Cardiac hypertrophy (CH) is a major risk factor for cardiac death and commonly precedes the development of heart failure (HF). This is motivating the search for novel pharmacological strategies to prevent the development and/or regress CH. Although the signaling pathways leading to myocardial hypertrophy are complex, one important set of pathways involves the mitogen-activated protein kinases (MAPKs). MAPKs phosphorylate numerous substrates, including nuclear transcription factors that activate the expression of different genes. The Na\(^+-\)H\(^+\) exchanger (NHE) is a common downstream effector of this cascade and has been implicated in different models of hypertrophy, such as “hypertensive” myocardium, aortic constriction-induced hypertrophy, and postinfarction myocardial hypertrophy. Interestingly, stretch-induced hypertrophy of cultured neonatal cardiomyocytes is also accompanied by an increase in MAPK activity and NHE activation. Furthermore, stretch-induced MAPK stimulation is partially prevented by inhibition of NHE activity.

The article published in this issue of Circulation Research by Engelhardt et al reports another example of a link between NHE activity and cellular growth, employing a different experimental model of CH induced by overexpression of \(\beta_1\)-adrenergic receptors in transgenic mice. CH, fibrosis, and failure induced by this model were prevented by NHE inhibition. The overstimulation of \(\beta_1\)-adrenergic receptors with isoproterenol is perhaps a similar experimental model of hypertrophy that has been extensively studied before and reported to be mediated by p41/p42-MAPK activation. Karmazyn’s group reported that the inhibition of NHE activity attenuated the hypertrophy that follows myocardial infarction. Camilión de Hurtado et al recently reported that chronic NHE blockade in vivo induces regression of CH in spontaneously hypertensive rats (SHR) without a significant decrease in arterial pressure. The in vivo blockade of NHE also decreases the cellular proliferation detected in vessels from diabetic rats. Taken together, these findings provide compelling evidence of a common role played by NHE in different models of myocardial hypertrophy.

Which would be the relationship between NHE activity and myocardial hypertrophy? Perhaps the most convincing demonstration of a signaling role for NHE activation in cellular growth is found in sea urchin eggs, where fertilization is followed by NHE activation, and cellular growth is precluded if NHE activation is prevented. Because NHE exchanges intracellular H\(^+\) for extracellular Na\(^+\) in a one-by-one stoichiometry, the intracellular ionic changes resulting from its activation will be a decrease in [H\(^+\)], and an increase in [Na\(^+\)]. However, whereas the activation of NHE may result in nonsignificant changes in pH\(_i\) (under physiological conditions where the bicarbonate-dependent mechanisms are active), the increase in [Na\(^+\)], is always detected. This rise in [Na\(^+\)], might be responsible for an increase in [Ca\(^{2+}\)], levels mediated by Na\(^+-\)Ca\(^{2+}\) exchange (NCX). The increase in [Ca\(^{2+}\)], is recognized as a cell growth signal. NHE can carry ~50% of the Na\(^+\) entering the cells. We should therefore, learn to think more of increases of [Na\(^+\)], than in increases of pH\(_i\), when NHE is activated by “growth factors.” Conversely, blockade of NHE activity will promote the decrease of [Na\(^+\)], levels.

Recently, a new factor has been identified to contribute to the NHE hyperactivity-hypertrophy relationship: the anion exchanger (AE). Some isoforms of the AE are upregulated in the hypertrophied myocardium. This exchanger is, even at steady pH\(_i\), continuously loading the cell with acid. This acid load is balanced by other acid extruder mechanisms, and under normal conditions, pH\(_i\) is kept within normal limits. AE hyperactivity, by increasing [H\(^+\)], will stimulate the NHE leading to the increase of [Na\(^+\)]. Interestingly, \(\beta_1\)-adrenergic receptor stimulation enhances AE activity. It is possible that isoproterenol (or overexpression of \(\beta_1\) receptors), through AE stimulation, increases [H\(^+\)], thereby causing NHE activation. The possible linkage between NHE and other ionic membrane transport mechanisms is depicted in the Figure.

It has been previously demonstrated that [Na\(^+\)], increases in hypertrophied myocardium. Furthermore, in isolated myocytes and vascular smooth muscle cells, Na\(^+\) has a direct effect of increasing protein synthesis and decreasing protein degradation. Epidemiological and basic studies support the notion that Na\(^+\) is an independent factor for the development of salt-induced CH. Frohlich and colleagues reported that a high Na\(^+\) diet increased not only cardiac enlargement in SHR but also cardiac mass in normotensive rats without detectable change of arterial pressure. Therefore, given the fact that NHE is a pathway for Na\(^+\) entry, its pharmacological blockade appears to be an intervention capable of reducing Na\(^+\) influx.

An increased activity of the NHE has been detected in HF and cariporide has been shown to have antiapoptotic effect.
that, as proposed by Humphreys et al., 33 could be of help in HF. It is not evident to us why, in the article by Engelhardt et al., 9 the regression of hypertrophy was accompanied by normalization (through a translational mechanism) of NHE activity after the blockade. This finding deserves further investigation but it is interesting that the regression of CH after antihypertensive treatment is also accompanied by normalization (through a posttranslational mechanism) of NHE activity in SHR. 34

Engelhardt et al. 9 also reported fibrosis in accompanying CH in the mice overexpressing β1-adrenergic receptors. However, neither fibrosis nor increase in myocardial stiffness has been detected in previous experiments 10–13 in which hypertrophy is induced by isoproterenol. The possibility of “reparative fibrosis” instead of “reactive fibrosis” that characterizes the hypertensive hypertrophy was raised by the authors. Further studies about possible changes in diastolic compliance, collagen cross-linking, and/or accumulation of different collagen subtypes 35 will be required to properly characterize this model of hypertrophy.

References


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Na\textsuperscript{+}-H\textsuperscript{+} Exchanger Inhibition: A New Antihypertrophic Tool
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