Effect of hexarelin on transient outward potassium current in rat ventricular myocytes

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Hexarelin is a synthetic peptide growth hormone secretagogue (GHS), which possesses a variety of cardiovascular protective effects mediated by the GHS receptor (GHSR), including improving cardiac dysfunction and remodeling (Xu *et al.*, 2005). It has been reported that GHRP increased Ca^{2+} influx *via* voltage-gated Ca^{2+} channels in cultured neonatal rat cardiomyocytes (Xu *et al.*, 2003). This increase in Ca^{2+}-influx can be achieved by a direct increase in Ca^{2+} channel conductance and/or a decrease in K^+ channel conductance with prolonged depolarization. Modification of ion channels and the intracellular signaling pathways by GHS are currently unknown and this study aims to fill this gap. Ventricular myocytes were enzymatically isolated from adult male Sprague-Dawley rats and kept in Tyrode solution. Nystatin-perforated whole-cell patch-clamp recording was performed on isolated cells within 6 hours after successful cell preparetion. Hexarelin (100 nmol, 10 nmol, 1 nmol, 0.1 nmol, and 0.01 nmol) inhibited transient outward potassium current (I_{to}) in a dose-dependent manner. The inhibition appeared at doses above 0.01 nmol. Ghrelin evoked similar inhibition on this K^+ current. The inhibition was abolished in the presence of the GHS-R1a specific antagonist BIM28163. In term of triggered action potential duration (APD), ghrelin and hexarelin significantly prolonged APD in the presence of the calcium channel blocker $CoCl_2$ (2 mmol) and the delayed rectifier K^+ channel blocker tetraethylamonium (50 mmol/l) in bath solution. The hexarelin-induced Ito inhibition was abolished by the protein kinase C (PKC) inhibitor, Gö-6983, but not by the PKA inhibitor, H89. We therefore conclude that hexarelin and ghrelin activate PKC system through the stimulation of GHS-R1a, resulting in a decrease in the I_{to} amplitude, prolongation of action potential duration, and increase in Ca^{2+}-influx.

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