Chapter 14

ROLE OF NHE-1 IN CARDIAC HYPERTROPHY AND HEART FAILURE

Morris Karmazyn
Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada

1. INTRODUCTION

Heart failure has become an immense medical problem which is reaching epidemic proportions. Death rates from heart failure more than doubled in the past 10 years. In the United States alone, there are almost 5,000,000 individuals who have heart failure with more than a half-million new cases diagnosed each year. Currently, the 5-year mortality rate for heart failure is about 50 percent. In addition to mortality from pump failure, these patients exhibit an incidence of sudden cardiac death at 6–9 times the rate of the general population. In developing strategies for the treatment of heart failure, it is important to appreciate that this is not a disease per se but rather a complex clinical syndrome which is the final common pathway for numerous cellular and molecular defects caused by many instigating factors, the most common of which being myocardial infarction. Indeed, improved survival rates in patients who have had a myocardial infarct represents one of the major reasons for the tremendous increase in heart failure although other factors such as an aging population also represent important contributing factors. As a result of advances in molecular and cellular biology, it is now known that heart failure extends beyond abnormal heart function and organ physiology but involves numerous intracellular defects. Moreover, the complexity of the heart failure process is well-known, particularly in view of the numerous cellular and molecular changes that are seen in heart failure many of which appear to be interrelated. Two important components underlying heart failure include the initial adaptive hypertrophic
response which follows myocardial injury and the second, the subsequent evolution to heart failure (1). Indeed, inhibition of the early (mal)adaptive hypertrophy is an important therapeutic component which can result in an attenuation of the heart failure response. NHE-1 represents a key intracellular pH regulatory process in the cardiac cell after induction of acidosis (2). Emerging evidence suggests that it may play an important role in cell growth (2). In this review the basis for NHE-1 involvement in the heart failure process is discussed as is the experimental evidence from both in vitro and in vivo studies that NHE-1 inhibition prevents both the maladaptive remodelling resulting in heart failure as well as heart failure itself.

2. RATIONALE FOR NHE-1 INVOLVEMENT IN CARDIAC HYPERTROPHY AND HEART FAILURE

There are a number of lines of evidence suggesting that NHE-1 may represent a key factor mediating hypertrophic responses, especially after myocardial infarction, and thus suggesting that the exchanger could be an important cellular target for attenuation of both the hypertrophic responses as well as heart failure. As already discussed in this volume in a number of chapters, particularly Chapters 9 and 13, from a theoretical perspective, it is important to indicate that NHE-1 stimulation can occur through receptor-dependent mechanisms. As illustrated in Figure 1, this reflects the fact that the antiporter is the target of multiple signalling pathways such as those activated by various kinases and G protein-coupled receptors (3, 4). The intracellular pathways leading to activation of NHE-1 are not well understood. Increasing evidence suggests that NHE-1 activation through signalling mechanisms is dependent on mitogen-activated protein (MAP) kinases especially in response to growth factors which are potential candidates as hypertrophic agents. Indeed, NHE-1 possesses consensus sequences for MAP kinase and various studies have implicated MAP kinase in NHE-1 phosphorylation and activation (5). Recently a role for p90rsk in endothelin-1-induced MAP kinase-dependent phosphorylation of NHE-1 has been demonstrated in rat myocardium (6). In addition, protein kinase C activation may represent an important mechanism in the hypertrophic and remodelling process particularly in response to various paracrine and autocrine factors such as endothelin-1, angiotensin II and $\alpha_1$ adrenergic agonists. Thus, there appears to be a casual relationship between hypertrophic factors and their ability to activate NHE-1 in the sense that a large number of these agents exhibit this property. In addition, as discussed in Chapter 9, stretch-induced activation of receptors leads to stimulation of NHE-1 activity which then contributes to hypertrophic responses.