Regulation of cell survival by Na\(^{+}/\)H\(^{+}\) exchanger-1

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Schelling JR, Abu Jawdeh BG. Regulation of cell survival by Na\(^{+}/\)H\(^{+}\) exchanger-1. Am J Physiol Renal Physiol 295: F625–F632, 2008. First published May 14, 2008; doi:10.1152/ajprenal.90212.2008.—Na\(^{+}/\)H\(^{+}\) exchanger-1 (NHE1) is a ubiquitous plasma membrane Na\(^{+}/\)H\(^{+}\) exchanger typically associated with maintenance of intracellular volume and pH. In addition to the NHE1 role in electroneutral Na\(^{+}/\)H\(^{+}\) transport, in renal tubular epithelial cells in vitro the polybasic, juxtamembrane NHE1 cytosolic tail domain acts as a scaffold, by binding with ezrin/radixin/moesin (ERM) proteins and phosphatidylinositol 4,5-bisphosphate, which initiates formation of a signaling complex that culminates in Akt activation and opposition to initial apoptotic stress. With robust apoptotic stimuli renal tubular epithelial cell NHE1 is a caspase substrate, and proteolytic cleavage may permit progression to apoptotic cell death. In vivo, genetic or pharmacological NHE1 loss of function causes renal tubule epithelial cell apoptosis and renal dysfunction following streptozotocin-induced diabetes, ureteral obstruction, and adriamycin-induced podocyte toxicity. Taken together, substantial in vivo and in vitro data demonstrate that NHE1 regulates tubular epithelial cell survival. In contrast to connotations of NHE1 as an unimportant “housekeeping” protein, this review highlights that NHE1 activity is critical for countering tubular atrophy and chronic renal disease progression.

apoptosis; chronic kidney disease; ezrin/radixin/moesin; necrosis; tubular atrophy

ALTHOUGH CHRONIC KIDNEY DISEASE (CKD) is initiated by glomerular injury in most instances, careful morphometric studies have demonstrated that interstitial fibrosis and tubular atrophy correlate better than glomerular pathology with glomerular filtration rate (92, 97), suggesting that tubular atrophy is a superior predictor of CKD progression. A commonly cited hypothesis for the pathogenesis of tubular atrophy, which is merely a term for the absence of renal tubular epithelial cells, has been ischemia secondary to an imbalance between high oxygen demand of tubule cells (particularly proximal tubule) and relatively decreased blood flow and oxygen supply following peritubular capillary loss (14, 49). However, if ischemia were the only mechanism, one would expect tubulointerstitial pathology to parallel glomerular pathology in severity, which is often not observed (92, 97). Furthermore, chronic ischemia usually leads to a combination of apoptosis and necrosis, and the latter is a rare pathological feature of most types of CKD. Additional factors must therefore contribute to the pathogenesis of tubular atrophy.

Enhanced tubular epithelial cell apoptosis has been noted in both human renal disease and animal models of CKD (80). Because cell number is tightly regulated by a balance between apoptosis and survival factors (113), these data suggest that tubular atrophy may be partially governed by apoptosis pathways (49, 98, 99). The purpose of this review is to summarize data regarding the role of Na\(^{+}/\)H\(^{+}\) exchanger-1 (NHE1) in cell survival, particularly in proximal tubule, in the context of CKD.

NHE1 Biology

Na\(^{+}/\)H\(^{+}\) exchange activity was initially demonstrated in 1972 in the bacterium Streptococcus faecalis (38), and cDNA encoding the first mammalian NHE isoform (NHE1) was cloned in 1989 (96). Since then, NHEs have been described in virtually all prokaryotic and eukaryotic cells and nine mammalian isoforms have been identified (reviewed in Refs. 74, 79). Human NHE1 is an 815-amino acid glycoprotein with conserved sequence between mammalian isoforms. NHE1 structure includes a 14-amino acid NH2-terminal cytoplasmic tail, 12 \(\alpha\)-helical transmembrane domains through which Na\(^{+}\) and H\(^{+}\) are exchanged, and a long (315 amino acids in human) cytoplasmic domain that serves a regulatory function. The NHE1 gene (SLC9A1) maps to chromosome 1p36.11 in humans and to chromosome 4D2.3 in mice.

