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Pathological Role of the Na⁺/H⁺ Exchanger 1 on the Genesis of Cardiac Hypertrophy and Heart Failure

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Summary

Activation of the sarcolemmal Na⁺/H⁺ exchanger 1 (NHE1) is increasingly documented as a process involved in cardiac hypertrophy and heart failure (HF). However, whether NHE1 activation alone is sufficient to induce such remodeling remains unknown. We generated transgenic (Tg) mice that overexpress a constitutively active form of human NHE1 in hearts. The hearts of these mice developed cardiac hypertrophy, contractile dysfunction, and HF. In isolated Tg myocytes, in addition to elevated intracellular pH and Na⁺ concentration, both diastolic and systolic Ca²⁺ levels were significantly increased as a consequence of Na⁺-induced cytoplasmic Ca²⁺-overload; this was accompanied by enhanced sarcoplasmic reticulum Ca²⁺-loading via CaMKII-dependent phosphorylation of phospholamban. Negative force-frequency dependency was observed with preservation of high Ca²⁺, suggesting a decrease in myofibril Ca²⁺-sensitivity. Furthermore, the Ca²⁺-dependent prohypertrophic molecules calcineurin and CaMKII were highly activated in Tg hearts. These effects observed *in vivo* and *in vitro* were largely prevented by administration of the NHE1-specific inhibitor cariporide. Interestingly, overexpression of NHE1 in neonatal rat ventricular myocytes induced cariporide-sensitive nuclear translocation of nuclear factor of activated T cells (NFATc) and nuclear export of histone deacetylase 4 (HDAC4), suggesting that increased cardiac Na⁺/H⁺ exchange activity alters hypertrophy-associated gene expression by activating Ca²⁺-dependent signaling pathways. However, in Tg myocytes, contrary to exclusive translocation of HDAC4, NFAT only partially translocated to nucleus, possibly due to marked activation of p38, a negative regulator of NFAT signaling. We conclude that activation of NHE1 is sufficient to initiate cardiac hypertrophy and HF mainly through activation of CaMKII-HDAC4 pathway.