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NEBIVOLOL, A BETA ADRENERGIC RECEPTOR ANTAGONIST BLOCKS ANGIOTENSIN II-MEDIATED SIGNALING IN HEART

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Abstract

We recently showed that Nebivolol, a β-adrenergic receptor (AR) antagonist attenuates myocardial oxidative stress and promotes insulin metabolic signaling in 9 week old Zucker obese (ZO) insulin resistant rats. Here, we demonstrate that Nebivolol suppresses angiotensin II type I receptor (AT1R)-mediated signaling in ZO hearts as well as in HL-1 cardiomyocytes. We treated 9 week old ZO and Zucker lean rats (ZL) with Nebivolol (10 mg/kg/day) via osmotic mini pumps for a period of 21 days. Pressure volume studies of ZO rats showed abnormalities in LV diastolic function with increased static diastolic stiffness and decreased myocardial relaxation compared to age matched ZL rats, and Nebivolol blunted these effects. To investigate the cardioprotective mechanisms of Nebivolol we used a mouse cardiomyocyte HL-l cell line. Treatment of cardiomyocytes with angiotensin (Ang) II showed an increase in Ang II type 2 receptor (AT2R) protein levels and phosphorylation of Ser2448 of mammalian target of rapamycin (mTOR) and Thr389 of p70S6 kinase (S6K-1), and Nebivolol significantly reduced these effects. Moreover, a similar trend of increases in the AT2R protein levels and phosphorylation of S6K1 and mTOR was observed ZO hearts, and these effects were significantly ameliorated in ZO rats treated with Nebivolol. Increases in AT2R and reductions in S6K1 are known to mitigate maladaptive cardiac remodeling. Taken together, these results indicate that Nebivolol treatment may provide a new strategy for targeting Ang II-mediated cardiac disorders.