NHE1 is ubiquitously expressed in a plasma membrane distribution. In polarized epithelial cells, newly synthesized NHE1 sorts to both apical and basolateral plasma membranes, but mature NHE1 is localized almost exclusively to the basolateral membrane (27). Detailed NHE1 targeting mechanisms have not been described, although NHE1 appears to specify its own membrane distribution and retention through organization of, and docking with, actin (30) as well as through interactions with other basolateral membrane proteins within lipid rafts (18). Additional studies have confirmed that NHE1 localizes to lipid rafts (21, 32), which are enriched for phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2], an inner leaflet phospholipid that binds and activates both NHE1 and ezrin/radixin/moesin (ERM) (see below). However, the significance of NHE1 within lipid rafts has been questioned because lipid raft disruption with \(\beta\)-methylcyclodextrin did not affect NHE1-dependent Na\(^{+}/\)H\(^{+}\) exchange and NHE1 regulation by clustering within

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lipid domains may be cell type specific (21, 32). NHE1 anchorage to cytoskeleton and discrete membrane domains is consistent with minimal NHE1 regulation by endocytic cycling (102) and a long basolateral membrane half-life of 20–24 h (23, 27).

NHE1 is often referred to as a housekeeping protein because major functions include maintenance of intracellular pH and volume. H⁺-sensing and osmotic regulatory domains have been localized to specific transmembrane and cytosolic regions of the transporter, respectively (13, 119). NHE1 activation by either intracellular acidosis or cell shrinkage results in electro-neutral (1:1 stoichiometry) Na⁺/H⁺ exchange. Under basal conditions, NHE1 activity is minimal. However, multiple extracellular cues, including growth factors, hormones, integrin engagement, and shear stress activate NHE1, which then cooperatively regulates many cell phenotypes, such as proliferation (12, 72, 83), differentiation (84, 121), adhesion (114), and migration (29, 100).

The NHE1 cytosolic tail regulates Na⁺/H⁺ exchange by binding to multiple partners [calmodulin, calcineurin homologous protein (CHP), carbonic anhydrase II, ER, heat shock protein 70 (HSP70), PI[4,5]P2, and the 14-3-3 adaptor protein]. The COOH-terminal portion of the NHE1 cytoplasmic tail contains several Ser/Thr residues, which are constitutively phosphorylated in quiescent cells (95) but can then be further phosphorylated in response to the above-mentioned extracellular stimuli. A notable exception is NHE1 activation by hypertonicity, which does not require NHE1 phosphorylation (37, 69).

Multiple Ser/Thr kinases phosphorylate NHE1, including Ca²⁺/calmodulin-dependent kinase II (CaMKII), extracellular signal-regulated kinases (ERK1/2), Janus-activated kinase 2 (JAK2), NCK-interacting kinase (NIK), p38 MAP kinase, p90 ribosomal S6 kinase (p90Rsk), and Rho kinase (p160ROCK) (reviewed in Refs. 8, 103). Protein kinase C and phosphatidylinositol 3-kinase (PI3K) have also been implicated in NHE1 regulation, although neither kinase directly phosphorylates NHE1 (reviewed in Ref. 103). Rho kinase is of particular interest because, in addition to directly phosphorylating NHE1 (114, 115, 118), it also contributes to activation of ERM by phosphorylating a conserved COOH-terminal Thr (5, 20, 66, 116), suggesting a pivotal role for Rho kinase in the assembly of an NHE1-based signaling complex that regulates cell survival (discussed below).

To summarize, NHE1 is ubiquitously expressed along the basolateral membranes of polarized epithelial cells. NHE1 is normally inactive, but in response to specific stimuli (including apoptotic stress), the exchanger maintains homeostatic cell volume and pH through Na⁺/H⁺ transport. In most circumstances, Na⁺/H⁺ antiporter activity is regulated by NHE1 cytosolic tail phosphorylation and interaction with adaptor proteins.

**Pharmacological Inhibitors of NHE1**

NHE1-dependent Na⁺/H⁺ exchange is inhibitable by both amiloride analogs [5-(N-ethyl-N-isopropyl)amiloride (EIPA), 5-(N,N-hexamethylene)amiloride (HMA)] as well as a newer class of NHE1-selective acylguanidine-derived compounds (51, 65), such as cariporide, eniporide, and sabiporide. Orłowski and Grinstein (78) previously showed enhanced NHE1 sensitivity to amiloride derivatives compared with NHE3, the other major Na⁺/H⁺ antiporter in proximal tubule. Amiloride binds NHE1 at the extracellular face of transmembrane segment IV, as evidenced by a single mutation (Phe167Leu) in this region, which abrogates the amiloride effect on Na⁺/H⁺ exchange (78, 120).

