Hindawi Publishing Corporation
Journal of Biomedicine and Biotechnology
Volume 2010, Article ID 238080, 10 pages
doi:10.1155/2010/238080

Review Article

Mechanisms of the Regulation of the Intestinal Na^+/H^+ Exchanger NHE3

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Received 21 July 2009; Accepted 11 September 2009

Academic Editor: Kenichiro Kitamura

A major of Na^+ absorptive process in the proximal part of intestine and kidney is electroneutral exchange of Na^+ and H^+ by Na^+/H^+ exchanger type 3 (NHE3). During the past decade, significant advance has been achieved in the mechanisms of NHE3 regulation. A bulk of the current knowledge on Na^+/H^+ exchanger regulation is based on heterologous expression of mammalian Na^+/H^+ exchangers in Na^+/H^+ exchanger deficient fibroblasts, renal epithelial, and intestinal epithelial cells. Based on the reductionist's approach, an understanding of NHE3 regulation has been greatly advanced. More recently, confirmations of in vitro studies have been made using animals deficient in one or more proteins but in some cases unexpected findings have emerged. The purpose of this paper is to provide a brief overview of recent progress in the regulation and functions of NHE3 present in the luminal membrane of the intestinal tract.

1. Overview

The primary non-motor function of the intestine is absorption. The human intestine absorbs 8.6–9 L of electrolyte-rich fluid per day. This seems small compared to the kidney, which filters about 180 L of fluid per day. The conventional dogma is that the absorption of water results principally from the osmotic gradient created across the epithelium by absorption of electrolytes and nutrients. Water flux can occur through the paracellular and transcellular routes, but the large surface area of the brush border membrane aided by the presence of aquaporin water channels favors the transcellular water flux [1].

The process of Na^+/H^+ exchange is present in all organisms from single cell bacteria to multicellular organisms [2]. Na^+/H^+ exchanger type 3, NHE3 (SLC9A3), is highly expressed at the apical membrane of the small intestine, colon, and proximal tubules of the kidney. In the intestine and colon, NHE3 plays a major role in transepithelial absorption of Na^+ and water. Apart from NHE3, other contributors to Na^+ and water absorption include the ep-ithelial Na^+ channel that is predominantly expressed in the colon and Na^+-coupled cotransporters, such as Na^+-glucose cotransporter and Na^+-coupled amino acid transporters.

In the intestinal tract, NHE3 is often functionally coupled to the Cl^-/HCO_3^- exchanger DRA (downregulated in adenoma; SLC26A3) or PAT1 (putative anion transporter1; SLC26A6) mediates electroneutral NaCl absorption [3]. In the kidney, NHE3 is the main Na^+/H^+ exchanger expressed at the apical membrane of the proximal tubule but also located at the apical membrane of the thick ascending and thin descending limbs of Henle [4, 5]. In the proximal tubule, NHE3 is coupled with a Cl^-/base exchanger, Cl^--formate or Cl^--oxalate exchanger [6, 7] and accounts for approximately 50% of the NaCl and 70% of the $NaHCO_3$ reabsorption from the glomerular filtrate [8, 9]. In addition to its role in Na^+ and water absorption, NHE3 modulates the absorption of other nutrients, such as dipeptides and amino acids, by creating an H^+-gradient [10, 11]. Conversely, short-chain fatty acids activate NHE3 as well as NHE2 activity by the cellular acidification [12, 13].

Table 1: Expression of Na^+/H^+ exchangers in the gastrointestinal tract.

