Chapter 18

CARDIAC PROTECTION BY NHE INHIBITORS
Comparison With Other Cardioprotective Strategies

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1. INTRODUCTION

The sodium/hydrogen antiport is the major cardiac sarcolemmal membrane transporter responsible for the control of intracellular pH under normal physiological conditions and is thought to be activated and play a major role in the control of intracellular Na⁺ and Ca²⁺ concentrations during ischemia and/or reperfusion (1). In this regard, Karmazyn (2) in 1988 was the first investigator to demonstrate that amiloride, a potassium-sparing diuretic which also inhibits NHE activity in the heart, resulted in a marked improvement in the recovery of global contractile function in the isolated perfused Langendorff rat heart subjected to an ischemia-reperfusion protocol. These findings resulted in a surge of interest in developing inhibitors of NHE for use as cardioprotective agents. Initially, most compounds developed and tested were 5-amino substituted pyrazinoyl guanidine derivatives structurally related to amiloride, which were all found to be markedly cardioprotective. However, it was subsequently found that these compounds were not selective blockers of NHE alone and had other properties such as direct sodium channel blocking effects and cardiodepressant properties (3). Subsequently, chemists at Hoechst (3) and E. Merck (4) synthesized a new class of more selective inhibitors of the NHE-1 isoform, the benzoylguanidine derivatives, of which HOE-642 or cariporide, is the prototype. All of these compounds have been subsequently shown to be cardioprotective in all animal species and experimental models studied.
2. NHE-1 INHIBITION AND CARDIOPROTECTION

Since the original findings of Karmazyn demonstrating the cardioprotective effects of amiloride (2), many papers have been published which uniformly demonstrate the remarkable anti-ischemic efficacy of inhibiting NHE-1 in the myocardium. Therefore, a summary of the results obtained from many laboratories supporting a cardioprotective role for NHE-1 inhibitors and a comparison to that of ischemic and pharmacological preconditioning (IPC, PPC) will be the primary focus of this chapter.

2.1 Mechanisms Responsible For Cardioprotection

Prior to discussing the evidence for a cardioprotective effect of NHE-1 inhibition, it is essential to understand the pathophysiological basis and mechanisms responsible for the use and efficacy of these agents in alleviating the deleterious effects of ischemia and reperfusion in the heart. During myocardial ischemia the inside of the cell becomes acidotic which results in the activation of the NHE. This effect results in the extrusion of $H^+$ in exchange for $Na^+$. Since ischemia results in the inhibition of the $Na^+\text{-}K^+$ ATPase, which would normally extrude the excess $Na^+$, intracellular $Na^+$ accumulates. The increase in intracellular $Na^+$ leads to an accumulation of $Ca^{++}$ since the $Na^+$ gradient normally present in the nonischemic heart is reduced and results in a decreased activity or reversal of the $Na^+\text{/}Ca^{++}$ exchanger. Thus, during ischemia an increase in intracellular $Ca^{++}$ would be expected to occur which would result in cell death due to activation of proteases and the rapid onset of rigor contracture unless timely reperfusion were to occur. However, during reperfusion further damage might also be expected as a result of the rapid washout of extracellular $H^+$ and a further enhancement of NHE activity to extrude the accumulated intracellular $H^+$. This would lead to a rapid increase in intracellular $Na^+$ and $Ca^{++}$ and perhaps further damage to the myocardium. Based upon this sequence of events, it is not surprising that inhibitors of NHE-1 possess such a potent cardioprotective efficacy. However, whether this sequelae of events actually occurs is open to debate based on experimental evidence obtained in several in vitro isolated heart and myocyte studies where investigators have not been able to demonstrate increases in $Na^+$ or $Ca^{++}$ during simulated ischemia or in globally ischemic isolated rat hearts (5,6). On the other hand, recent results from our laboratory addressed this question in isolated guinea pig hearts where we were able to directly determine cellular concentrations of $Na^+$ and $Ca^{++}$ by the use of fluorescent dyes in the intact beating heart during global ischemia and following reperfusion in the presence and absence of an NHE-1 inhibitor, BIIB-513 (7). In these experiments, hearts were subjected to 30 minutes of ischemia and 70 minutes of reperfusion in