**Role of NHE1 as a Tubular Epithelial Cell Survival Factor**

In studies involving ROP-Os/+ and p53 transgenic mouse models of glomerulosclerosis due to reduced nephron number (35, 39, 127), progressive renal disease was accompanied by significant tubular epithelial cell apoptosis within the proximal tubule (49, 98, 99). One plausible mechanism by which NHE1 might regulate proximal tubule cell survival is enhancing Na⁺ entry as a part of regulatory volume increase (RVI)-mediated defense against apoptotic volume decrease (77). When cells are induced to shrink, RVI is coordinated by activation of NHE1 and, in some cells, the AE2 Cl⁻/HCO₃⁻ exchanger and the Na⁺-K⁺-2Cl⁻ symporter (57, 68, 77). The net effect of RVI activation is Na⁺, K⁺, Cl⁻, and H₂O influx, which leads to cell volume reexpansion. However, neither AE2 nor the BSC1 or BSC2 isoforms of the Na⁺-K⁺-2Cl⁻ symporter are expressed in proximal tubule (2, 34, 45), suggesting a prominent role for NHE1 in the opposition of proximal tubule cell volume decrease induced by apoptotic or hypertonic stress (58, 77, 82, 91, 124).

Neither mice with targeted NHE1 gene deletion nor a spontaneous point mutation that introduces a premature stop codon, resulting in truncation between the 11th and 12th NHE1 isoforms of the Na/Cl⁻ symporter (57, 68, 77). The net effect of RVI activation is Na⁺, K⁺, Cl⁻, and H₂O influx, which leads to cell volume reexpansion. However, neither AE2 nor the BSC1 or BSC2 isoforms of the Na⁺-K⁺-2Cl⁻ symporter are expressed in proximal tubule (2, 34, 45), suggesting a prominent role for NHE1 in the opposition of proximal tubule cell volume decrease induced by apoptotic or hypertonic stress (58, 77, 82, 91, 124).

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Invited Review

**REGULATION OF CELL SURVIVAL BY NHE1**
vivo data from multiple renal disease models indicate that tubular epithelial cell NHE1 is cytoprotective.

In vitro, proximal tubule cell lines subjected to staurosporine-induced apoptotic stress demonstrate increased NHE1 Na\(^+/H^+\) exchange activity, which peaks at 30–60 min and decreases precipitously thereafter (123). The explanation for subsequent loss of NHE1 function, which correlates with apoptotic features, has not been thoroughly investigated. However, preliminary studies indicate that the NHE1 cytosolic tail may be a caspase-3 substrate (124). Because the cleavage site(s) has not yet been identified, we can only speculate that decreased NHE1 function may be due, at least in part, to caspase-mediated degradation. A cytoprotective role of NHE1 is also supported by experiments in which NHE1-null proximal tubule cells demonstrated enhanced sensitivity to multiple apoptotic stimuli compared with wild-type cells (50, 123). PS120 fibroblasts, which do not express NHE1, are also more susceptible to apoptotic stress compared with wild-type fibroblasts (6, 124), a phenomenon that is partially reversed by NHE1 reconstitution (61, 124).

Collectively, the data indicate that NHE1 activation represents an initial defense against apoptotic stress. However, with overwhelming or sustained apoptotic stimuli, the prosurvival NHE1 effect can be surmounted, which allows cells to proceed toward apoptosis.

**Regulation of Cell Survival by NHE1-Mediated Na\(^+/H^+\) Exchange**

In studies with lymphocytes, Bortner and Cidlowski (16, 17) demonstrated that apoptosis induction is accompanied by initial, rapid exchange of intracellular K\(^+\) for Na\(^+\), although the net intracellular ion content is decreased, resulting in cell shrinkage (77). In contrast to lymphocytes and mesenchymal cells, epithelial cells are relatively resistant to shrinkage (15) because of robust expansion through activation of RVI pathways (77). As mentioned above, NHE1 is an important component of this pathway (68, 77, 107), with activation resulting in Na\(^+\) and H\(_2\)O influx that effects cytoplasmic volume expansion. Consistent with this notion, NHE1 regulation of cell volume has been implicated as a mechanism of survival in multiple cell lines (Fig. 1, left; Refs. 58, 59, 61, 124).

