Ghrelin and its synthetic analogues, growth hormone secretagogues (GHS), act on GHS receptor to regulate the cardiac function and suppress cardiomyocyte apoptosis in chronic heart failure rats

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In addition to stimulate pituitary GH secretion, GHS activate GHS-R to evoke various effects on a variety of peripheral tissues. GHS-R has been confirmed in heart tissue by both RT-PCR and receptor binding studies. Ghrelin and synthetic peptidyl GHS have been reported to exert a cardioprotective effect on cardiac ischemia. Four peptidyl GHS, GHRP-1, GHRP-6, GHRP-2, and hexarelin, increase intracellular free Ca^{2+} concentration ($[Ca^{2+}]i$) via both Ca^{2+} influx through membrane Ca^{2+} channels and release of intracellular Ca^{2+} from storage sites (1). This increase in $[Ca^{2+}]i$ induced an increase in both contraction and relaxation of cardiac muscle cells. In primary cultured neonatal cardiac myocytes, an anti-apoptotic effect of hexarelin through an increase in the ratio of Bcl-2/Bax has also been demonstrated (2). In pressure-overload chronic heart failure (CHF) rats, effects of peptidyl GHS (GHRP-1, -2, -6 and hexarelin, 100 $\mu g:kg^{-1}$ SC BID) treatment for 3 weeks are studied. Plasma nonepinephrine, renin, angiotencin II, aldosterone, endothelin-1 and atrial natriuretic peptide levels are significantly higher in CHF rats. In CHF rats treated with GHS, levels of these stress-related hormones were significantly decreased whereas plasma levels of GH and insulin-like growth factor 1 (IGF-1) increased. The treatment also significantly increased the body weight of CHF rats and significantly mitigated left ventricular (LV) dysfunction and cardiac remodeling in CHF rats, with increased ejection fraction, LV end-systolic pressure and diastolic posterior wall thickness, and decreased LV end-diastolic pressure and LV end-diastolic dimension. GHS also increased cardiac GHS-R mRNA expression and suppressed cardiomyocyte apoptosis in CHF rats and decreased cardiac creatine kinase release in hypophysectomy rats subjected to acute cardiac ischemia. These results indicate that chronic administration of GHS alleviates LV dysfunction and pathological remodeling in CHF rats. Above data also strongly support a therapeutic effect of GHS on cardiac system. Supported by Australian NHMRC and Natural Science Foundation of China.

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