	Tissue expression	Cellular distribution	References
NHE1	Ubiquitous, jejunum, ileum, colon, stomach	Basolateral membrane	[21, 122]
NHE2	Jejunum, ileum, colon, stomach	Apical membrane	[19]
NHE3	Jejunum, ileum, colon, stomach	Apical membrane, recycling endosome	[19]
NHE4	Stomach	Basolateral membrane	[28, 39, 123]
NHE5	Brain		[124, 125]
NHE6	Ubiquitous	Recycling endosome	[126]
NHE7	Ubiquitous	Trans-Golgi	[126]
NHE8	Ubiquitous, Jejunum, duodenum, ileum, colon	Apical membrane, recycling endosome	[20, 42, 43, 126, 127]
NHE9	Ubiquitous	Recycling endosome	[126]

To date, 9 mammalian Na^+/H^+ exchangers have been identified at molecular level (Table 1). All the mammalian Na^+/H^+ exchangers share similarities in size (between 645 and 898 amino acids) and the secondary structure with two structurally and functionally distinct domains: an N-terminal domain with 12 transmembrane helices and an equally large C-terminal cytoplasmic domain [3, 14–16]. The conservation of amino acid residues among the exchangers is significantly greater along the N-terminal membranous domain (50–60%) than the C-terminal cytoplasmic domain (20–23%). The N-terminal domain functions in ion transport; whereas the C-terminal domain determines the regulatory nature of the exchanger [17]. The divergence in this C-terminal region is likely to reflect the differences in kinase regulation among different Na^+/H^+ exchangers.

2. Na^+/H^+ Exchangers in the Intestinal Tract

Four Na^+/H^+ exchangers in the intestinal tract, NHE1-3 and NHE8, are located on the plasma membrane of intestinal epithelial cells (Figure 1) [18–20]. NHE1, NHE2, and NHE3 are most abundantly expressed in the plasma membrane of epithelial cells in the intestinal tract. NHE1 (SLC9A1) is the first Na^+/H^+ exchanger cloned in 1989 and is ubiquitously expressed in all cells where it is a primary regulator of pH homeostasis and cell volume regulation [14, 21]. In addition, the roles of NHE1 as an anchor for actin filaments and a scaffold for signaling molecules have been reported by Barber and others [22–25]. As expected, NHE1-deficient ($Nhe1^{-/-}$) mice exhibit severe defects, including ataxia, growth retardation, and seizures that are often lethal [26, 27]. However, $Nhe1^{-/-}$ mice do not display a morphological aberration in the intestine, although mild atrophy of the glandular mucosa and a thickening of the lamina propria in the stomach were observed [26]. The absence of a major defect in $Nhe1^{-/-}$ mice appears to suggest that NHE1 does not play a significant role or that a compensatory mechanism probably involving other NHEs makes up for the absence of NHE1, but the functions of NHE1 in the intestine have not been closely scrutinized.

NHE3 is the major Na^+/H^+ exchanger at the apical membrane of surface epithelial cells as supported by a number of studies based on in situ hybridization, immunohistochemical analysis, and a targeted deletion of Nhe3 gene in mouse [19, 28–31]. Genetic disruption of NHE3 expression in mice resulted in modest diarrhea, relatively low blood pressure, and mild metabolic acidosis [31]. However, ablation of NHE3 did not completely inhibit small intestinal salt absorption [32], suggesting that other Na^+ absorptive transporters must exist, but their molecular identity is under debate [30, 32, 33].

Primarily due to its presence at the apical membrane of intestinal epithelial cells, NHE2 (SLC9A2) was thought to function in Na^+ absorption. Quantitative analysis of functional Na^+/H^+ exchange activity in rabbit ileum showed that both NHE2 and NHE3 contribute equally to basal Na^+ absorption [34]. Moreover, Na^+ depletion enhanced both NHE2 and NHE3 expression and activities in rat colon further suggesting the role of NHE2 in Na^+ absorption [35]. However, mice with targeted deletion of Nhe2 gene have a distinctly different phenotype from $Nhe3^{-/-}$ mice [36]. $Nhe2^{-/-}$ mice do not display any morphological defect, and the overall rate of Na^+ absorption is not affected by the absence of NHE2 in the intestine [36]. A similar result was obtained when NHE2 was pharmacologically inhibited in wild-type intestine [32], and compound deletion of NHE2 and NHE3 in mice did not increase the severity of diarrhea compared with $Nhe3^{-/-}$ mice [37]. Instead, $Nhe2^{-/-}$ mice develop gastric mucosa atrophy with a severe decrease in the number of mature parietal cells [36]. NHE2 is necessary for long-term viability of parietal cells but is not required for acid secretion by the parietal cells. Hence, despite the high level of NHE2 expression in the intestine and its localization to the brush border membrane of epithelial cells, the physiological role of NHE2 remains elusive. On the other hands, it was shown that the expression of NHE2 is high in mouse colonic crypts and the absence of NHE2 results in upregulation of NHE3 expression at the crypt base, suggesting the role of NHE2 in Na^+ absorption and pH_i regulation in the colonic crypts [30, 38].

