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**Cathepsin B induced cardiomyocyte hypertrophy requires activation of the Na+/H+ exchanger isoform-1**

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**Background:** Multiple studies have demonstrated that Na+/H+ exchanger isoform-1 (NHE1), cathepsin B (Cat B) and matrix metalloproteinase-9 (MMP-9) contribute to the progression of cardiac hypertrophy (CH). Cat B is activated under acidic conditions, a key stimuli of NHE1, suggesting that NHE1 and Cat B activities are related. Although the inhibition of NHE1 reduces hypertrophy, the mechanisms underlying this effect remain unknown.

**Purpose and Methods:** To understand the mechanistic bases for Cat B in the anti-hypertrophic effect of NHE1 inhibition, H9c2 cardiomyoblasts were stimulated with Angiotensin (Ang) II in the presence and absence of N-[2-methyl-4,5-bis(methylsulphonyl)-benzoyl]-guanidine, hydrochloride (EMD, EMD 87580), an NHE1-specific inhibitor or CA-074Me, a Cat B inhibitor and characterized for changes in the cell surface area, protein content and atrial natriuretic peptide (ANP) mRNA, indices of hypertrophy.

**Results:** EMD significantly suppressed markers of hypertrophy and inhibited the Ang II stimulated Cat B protein and gene expression. Cat B is localized primarily within the acidic environment of lysosomes. The loss of integrity of the lysosomes releases Cat B proteases into the cytosol. EMD or CA-074Me prevented the dispersion of the lysosomes induced by Ang II and reduced the ratio of LC3-II to LC3-I, a marker of autophagy. Moreover, Cat B protein expression and MMP-9 activity in the extracellular space were significantly reduced upon the inhibition of NHE1.

**Conclusion:** Our study demonstrates a novel mechanism for attenuation of the hypertrophic phenotype by NHE1 inhibition that is mediated by a reduction in Cat B expression, the autosomal-lysosomal pathway and MMP-9 activation.