NHE1-dependent Na\(^+\) entry is also accompanied by H\(^+\) extrusion and intracellular alkalization, which could defend against apoptosis by inhibiting caspase (67, 94, 101), endonuclease (3, 7) or acidic sphingomyelinase (86) catalysis, preventing conformational changes in Bax, a proapoptotic Bcl-2 family member (4, 108), or removing cytosolic H\(^+\) resulting from apoptosis-induced mitochondrial H\(^+\) release (67). Stimulation of mitochondrial-mediated apoptosis has been associated with brief intracellular alkalization (10, 47) due to NHE1 activation (41, 48, 123), consistent with an NHE1 role in the early rescue response to apoptotic stress (Fig. 1).

Most studies have demonstrated that apoptosis is ultimately accompanied by cytosol acidification (reviewed in Ref. 55). NHE1 inhibition has been implicated as an explanation for diminished intracellular pH (pHi) (40, 64), with possible mechanisms of inactivation including ATP depletion, NHE1 dephosphorylation, or cleavage (55, 124). Defining the exact role of NHE1-regulated H\(^+\) transport in apoptosis is complicated, though, because in vitro experiments often do not employ HCO\(_3^-\)-containing buffer, in which pH\(_i\) can be controlled by multiple ion exchangers, resulting in minimal change in pH\(_i\) (61). In addition, it has recently been recognized that NHE1-dependent H\(^+\) extrusion and acidification of the extracellular microenvironment regulates membrane protein and cell behavior (9, 18, 106).

In light of these findings, we postulate that apoptotic stress triggers early NHE1-dependent defense against cell volume reduction and intracellular acidification. Later stages of apoptosis are accompanied by diminished NHE1 activity, which facilitates apoptotic cell death by allowing cell shrinkage and intracellular acidification, which is favorable for the activity of many proapoptotic proteins.

**Regulation of Cell Survival by NHE1 Na\(^+/H^+\) Transport-Independent Mechanisms**

In renal tubular epithelial cells exposed to apoptotic stress (123) or migrating fibroblasts (29, 31), a region of polybasic amino acids within the juxtamembrane domain of the NHE1 cytosolic tail physically associates with the NH\(_2\) terminus of ERM proteins, which tether transmembrane proteins, such as NHE1, to cytoskeleton (31). ERM are predominantly expressed in an apical distribution of polarized epithelial cells and, in proximal tubule cells, indirectly interact with NHE3 through Na\(^+/H^+\) exchanger regulatory factor (NHERF) (56, 73). Because NHE1 localizes to the basolateral membrane, it is important to note that in epithelial cells expressing endogenous NHE1 and ERM ezrin transiently shuttled to the lateral membrane in response to NHE1 stimulation (50), where it could then potentially interact with NHE1.

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Fig. 1. Na\(^+/H^+\) exchanger-1 (NHE1)-dependent mechanisms of cell survival. Apoptotic stress elicits 2 major, NHE1-regulated cell survival pathways. Decreased cytoplasmic volume leads to NHE1-dependent Na\(^+/H^+\) exchange, which mediates regulatory volume increase (RVI) and cytosolic alkalization. NHE1 activation also stimulates phosphorylation and recruitment of cytoskeleton ezrin/radixin/moesin (ERM) linkers to the NHE1 cytosolic tail. The NHE1-ERM interaction leads to the formation of a signaling complex that includes phosphatidylinositol 3-kinase (PI3K) and, ultimately, the prosurvival kinase Akt, which phosphorylates multiple substrates, some of which are depicted, resulting in apoptosis inhibition. Apaf1, apoptotic protease-activating factor-1; BAD, proapoptotic Bcl-2 family member; CytoC, cytochrome c; FKHR, forkhead transcription factor; PH, pleckstrin homology domain; Pip2, phosphatidylinositol 4,5-bisphosphate; Pip3, phosphatidylinositol 3,4,5-trisphosphate; STS, staurosporine. Reprinted with permission from Wu et al. (123).
The NHE1-ERM interaction is at least partly independent of Na\(^+/\)H\(^+\) exchange (31, 123), indicating that the NHE1 cytoplasmic tail appears to serve as a scaffold to direct signal transduction pathways and regulate ion transport-independent cell functions (Fig. 1, right; Ref. 70). On exposure to apoptotic stress or growth factor stimulation, NHE1 and ERM are both rapidly activated and bind to one another (25, 123). ERM activation requires both phosphorylation of a conserved COOH-terminal Thr and localization with the membrane phospholipid PI(4,5)P\(_2\) (20). Interestingly, PI(4,5)P\(_2\) binding is also required for NHE1 activation (1); we speculate that PI(4,5)P\(_2\) may therefore target NHE1 and ERM to the same plasma membrane domain and dock these molecules for juxtaposition to downstream effectors. Phosphorylation of activated ERM at Tyr353 recruits the prosurvival PI3K (33), which phosphorylates PI(4,5)P\(_2\) and subsequently leads to Akt-dependent regulation of multiple survival pathways (Fig. 1), including in renal tubular epithelial cells (110, 123). This specific cell survival pathway has also been demonstrated in the DU-145 prostate carcinoma cell line, which revealed that amiloride survival pathway has also been demonstrated in the DU-145 renal tubular epithelial cells (110, 123). This specific cell survival pathway has also been demonstrated in the DU-145 prostate carcinoma cell line, which revealed that amiloride enhanced TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis by preventing PI3K and Akt phosphorylation (52).

