Anti-hypertrophic effect of NHE-1 inhibition involves GSK-3beta-dependent attenuation of mitochondrial dysfunction.


Source
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Abstract
Although Na(+)-H(+) exchanger 1 (NHE-1) inhibition has been demonstrated to have anti-hypertrophic effect indirectly through mitochondria, the detailed cellular mechanisms mediating this effect remain elusive. In this study we sought to determine whether NHE-1 inhibition exerts an anti-hypertrophic effect by modulating the mitochondrial permeability transition pore (mPTP) opening through the AMP-activated protein kinase (AMPK)/glycogen synthase kinase 3beta (GSK-3beta) pathway during hypertrophy in cardiomyocytes. An in vivo model of hypertrophy was induced in male Sprague-Dawley rats by subjecting them to 3, 7 or 28 days of coronary artery ligation (CAL). To induce hypertrophy in vitro, cardiomyocytes isolated from hearts of neonatal (1-3 days) Sprague-Dawley rats were exposed to endothelin-1 (ET-1, 10 nM) in the presence or absence of various treatments. The results demonstrate that CAL affected both AMPKalpha and GSK-3beta phosphorylation in a time-dependent manner. In cultured cardiomyocytes, ET-1 increased phosphorylation of AMPKalpha(1)/alpha(2) (Ser485/Ser491) and GSK-3beta(Ser9) by 80% (P<0.05) and 225% (P<0.05) respectively, both of which were significantly blunted by the NHE-1 inhibitor AVE-4890 (5 microM). ET-1-induced phosphorylation of GSK-3beta(Ser9) was attenuated by inhibitors of phosphatidylinositol 3-kinase (LY294002), Akt (Akt inhibitor VIII), ERK1/2 (PD98059) and by the AMPK agonist 5-aminimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR). Prevention of GSK-3beta(Ser9) phosphorylation was also accompanied by suppression of ET-1-induced increases in cell surface area, ANP and alpha-skeletal actin gene expression. Co-immunoprecipitation studies revealed that GSK-3beta interacts with components of the mPTP, voltage-dependent anion channel (VDAC) and adenine nucleotide translocase. Furthermore, ET-1 reduced
phosphorylation of VDAC, which was associated with both mPTP opening and mitochondrial membrane depolarization. These effects were mimicked by the GSK-3beta inhibitor SB216763, thus showing that modulation of mPTP formation is GSK-3beta-dependent. In conclusion, anti-hypertrophic effect of NHE-1 inhibition can be mediated through activation of GSK-3beta which in turn induces inhibition of mPTP opening due to VDAC phosphorylation.

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