Phosphorylation of Cav1.2 on S1928 uncouples the L-type Ca2+ channel from the β2 adrenergic receptor.

Abstract:

Agonist-triggered downregulation of β2-adrenergic receptors (ARs) constitutes vital negative feedback to prevent cellular overexcitation. Here, we report a novel downregulation of β2AR signaling highly specific for Cav1.2. We find that β2-AR binding to Cav1.2 residues 1923-1942 is required for β2-AR binding to Cav1.2. Despite the prominence of PKA-mediated phosphorylation of Cav1.2 S1928 within the newly identified β2AR binding site, its physiological function has so far escaped identification. We show that phosphorylation of S1928 displaces the β2AR from Cav1.2 upon β2-adrenergic stimulation rendering Cav1.2 refractory for several minutes from further β2-adrenergic stimulation. This effect is lost in S1928A knock-in mice. Although AMPARs are clustered at postsynaptic sites like Cav1.2, β2AR association with and regulation of AMPARs do not show such dissociation. Accordingly, displacement of the β2AR from Cav1.2 is a uniquely specific desensitization mechanism of Cav1.2 regulation by highly localized β2AR/cAMP/PKA/S1928 signaling. The physiological implications of this mechanism are underscored by our finding that LTP induced by prolonged
theta tetanus (PTT-LTP) depends on Cav1.2 and its regulation by channel-associated ?2AR.

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