In migrating cells NHE1, ERM, and Akt colocalize at the leading edge of fibroblasts (29), and PI3K is activated in conjunction with NHE1 in breast cancer cells (88), suggesting confluence of cell migration and survival signaling pathways. This concept is consistent with the hypothesis that integrins, which mediate cell migration and are cooperatively activated with NHE1 (42, 100, 106, 114), represent a type of dependence receptor that regulates cell survival (19, 104). According to this hypothesis, migrating cells survive through perpetual probing of the extracellular environment by integrins for the appropriate matrix ligand. Adherent cells expressing unligated integrins undergo apoptosis by a mechanism, which is distinct from detachment and anoikis, that involves recruitment of caspase-8 (104, 105). This phenomenon of integrin-mediated cell death suggests that migration may be an in vitro surrogate for cell survival and further substantiates a role for NHE1/ERM/PI3K/Akt complex in this process.

The preponderance of evidence indicates that NHE1 and ERM localization and activation are concomitantly upregulated (29, 31, 43, 123) and culminate in inhibition of apoptosis (43, 123). In addition to a role in apoptosis, the NHE1-ERM interaction has also been implicated in the pathophysiology of necrosis. In a recent study by Jung et al. (44), the death domain-associated protein Daxx was shown to interact with NHE1 at the ERM binding domain. In vitro models of ischemia, Daxx displaced ezrin binding to NHE1, which was associated with NHE1 activation and release of lactate dehydrogenase, a marker of necrotic cell death. This observation is consistent with NHE1 mediation of Na\(^+\) influx, leading to cell swelling and necrosis (77). The precise role and ordering of NHE1-ERM interaction will require further investigation, however, inasmuch as ERM have also recently been described to be upstream and inhibitory to NHE1 in some systems (62, 85).

As mentioned above, the best-described function of ERM is to provide structural support by linking transmembrane proteins with actin cytoskeleton (20). Although ERM function in this capacity has not been specifically addressed in the setting of NHE1-regulated cell survival, multiple studies have shown that ERM-directed cytoarchitecture is critical for normal and apoptotic cell morphology. In the initial stages of CD95 (Fas)-stimulated T-cell apoptosis, Fas is clustered in a polarized fashion, and both the Fas expression pattern and apoptosis execution require ERM colocalization and actin polymerization (81). We speculate that one ramification of ERM translocation to these polarized death domains could be depletion from prosurvival sites, such as the NHE1-regulated survival signaling complex. In later stages of apoptosis, multiple cytoskeletal and structural proteins are degraded by caspases (26), which leads to the apoptotic cell volume decrease. We therefore propose that by binding the NHE1 cytosolic tail ERM promote cell survival signaling as well as structural integrity in cells under apoptotic siege.

**Fig. 2.** Working model to address different NHE1 roles in common pathophysiological processes. NCX1, Na\(^+\)/Ca\(^2+\) exchanger-1; Na\(\text{in}\), intracellular Na\(^+\).