NHE4 (SLC9A4), though not present in the intestine or colon [28], is highly expressed in parietal and chief cells of the stomach [39]. Deletion of Nhe4 in mice resulted in hypochlorhydria with reduced numbers of parietal cells and a loss of mature chief cells [40].

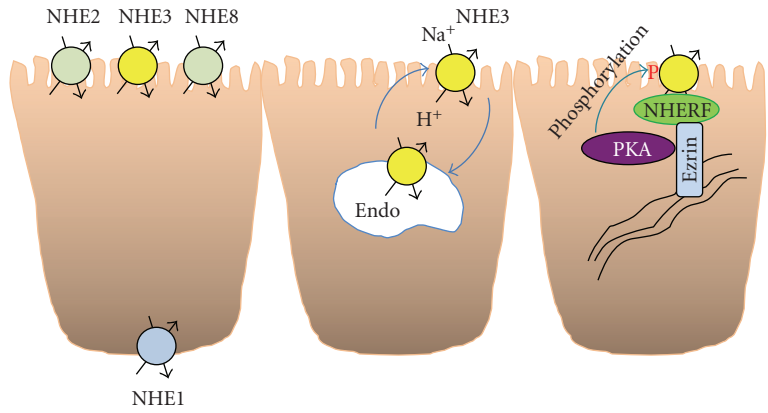

Figure 1: Regulation of NHE3 by multiple mechanisms.

NHE8 (SLC9A8) is ubiquitously expressed with the highest levels of expression in the kidney, testis, muscle, and liver [41]. Localization of NHE8 in the apical membrane of intestinal epithelia cells was shown, and upregulation of NHE8 mRNA expression in young animals compared with adult animals suggests a possible role of NHE8 in Na^+ absorption during early development [20]. Similarly, it was shown that NHE8 expression is most abundant in the proximal tubules of neonate rats than in adults, suggesting that NHE8 may account for the Na^+-dependent H^+ efflux in neonatal proximal tubules [42]. The localization of NHE8 overlaps with that of NHE3 in the intestinal tract and the renal proximal tubules [20, 43], but the relative contribution by NHE8 in Na^+ absorption remains to be determined. The expression of NHE8 in $Nhe3^{-/-}$ mice was reported, but without a detectable change in the expression level [20, 43]. It has been demonstrated that Na^+-dependent H^+ secretion in the renal proximal tubules of $Nhe3^{-/-}$ mice is approximately 50% that of wild-type mice and that the residual Na^+-dependent H^+secretion is mediated by a previously unrecognized EIPA-sensitive protein secretory mechanisms [44]. Congruently, it was suggested that colonic cryptal Na^+-dependent pH_i recovery in $Nhe2^{-/-}$ mice is mediated by an EIPA-sensitive but not NHE3-dependent mechanism [38]. Pharmacological characterization of NHE8 in cultured renal epithelial cells has shown its sensitivity to EIPA [45], but whether NHE8 is responsible for these unidentified EIPA-sensitive transport processes is yet to be determined.

