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Mini Review

Role of the Na^+/H^+ exchanger on the development of diabetes mellitus and its chronic complications

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ABSTRACT

Micro- and macrovascular complications are the main cause of morbidity and mortality in diabetes mellitus. The Na^+/H^+ exchanger (NHE) is a family of proteins which exchange Na^+ for H^+ according to their concentration gradients in an electroneutral manner. The exchanger also plays a key role in several other cellular functions including proliferation, differentiation, apoptosis, migration, and cytoskeletal organization. Since not much is known on the relationship between NHE and diabetes mellitus, this review outlines the contribution of NHE to chronic complications of diabetes mellitus, such as diabetic nephropathy; diabetic cardiomyopathy.

1. Introduction

The stability of cytoplasmic pH (pH_i) in a controlled physiological range is critical for normal cell functions. In fact, the activity of intracellular enzymes, the interaction of cytoskeletal elements, the rate at which cells grow and differentiate all depend on pH_i [1]. Cells can minimize significant pH_i fluctuations through several H^+ transport systems; the best known system is represented by the Na^+/H^+ exchanger (NHE) family, which exchanges Na^+ for H^+ according to their concentration gradients, thus promoting the regulation of pHi and cell volume [2]. NHE is an amiloride-sensitive, electroneutral exchange system present in the plasma membrane of most mammalian cells [3]. NHE is a transmembrane protein responsible for alkalinization and control of intracellular acidosis by the removal of hydrogen and influx of sodium. It is one of the most studied plasma membrane mechanisms involved in proton transport and directly controls essential parameters such as cellular pH, volume and growth. Among a number of cellular acid–base transport systems, each regulating pHi set points [4,5], NHE is the main mechanism correcting an acute load, and is the only mechanism working without carbonate. Altered NHE activity has been linked to the pathogenesis of several diseases, including essential hypertension, diabetes, congenital secretory diarrhea, tissue damage caused by ischemia/reperfusion and oncogenic transformation [6].

The 10 members of the NHE family described so far show a particular tissue distribution pattern. The isoform NHE-1 is found in the plasma membrane of most mammalian cells and is normally described as the housekeeping isoform [7]. Other isoforms have a more restricted tissue distribution and appear to regulate more specialized functions: NHE-2, NHE-3 and NHE-4 are expressed predominantly in the kidney and gastrointestinal tract, while NHE-5 is expressed mainly in the brain [8]. Two other classes of NHE isoforms called NHE-6 and NHE-7 seem exclusively localized in intracellular organelles such as mitochondrial and *trans*-Golgi, respectively; these isoforms are expressed in tissues with high metabolism rates such as heart, brain and skeletal muscle [9,10]. Recently, new isoforms called NHE-8, NHE-9 and NHE-10 have been discovered but their intracellular localization is not yet completely elucidated [11,12]. All NHE isoforms characterized consist of about 600–900 amino acids with approximately 40% amino acid homology. Similar NHE isoforms have been identified in a number of lower organisms including *Streptococcus faecalis*, *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, and *Drosophila melanogaster* [13,14].

2. NHE and diabetes mellitus

Normal glucose homeostasis requires precise regulation of insulin secretion, a complex process that pancreatic β-cells achieve through changes in their metabolism [15–17]. Glucose induces changes in β-cell cytosolic pH (pH_c), the mechanisms and role of which in stimulus-secretion coupling are still debated. Except for two studies reporting no effect of glucose on pH_c in mouse β-cells or an acidification in rat islets [18,19], there is a large consensus

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that high glucose increases pH_c in mouse islets [20,21], rat islets and insulin-secreting cell lines [22]. In contrast, there is no agreement on the mechanisms implicated in this alkalinization. Even more confusing is the issue of a possible role of these pH_c changes in insulin secretion. Studies in which changes in β-cell pH_c were imposed by manipulation of pH and ionic composition of the extracellular medium or by exposure to weak bases or acids have led to the contradictory proposals that alkalinization augments or inhibits insulin secretion, and that acidification increases it [23,24]. Other studies, relying on amiloride derivatives to inhibit NHE and cause β-cell acidification, also concluded that low pH_c is beneficial to glucose-induced insulin secretion [25,26]. These proposals are at odds with the fact that glucose increases islet pH_c and with the correlative evidence that only those fuels which increase β-cell pH_c amplify insulin secretion [27]. NHE-1 protects β-cells against strong acidification, but has no role in stimulus-secretion coupling [27].