**Role of NHE1 in Survival of Nonrenal Cells**

Because NHE1 is ubiquitously expressed, it is beyond the scope of this review to summarize the effects of NHE1 on survival in all tissues. Some of the studies mentioned above regarding NHE1 in cell migration were conducted in cancer cell lines (88, 106), and the role of NHE1 in tumor invasiveness and metastasis has been extensively reviewed (22). Re-
sistance to apoptosis is a cardinal feature of oncogenesis, although few studies have examined a direct role for NHE1 in this process. Several studies have demonstrated that pharmacological inhibition of NHE1 with amiloride analogs caused apoptosis in leukemia cells (24, 54, 82, 91). In a recent report with the HT29 colon carcinoma cell line, sensitivity to the chemotherapeutic agent cisplatin was associated with cytosol acidification, which may be due to NHE1 inhibition (86). Similar results were observed in breast cancer cells, because paclitaxel-induced apoptosis was accompanied by abrogation of NHE1 activity and administration of paclitaxel plus the NHE1 inhibitor cariporide caused synergistic induction of apoptosis (90). An interesting possible mechanism of tumor cell survival is related to NHE1-regulated intracellular alkalization and stimulation of aerobic glycolysis (Warburg effect) (89), which has been linked to Akt-mediated apoptosis suppression (53, 93). Taken together, the data support that the idea that NHE1 activation promotes cancer cell survival, proliferation, invasiveness, and metastasis, which has led to proposals that NHE1 might be an exploitable therapeutic target, particularly for metastasis blockade (22, 25, 91).

In contrast to studies in renal tubular epithelial or cancer cell lines, NHE1 activation has convincingly been found to promote cell death in studies involving cardiac myocytes (46). NHE1 is the predominant Na⁺/H⁺ exchanger isoform in sarcolemma and a major source of H⁺ extrusion in cardiac myocytes (117). NHE1 activation is deleterious in a number of cardiac conditions, including left ventricular hypertrophy, congestive heart failure, and myocardial infarction (36, 75, 126). Importantly, isolated perfused hearts from NHE1-null mice, or hearts pretreated with an NHE1 inhibitor, are protected from ischemia-reperfusion injury (122). These studies are consistent with limited in vitro experiments that demonstrate that NHE1 activation regulates cardiac myocyte apoptosis (60, 111).

The apparent opposite effects of NHE1 on cell survival in cardiac myocytes and proximal tubule cells are largely due to different stimuli for NHE1 activation and/or cell type specificity (see Fig. 2). In CKD we speculate that apoptotic proximal tubule cell volume shrinkage is the proximate trigger for NHE1 stimulation, whereas intracellular acidosis from anaerobic metabolism stimulates NHE1 in ischemic myocardial cells, which can lead to necrosis or apoptosis, both of which have been described in the pathophysiology of myocardial infarction (36, 109, 126). After apoptotic stress the resulting increase in intracellular Na⁺ (Na⁺) would lead to desirable restoration of cell volume, whereas with ischemia elevation in Na⁺ would cause pathologic cell swelling (77), a central feature of necrosis.

Compensatory mechanisms to extrude Na⁺ include reverse-mode activation of the NCX1 Na⁺/Ca²⁺ exchanger, which may lead to increased Ca²⁺ and apoptosis by the mitochondrial pathway. NCX1 is abundant in sarcolemma of cardiac myocytes, but in kidney NCX1 expression is scant and restricted to connecting tubules (87). A recent study demonstrates that ischemic kidney damage was abrogated by NHE1 inhibition (125), indicating that heart and kidney respond similarly to NHE1 blockade therapy for acute ischemic insults. Because proximal tubular epithelial cells do not express NCX1, and would therefore have limited capacity to generate compensatory Na⁺/Ca²⁺ exchange, we postulate that NHE1 primarily mediates cell swelling and necrosis in renal ischemia.

The NHE1 data in heart models are so compelling that large clinical trials have been undertaken to test the efficacy of the NHE1 inhibitor cariporide as adjunctive therapy for myocardial infarction. The GUARDIAN trial showed no mortality benefit compared with placebo (112). EXPEDITION showed decreased myocardial infarction incidence with cariporide therapy but overall increase in mortality, primarily from excess stroke (71). Interestingly, unspecified renal side effects were significantly more common in the cariporide group (http://www.medscape.com/viewarticle/464672), which raises the issue that NHE1 may theoretically be beneficial to the heart in the peri-infarct period, but could be deleterious to the kidney.

Summary

NHE1 is often referred to as a housekeeping protein, implying that it directs pedestrian functions. On the contrary, we propose that tubular epithelial cell NHE1 is a critical survival factor, which may regulate key aspects of CKD progression. In addition to facilitating Na⁺/H⁺ exchange, in vitro studies have shown that NHE1 functions as a molecular scaffold, by binding ERM and PI(4,5)P₂ and directing the formation of a signaling complex, which leads to opposition of renal tubular epithelial cell apoptosis. Data from multiple in vivo models of kidney disease demonstrate that NHE1 promotes renal tubule epithelial cell survival, suggesting that strategies to preserve NHE1 activity may be therapeutically beneficial for CKD.

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