3. Mechanisms of NHE3 Regulation

The activity of NHE3 at the apical membrane of epithelial cells is modulated by a number of mechanisms (Figure 1). These include transcriptional regulation [46–49], protein phosphorylation [50–52], protein-protein interaction [53–55], and trafficking [56–62]. A brief review of some of these pathways will be presented here but the readers can refer to [63–66] for more extensive reviews.

3.1. Phosphorylation. The C-terminal cytoplasmic domain of NHE3 contains multiple putative phosphorylation sites. NHE3 is believed to be phosphorylated by protein kinases as part of the signal transduction that modulates NHE3 activity. Changes in phosphorylation of NHE3 by protein kinase A (PKA) has been demonstrated in vitro using cultured cells as well as in vivo in rat kidney [50, 67, 68]. Specifically, mutation of either Ser-552 or Ser-605 abolished NHE3 inhibition by 8-Br-cAMP that activates PKA [50]. In addition to PKA, our lab showed that the serum- and glucocorticoid-inducible kinase 1 (SGK1) is capable of phosphorylating NHE3 at Ser-665 [52]. Mutation of Ser-665 abrogated NHE3 regulation by glucocorticoids.

The mechanisms by which phosphorylation alters NHE3 activity are not known. It seems likely that phosphorylation modulates NHE3 activity by an allosteric shift induced by the bulky phosphate side chain. However, a study by Kocinsky et al. [69] showed that there is a temporal dissociation of NHE3 phosphorylation and activity, suggesting that phosphorylation may not directly affect the transport activity of NHE3. Alternatively, phosphorylation of NHE3 may modulate NHE3 subcellular trafficking or interaction with other regulatory proteins. For instance, phosphorylation at Ser-552 and Ser-605 precedes inhibition of NHE3 activity by PKA [69]. In addition, NHE3 basal phosphorylation by casein kinase 2 has been suggested to modulate NHE3 trafficking [70].

3.2. Trafficking. NHE3 differs from other isoforms in that it recycles between the plasma membrane and intracellular compartments [71]. When epitope-tagged NHE3 was stably expressed in NHE-deficient Chinese hamster ovary (CHO) cells, a sizable fraction was found in recycling endosomes [71], and the plasma membrane NHE3 is endocytosed via a clathrin-mediated pathway [72]. Ectopic expression in Madin-Darby canine kidney (MDCK) cells showed that NHE3 exists in four distinct subcompartments: (i) a virtually immobile subpopulation that is retained on the apical membrane by interaction with the actin cytoskeleton in a manner that depends on the sustained activity of Rho GTPases; (ii) a mobile subpopulation on the apical membrane, which can be readily internalized; (iii)-(iv) two intracellular compartments that can be differentiated by their rate of exchange with the apical pool of NHE3 [73].

McDonough and colleagues have shown through a series of in vivo studies that NHE3 retracts in intact proximal tubules via a two-step process, from villi to the intermicrovillar cleft and then to a higher density membrane pool that appears to serve as a recruitable storage pool [61, 62]. Whether similar trafficking of NHE3 occurs at the brush border membrane of intestinal epithelial cells is not known.

Lipid rafts are discrete membrane domains that are enriched in glycosphingolipids and cholesterol and that are resistant to solubilization in cold Triton X-100 [74]. Studies based on detergent solubility, density gradient, and manipulation of membrane cholesterol content have shown that approximately half of apical membrane NHE3 is localized in lipid rafts and that NHE3 activity and trafficking are lipid rafts dependent [59, 75]. These findings imply that the presence of NHE3 with lipid rafts may be important for the temporal compartmentalization of membrane signaling, trafficking, and transport activity.

