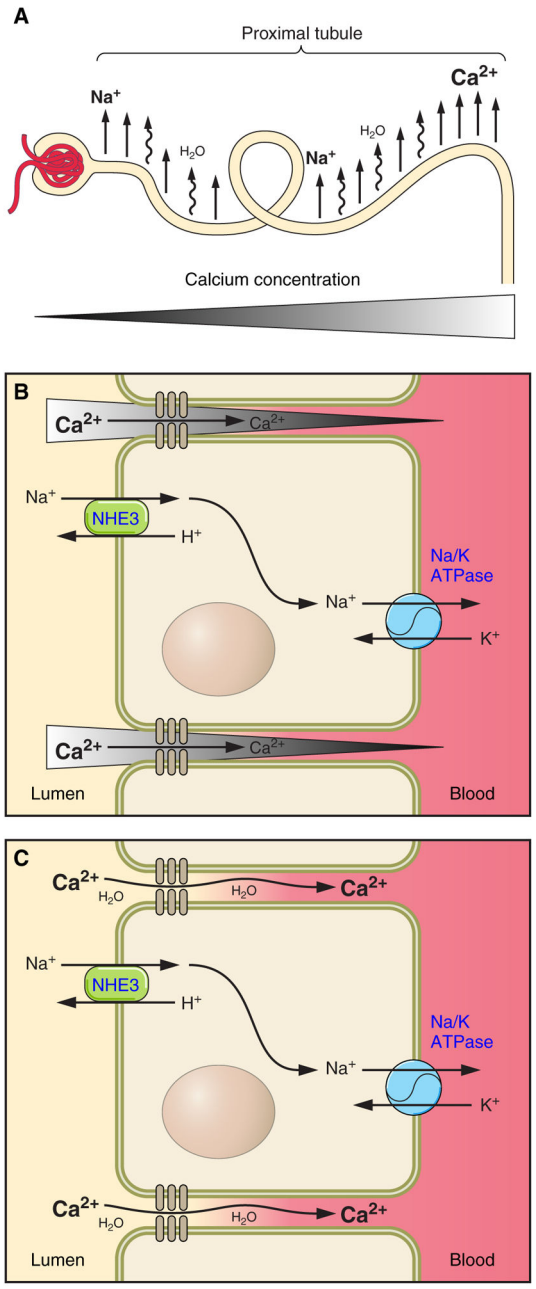

Fig. 1.

Diagrammatic representation of proximal tubular Ca^{2+} reabsorption. Filtered Na^+ is reabsorbed from the proximal tubule (*A*), creating the osmotic driving force for water reabsorption, which, in turn, drives paracellular Ca^{2+} reabsorption either by creating a concentration gradient for Ca^{2+} (water removal increases the luminal concentration of Ca^{2+}; *B*) or by convection/solvent drag (*C*). NHE3, Na^+/H^+ exchanger isoform 3.

Table 1

NHE expression, localization, and (proposed) function

	Location			
Isoform	**Tissue***	**Cellular**	**Proposed Function(s)**	**References**
NHE1	Ubiquitous	Plasma membrane (basolateral membrane in epithelia)	Cell volume and intracellular pH regulation	5, 92, 95, 104, 105
NHE2	Gastrointestinal tract, kidney, brain, uterus/ testis	Plasma membrane (apical membrane in epithelia)	Glandular secretory processes, minor role in intestinal Na^+ and water absorption?	25, 28, 98, 108
NHE3	Gastrointestinal tract, kidney, gallbladder, epididymis	Plasma membrane (apical), recycling endosomes	Intravascular volume homeostasis, pH regulation, Ca^{2+} homeostasis	17, 18, 96, 97, 109
NHE4	Stomach (kidney and brain)	Plasma membrane (basolateral membrane in epithelia)	Acid extrusion into the stomach, renal ammonia handling	21, 45, 96, 99
NHE5	Brain (neurons)	Plasma membrane and recycling endosomes/synaptic vesicles	Regulation of dentritic spine growth?	11, 33
NHE6	Ubiquitous	Recycling endosomes	Regulation of luminal pH?	24, 81, 89, 95
NHE7	Ubiquitous	*trans*-Golgi network and endosomes	Regulation of luminal pH in endosomes and/or Golgi?	89, 94, 95
NHE8†	Ubiquitous	Endomembrane (and apical plasma membrane)	Regulation of luminal pH? Role in intravascular pH and volume regulation?	12, 14, 53, 89, 126
NHE9	Ubiquitous	Late endosomes	Regulation of luminal pH?	89

NHE, Na^+/H^+ exchanger.

*The predominant tissue expression is listed only, i.e., this is not an exhaustive list.

†The NHE family can be divided into plasma membrane isoforms (NHE1–NHE5) and endomembrane isoforms (NHE6–NHE9). NHE8, although predominantly endomembrane, localizes to the plasma membrane in some cell types.