3. NHE and diabetic nephropathy

Diabetic nephropathy is characterized by the appearance of protein in the urine, elevated arterial blood pressure, and persistent decline in glomerular filtration rate. NHE-3 is responsible for the bulk of salt reabsorption in the proximal tubule, and its activity may be affected the most by the increase in length of this renal segment. Indeed, it has been demonstrated that NHE-3 activity is increased in rats with streptozotocin-induced diabetes [28,29]. The increase in NHE-3 activity in diabetic kidneys was further confirmed in several studies using cell culture models [30]. Administration of angiotensin-converting enzyme inhibitors and angiotensin receptors blockers reduces progression of diabetic nephropathy [31,32]. High glucose concentration and oxidative stress both stimulate NHE-3 activity via angiotensin II receptor activation. Multiple signal pathways are activated by angiotensin II to regulate NHE-3. In diabetic nephropathy where megalin expression is decreased it is possible that more NHE-3 is available to redistribute into the microvilli at the cell surface. Therefore, even more NHE-3 will be delivered to the plasma membrane, and, in absence of megalin, even more NHE-3 will migrate into the microvilli. A decrease in megalin expression would also be predicted to decrease albumin endocytosis and increase intratubular albumin concentration, which would further stimulate NHE-3 expression and further aggravate the renal damage. This model of a potential physiologic role of the formation of NHE-3–megalin complex in the proximal tubule of diabetic kidneys remains to be validated [33].

4. NHE and cardiovascular complications of diabetes

NHE activity has also been correlated with proliferation of vascular cells, and several authors have suggested that the activation of NHE could be considered an upstream event positively coupled to different affections such as diabetes and atherosclerosis [34]. Koliakos et al. [35] have shown that the increase of glucose levels above normal values caused an increase of NHE-1 activity in human monocytes that might be responsible for the subsequent increase in cell adhesion and migration. High glucose concentration can stimulate human monocyte sodium/hydrogen exchanger activity and thus modulate atherosclerosis-related functions. Several pre-clinic studies suggest that NHE inhibitors represent a useful tool to counteract tissue alterations due to myocardial ischemia and reperfusion [36]. Suzuki et al. [37] have investigated the pharmacological effect of *N*-aminoiminomethyl-1-methyl-1-*H*-indole-2-carboxamide methanesulfonate (SM-20220), an inhibitor of NHE, on ischemic brain damage, edema and neutrophil accumulation. The intravenous administration of SM-20220 significantly attenuated all ischemia-induced effects; in particular decreasing neutrophil accumulation. Such a protective effect linked to the inhibition of NHE is also reported in porcine myocardial infarction. Kristo et al. [38] have shown that in animals treated during the preischemic phase with cariporide the infarction size as well as neutrophil accumulation and reactive oxygen species generation were significantly reduced with respect to control animals. These findings suggest that NHE inhibition can represent a new strategy to reduce neutrophil-induced damage during reperfusion. Several other NHE inhibitors including zoniporide, eniporide, and ethylisopropylamiloride have also been shown to furnish cardioprotective effects in vivo [36]. For example, in a canine model of myocardial ischemia–reperfusion injury, the infusion of the NHE inhibitor BIIB-513 before the ischemic phase, was able to reduce the infarction as well as the accumulation of neutrophils and reactive oxygen species generation, suggesting that the BII-513-dependent attenuation of neutrophil activity can be responsible, at least partially, for cardiomyocyte protection [39].

In conclusion, Diabetes mellitus and its chronic complications are multifactorial diseases associated with both genetic and environmental risk factors. Knowledge on factors associated with diabetes mellitus will allow us to better understand the disease and its chronic complications, and may provide us with more effective approaches to treatment and prevention. NHE plays important roles in regulation of protection β-cells against strong acidification and intracellular hydrogen overload. These mechanisms are associated with the pathogenesis of diabetes mellitus or its micro- and macrovascular complications. Therefore, further studies characterizing the molecular basis and regulatory mechanisms of NHE will enable better understanding of the physiological role of this protein on the pathogenesis of diabetes mellitus. Development of drugs that modulate the activity of NHE could, in the future, become new strategies for the treatment of NHE or its chronic complications.

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