3.3. Protein-Protein Interaction. The C-terminal cytoplasmic tail of NHE3 is capable of interacting with a large number of cellular and structural proteins, some of which link NHE3 to the cytoskeletal network. Indeed, NHE3 protein exists as part of a large complex in rabbit ileal brush border membrane [76]. One area of NHE3 regulation that has been subjected to intense studies is the interaction with PDZ (postsynaptic density 95, discs large, and zonula occludens-1) domain-containing scaffold proteins, such as Na^+/H^+ exchanger regulatory factor 1 (NHERF1, SLC9A3R1) and NHERF2 (E3KARP, SLC9A3R2), and more recently with PDZK1 (CAP70/NHERF3) and IKKPP (PDZK2/NHERF4) [49, 52–55, 77–82]. These studies collectively raised the novel paradigm that the activity of NHE3 can be controlled by its state of association with other cellular proteins. Other well-studied interacting proteins include megalin, dipeptidyl peptidase IV, and calcineurin homologous protein [83–85]. In addition, binding of ezrin and phosphlipase C-γ has been reported [86, 87].

A bulk of NHE3 regulation by NHERF proteins is based on heterologous expression in Na^+/H^+ exchanger-deficient PS120 fibroblasts, opossum kidney (OK) cells, and intestinal Caco-2 cells [53–55, 77, 79, 87, 88]. In most part, there are significant overlaps on the regulation of NHE3 among the cultured cells of different origins. However, studies using mice with targeted deletion of NHERF1 have revealed an unanticipated disparity in the regulation of NHE3 in the kidney versus intestine. For example, the importance of NHERF1 in PKA-dependent inhibition of NHE3 was implicated from the studies based on heterologous expression of NHERF1 in PS120 fibroblasts and OK cells [54, 55, 89]. As expected, Nherf1$^{-/-}$ mice showed defective regulation of NHE3 by 8-br-cAMP in the kidney and cAMP-mediated phosphorylation of NHE3 was impaired [90, 91]. However, Murtazina et al. [92] found that 8-Br-cAMP-mediated regulation of NHE3 was intact in NHERF1-deficient ileum. Similarly, forskolin-mediated Na^+ absorption in the jejunum and proximal colon was unaffected by deletion of NHERF1, despite that forskolin-induced HCO3- secretion was abolished in Nherf1$^{-/-}$ duodenum [93]. An additional pathway regulating NHE3 involving EPAC (exchange protein directly activated by cAMP) was identified in the Nherf1$^{-/-}$ ileum [92, 94], but it does not explain the nonobligatory role of NHERF1 in NHE3 regulation in the intestine. On the other hand, forskolin- and Ca^{2+}-mediated inhibition of NHE3 was abolished in Pdzk1$^{-/-}$ colon, suggesting that PKA-dependent regulation of NHE3 in the intestine is facilitated by a different member of NHERF regulatory proteins [95]. Interestingly, the association of PDZK1 and NHE3 was never been determined in cultured cells, and likewise the role of NHERF1 in NHE3 regulation had not been tested in intestinal cells. The expectation that deletion of NHERF1 should abolish PKA-dependent regulation of NHE3 in the kidney and intestine might have been in part due to an assumption that NHE3 regulation in renal and intestinal epithelial cells is similar.

In the face of a growing list of proteins that interact with NHE3, it remains unclear how NHE3 associates with a large number of proteins. We do not fully understand the scope of protein interactions, but emerging data suggest that the interaction between NHE3 and many of these proteins is dynamic. For example, a change in intracellular Ca^{2+} is associated with inhibition as well as stimulation of NHE3 [96, 97]. The effects of Ca^{2+} agonists might vary depending on cell types and we recently showed that it is also subjected by the state of NHE3 association with one or more binding partner [98]. In this study (Figure 2), we showed that Ca^{2+}-dependent inhibition of NHE3 mediated by its association with NHERF2 was opposed by the interaction of NHE3 with IRBIT (IP_3 receptor binding protein released with IP_3), which enhanced translocation of NHE3 to the surface membrane via a mechanism dependent on calmodulin (CaM) and calmodulin-dependent kinase II [98]. Other studies have shown that the protein interaction of NHE3 also varies along the microdomains of the brush border membrane, and the specific interaction determines the functional state of NHE3. For example, the interaction between NHE3 and megalin occurs in intermicrovillar clefts, where megalin-bound NHE3 is inactive [84, 99]. On the contrary, the association of NHE3 with DPPIV occurs predominantly in the microvillar region in which NHE3 is active [85].

