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Physiological role of Na^+-dependent regulation of cardiac Na^+/Ca^{2+} exchanger

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Summary

Na^+/Ca^{2+} exchange is the primary mechanism of Ca^{2+} extrusion from cardiac myocytes during diastole. There are many reports indicating that NCX1 expression levels are elevated in heart failure; however, the role of NCX1 in the pathophysiology of cardiac disease is not well understood. To determine the *in vivo* cardiac function of NCX1, we generated transgenic mice with cardiac-specific overexpression of NCX1.1, and also mice where the exchanger had a mutated XIP region (Y224W/Y226W/Y228W/Y231W), devoid of Na^+-dependent inactivation. Cardiac-specific overexpression of exchangers in these transgenic mice was confirmed by western blotting and immunohistochemistry with an anti-NCX1 antibody. Increased Na^+/Ca^{2+} exchange activities were also demonstrated by measuring $^{45}Ca^{2+}$ uptake into membrane vesicles and exchange currents in whole cell patch-clamp myocytes. We found that homozygous NCX1.1-transgenic mice, but not heterozygous mice, develop cardiac hypertrophy, and heterozygous NCX1.1 mutant-transgenic mice produce dilated cardiomyopathy. These models will be useful for understanding the role of NCX1 in cardiac disease.