EDITORIAL: SODIUM-HYDROGEN EXCHANGE INHIBITION—A SUPERIOR CARDIOPROTECTIVE STRATEGY

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The heart cell possesses precisely regulated mechanisms for maintaining intracellular pH at physiologic values, particularly during pathologic conditions such as myocardial ischemia. Among these processes, the sodium-hydrogen exchanger (NHE) represents a major mode of proton extrusion after acidosis; stimulation of the exchanger is particularly strong at the time of reperfusion although it is also active during ischemia. The idiosyncrasies of nature, however, are often suggestive of much more complex consequences of homeostatic processes than are first apparent, and NHE activation is no exception. Accordingly, it has been proposed[1] that stimulation of the exchanger, despite its necessity for intracellular pH (pH_i) restoration after acidosis, may contribute to myocardial injury. The concomitant influx of sodium ions creates an osmotic imbalance but can also result in elevations in intracellular calcium concentrations through sodium-calcium exchange, thus producing potentially deleterious calcium overloading conditions. Therefore, the antiport is a paradoxic phenomenon because it is a major mechanism for restoration of pH_i after ischemia. As a consequence, however, cell injury occurs.

In this issue of the Journal, Koike and coworkers[2] report the beneficial effects of sodium-hydrogen exchange inhibition in a rabbit model of global normothermic ischemia followed by reperfusion. Using standard recording techniques coupled with phosphorus 31–nuclear magnetic resonance spectroscopy, they convincingly demonstrate that inhibition of the antiport reduces both ischemia- and reperfusion-induced mechanical dysfunction. Of further importance in this study is that the beneficial influence on function was associated with expected effects of NHE inhibition—increased acidosis during ischemia and depressed recovery from the acidosis during early reperfusion. Both of these effects reflect diminished proton extrusion thereby rendering acid neutralization dependent on other pH-regulatory systems. As this study also suggests, and as alluded to by the authors, moderate intracellular acidification as a consequence of NHE activity may produce other beneficial actions in the ischemic and reperfused myocardium as a result of the inhibition of calcium influx by direct inhibitory effects of protons on the calcium channel. The authors also report that the protection afforded by NHE inhibition can be dissociated from preservation of myocardial stores of high-energy phosphates, a finding in agreement with other but not all studies (reviewed in Karmazyn and Moffat[3] and Karmazyn[4]). Therefore this aspect of myocardial protection associated with NHE requires further studies.

The study by Koike and associates[2] adds further strength to the concept that the myocardial NHE represents an effective target for pharmacologic intervention for the protection of the ischemic and reperfused myocardium. This offers the prospect for novel and effective strategies for myocardial protection which, for reasons outlined herein, may be superior to current approaches. From the pharmacologic perspective, an abundance of drugs are available that are relatively potent and specific in their ability to inhibit NHE. Most of them are represented by analogs of amiloride, a potassium-sparing diuretic, such as dimethyl amiloride, which was used by Koike's group.[2] These drugs are not without nonspecific effects, however, particularly when used in higher amounts. Novel agents such as HOE 642 and HOE 694, which are unrelated to the amiloride series, offer perhaps more promise as effective and specific NHE inhibitors.[5, 6] HOE 642 in particular is conceptually a highly attractive potential therapeutic agent because it is specific to the major NHE isoform (termed NHE-1) in the heart. (At least five different NHE subtypes have been identified, which differ in structure, are generally

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Requested for publication April 3, 1996; received for publication May 6, 1996.

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J Thorac Cardiovasc Surg 1996;112:776-7

0022-5223/96 $5.00 + 0 **12/1/74705**

tissue and cell specific, and possess varied sensitivities to inhibition by pharmacologic agents.)

Does inhibition of NHE offer a superior approach to cardiac protection and preservation when assessed in relation to other cardioprotective agents? Current evidence is strongly supportive of this concept for at least the following four reasons (reviewed in detail in references 3 and 4): (1) The protective actions of NHE inhibitors have been uniformly demonstrated, with few, if any, studies failing to show protection. (2) Protection with NHE inhibitors has been observed in a variety of experimental models, animal species as well as modes of injury including both cell necrosis and myocardial stunning. In addition to protective actions against acute short-term myocardial ischemia, NHE inhibition also results in marked myocardial preservation in hearts subjected to prolonged (12-hour) hypothermic storage.[7] (3) An additional salutary effect of NHE inhibition may also involve attenuation of both platelet and neutrophil activation—two factors that are important mediators of cardiac injury—in addition to the direct effects of NHE inhibition on the cardiac cell. (4) Potential toxic effects of specific NHE inhibitors are likely to be minimal because of low activity of the antiport under physiologic conditions thus potentially precluding significant effects on normal homeostatic processes. Moreover, the development of selective tissue-specific NHE inhibitors further diminishes potential for untoward effects. Despite the need for further research, particularly with respect to defining precise mechanism of action, Koike and coworkers[2] further remind us of the potential promise of NHE inhibitors as therapeutic agents, particularly with respect to effective adjuncts in cardioplegic solutions for surgery as well as heart preservation for transplantation.[8]

REFERENCES

1. Lazdunski M, Frelin C, Vigne P. The sodium/hydrogen exchange system in cardiac cells: its biochemical and pharmacological properties and its role in regulating internal concentrations of sodium and internal pH. J Mol Cell Cardiol 1985;17:1029-42.
2. Koike A, Akita T, Hotta Y, Takeya K, Kodama I, Murase M, et al. Protective effects of dimethyl amiloride against postischemic myocardial dysfunction in rabbit hearts: phosphorus 31–nuclear magnetic resonance measurements of intracellular pH and cellular energy. J Thorac Cardiovasc Surg 1996;112: 765-75.
3. Karmazyn M, Moffat MP. Role of Na^+/H^+ exchange in cardiac physiology and pathophysiology: mediation of myocardial reperfusion injury by the pH paradox. Cardiovasc Res 1993;27:915-24.
4. Karmazyn M. Sodium-hydrogen exchange in myocardial ischemic and reperfusion injury: mechanisms and therapeutic implications. In: Fliegel L, editor. Sodium-hydrogen exchange. Austin: RG Landes Company, 1996:chapter 10.
5. Scholz W, Albus U, Lang HJ, et al. Hoe 694, a new Na^+/H^+ exchange inhibitor and its effects on cardiac ischaemia. Br J Pharmacol 1993;109:562-8.
6. Scholz W, Albus U, Counillon L, et al. Protective effects of HOE642, a selective sodium-hydrogen exchange subtype 1 inhibitor, on cardiac ischaemia and reperfusion. Cardiovasc Res 1995;29:260-8.
7. Myers ML, Karmazyn M. Improved cardiac function after prolonged hypothermic ischemia with the Na^+/H^+ exchange inhibitor HOE 694. Ann Thorac Surg 1996;61:1400-6.
8. Scholz W, Albus U. Potential of selective sodium-hydrogen exchange inhibitors in cardiovascular therapy. Cardiovasc Res 1995;29:184-8.