3.4. Transcriptional Regulation. Most of NHE3 regulation in the literatures describes acute regulation that occurs within the time span of minutes to a few hours of cellular activation. Acute regulation is rapid and reversible and often involves changes in phosphorylation, trafficking, and dynamic interaction with regulatory proteins. On the contrary, chronic regulation of NHE3 involves transcriptional and translational modification of NHE3. There is a great deal of information on NHE3 regulation by glucocorticoids, aldosterone, metabolic acidosis, and chronic hyperosmolality [35, 46–48, 79, 100–106]. Moreover, proinflammatory cytokines, such as IFN-γ and TNF-α, enteropatogenic microbial products downregulate NHE3 expression [107–110].

In short, the regulation of NHE3 is complex with a myriad of cellular signals converge onto a single protein at different levels. One prime example of the complex and integrated

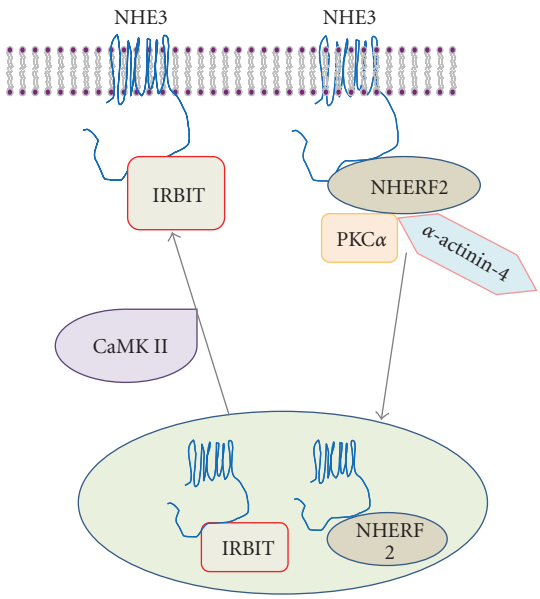

Figure 2: NHE3 can be regulated via interaction with different proteins. A tentative model of regulation of NHE3 by IRBIT and NHERF2 is shown as an example. NHE3 is retrieved into a cytoplasmic pool by a mechanism dependent on NHERF2-PKCα-actinin-4 [53]. IRBIT stimulates NHE3 activity by inducing exocytic trafficking of NHE3 to the surface membrane (adapted from He et al. [111]).

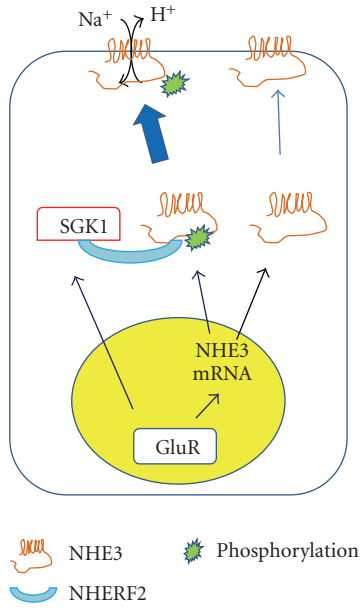

Figure 3: Activation of NHE3 by glucocorticoids. Glucocorticoids stimulate NHE3 mRNA and protein expression. This stimulation results in an increase in NHE3 protein expression at the apical membrane. In addition, scaffolding of SGK1 by NHERF2 allows phosphorylation of NHE3. The phosphorylation of NHE3 by SGK1 facilitates sorting of NHE3 to the apical membrane.

