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Phosphatidylinositol 3-kinase functionally compartmentalizes the concurrent G_s signaling during β_2-adrenergic stimulation

Su-Hyun Jo

Department of Physiology, Cheju National University College of Medicine,
Ara 1-Dong, Jeju 690-756, Korea

Compartmentation of intracellular signaling pathways serves as an important mechanism conferring the specificity of G protein-coupled receptor (GPCR) signaling. In the heart, stimulation of β_2-adrenoceptor (β_2-AR), a prototypical GPCR, activates a tightly localized protein kinase A (PKA) signaling, which regulates substrates at cell surface membranes, bypassing cytosolic target proteins (eg, phospholamban). Although a concurrent activation of β_2-AR-coupled G_i proteins has been implicated in the functional compartmentation of PKA signaling, the exact mechanism underlying the restriction of the β_2-AR-PKA pathway remains unclear. In the present study, we demonstrate that phosphatidylinositol 3-kinase (PI3K) plays an essential role in confining the β_2-AR-PKA signaling. Inhibition of PI3K with LY294002 or wortmannin enables β_2-AR-PKA signaling to reach intracellular substrates, as manifested by a robust increase in phosphorylation of phospholamban, and markedly enhances the receptor-mediated positive contractile and relaxant responses in cardiac myocytes. These potentiating effects of PI3K inhibitors are not accompanied by an increase in β_2-AR-induced cAMP formation. Blocking G_i or $G_{\square\square}$ signaling with pertussis toxin or βARK-ct, a peptide inhibitor of $G_{\square\square}$, completely prevents the potentiating effects induced by PI3K inhibition, indicating that the pathway responsible for the functional compartmentation of β_2-AR-PKA signaling sequentially involves G_i, $G_{\square\square}$, and PI3K. Thus, PI3K constitutes a key downstream event of β_2-AR-G_i signaling, which confines and negates the concurrent β_2-AR/G_s-mediated PKA signaling.