regulation of NHE3 is the regulation by glucocorticoids that affect NHE3 via multiple pathways that are often overlapping (Figure 3) [49, 52, 79, 112–114]. The major mechanism of NHE3 regulation by glucocorticoids is by genomic regulation of NHE3 resulting in increased NHE3 mRNA level [47, 102, 112]. However, an acute effect of glucocorticoids on Na^+/H^+ exchange in the absence of a parallel change in NHE3 mRNA abundance led to the identification of SGK1 as a key kinase targeting NHE3 [79]. Scaffolding of NHE3 and SGK1 by NHERF2 facilitates phosphorylation of NHE3 by SGK1 and leads to the translocation of NHE3 to the cell surface [49, 52]. These findings were supported by the study using mice deficient in SGK1 expression, in which glucocorticoid-mediated stimulation of NHE3 activity and NHE3 translocation to the apical membrane of mouse intestine were significantly attenuated [115].

Is NHE3 More than a Transporter? NHE3 is thought to mediate bulk of Na^+ and water absorption by the intestine and colon. NHE3 is a target of proinflammatory cytokines, such as TNF-α and INF-γ [107, 110]. $Nhe3^{-/-}$ mice overexpress INF-γ and INF-γ-inducible genes in the small intestine as part of a homeostatic response to impaired transepithelial Na^+ absorption. In inflammatory bowel disease (IBD), INF-γ expression is characteristically elevated [116]. Sullivan et al. [117] recently demonstrated that the expression level of NHE3 along with NHERFs was decreased in mucosal biopsies of IBD patients and the mouse colon of dextran sodium sulfate (DSS)-induced colitis. Similarly, the characteristic watery diarrhea in collagenous colitis was in part attributed to reduced net NaCl absorption [118]. Microarray analysis of $Nhe3^{-/-}$ mice revealed that, in addition to the genes of ion transporters and ion channels, genes involved in response to stress, inflammation, and chemotaxis were altered [119]. A following study by the same group showed that NHE3 deficiency compromised innate immune response rendering the animals more susceptible to DSS-induced colitis, and the authors suggested a role of NHE3 as a modifier gene [120]. This is not the first case that an Na^+/H^+ exchanger assumed a role of modifier of other genes. The absence of NHE1 can induce distinct changes at the expression level of several genes in various brain regions [121]. One question that arises from the studies of $Nhe3^{-/-}$ mice is whether the dysregulation of innate immune response in $Nhe3^{-/-}$ mice arises from the decreased NaCl and water uptake or as a secondary response to stress exerted by the absence of NHE3 protein. Or is it possible that some of these changes are related to the ability of NHE3 to interact with structural proteins? For instance, NHE3 is indirectly linked to the junction complexes through its interaction with PDZ-containing proteins such that absence of NHE3 disrupts the intermolecular network, altering the gene expression levels and the barrier function. However, there is yet no report of colitis in mice deficient in NHERF proteins, albeit decreased NHE3 expression was shown [80, 92, 93]. Although the mechanisms underlying the occurrence of colitis in $Nhe3^{-/-}$ mice require further study, these new findings represent a novel paradigm that NHE3 may serve multifunctions in addition to the transepithelial absorption of Na^+.

4. Future Directions

The activity of NHE3 is maintained and modulated so as to regulate intracellular volume, pH, and blood pressure. As discussed in this paper, multiple cellular pathways involving phosphorylation, trafficking, and interaction with cellular proteins are integrated to regulate NHE3 activity. Among the mechanisms of NHE3 regulation, the dynamic and coordinated nature of the increasing list of NHE3 interacting proteins should be a subject of future studies. The recent in vivo findings from animals with targeted deletion of a Na^+/H^+ exchanger or an accessory protein have helped to validate the previous findings, but in some cases several new paradigms have emerged from the in vivo studies. In particular, the findings in nontransport roles of NHE3 add a new dimension to the pathological function of NHE3 and warrant further studies in the roles of NHE3 in diarrhea associated with inflammation.

Acknowledgments

This work was supported in part by a Grant (DK061418) from the National Institutes of Health. P. He was supported by a postdoctoral fellowship from the American Heart Association.

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