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Review

Cardiac GPCRs: GPCR signaling in healthy and failing hearts

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Abstract

G protein-coupled receptors (GPCRs) are widely implicated in human heart disease, making them an important target for cardiac drug therapy. The most commonly studied and clinically targeted cardiac GPCRs include the adrenergic, angiotensin, endothelin, and adenosine receptors. Treatment options focusing on the complex and integrated signaling pathways of these GPCRs are critical for the understanding and amelioration of heart disease. The focus of this review is to highlight the most commonly studied and clinically targeted cardiac GPCRs, placing emphasis on their common signaling components implicated in cardiac disease.

Keywords: G protein-coupled receptors; Signaling; Beta-Arrestin; Endocytosis

Contents

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1. GPCR signaling overview

G-protein-coupled receptors (GPCRs) are a conserved family of seven transmembrane receptors that is one of the largest classes of receptors to be targeted for drug therapy [1–2]. Among an estimated 200 cardiac GPCRs, drugs targeting adrenergic and angiotensin GPCR signaling pathways alone account for the majority of prescriptions for cardiovascular diseases [3–4]. However, heart failure remains a leading cause of global morbidity and mortality [4], and a better understanding of the components that make up GPCR signaling pathways in healthy and failing hearts may provide a mechanistic basis for improving heart failure treatment. GPCR signaling is activated by ligand binding to an extracellular active site of the receptor. Depending on the ligand and type of GPCR, the active site is located on either the N-terminal tail, extracellular loops, or exofacial transmembrane helices [5,6]. Ligand binding induces a conformational change in the GPCR, which disrupts the ionic interactions between the third cytoplasmic loop and the sixth transmembrane segment and allows for coupling with heterotrimeric guanine-nucleotide regulatory proteins (G-proteins) [6–11].

G-proteins consist of α, β, and γ subunits and, upon GPCR coupling, the G-protein converts GTP to GDP on its α subunit resulting in dissociation of the Gα from the Gβγ subunits to mediate downstream signaling[12,13]. The four primary families of Gα-proteins ($G\alpha_s$, $G\alpha_i$, $G\alpha_q$, and $G\alpha_{11/12}$) [12] diverge at this point with respect to downstream signaling molecules and consequential physiological responses. Dissociated Gα subunits couple with an effector, an enzyme such as adenylyl cyclase (AC) and phospholipase C β (PLCβ), or an ion channel [12]. Dissociated Gβγ subunits target a range of signaling pathways involved in desensitization, downregulation, apoptosis, and ion channel activation (I_{KAch}) [12,14,15] (see Fig. 1).

This review will first discuss each G-protein family in terms of its signaling pathway in the healthy heart and follow with a description of individual signaling components and receptors in heart disease. Among the most commonly studied receptors are $G\alpha_s$ and $G\alpha_i$-coupled β-adrenergic receptors; $G\alpha_q$-coupled angiotensin, α-1-adrenergic, and endothelin receptors; $G\alpha_i$-coupled adenosine-1, α2-adrenergic, and muscarinic-2 receptors; and common to all of these receptors is the corresponding Gβγ signaling, G-protein independent signaling, and the consequences of receptor downregulation and desensitization in the heart.

2. G_s signaling and G_s-coupled receptors

2.1. Overview of G_s signaling

Following ligand stimulation, the dissociated $G\alpha_s$ subunit activates signaling with the stimulation of AC (giving G_s or '$G_{stimulatory}$' its name). AC exists in the human myocardium primarily as AC Types V and VI, though types IV and VII are also present at lower levels. AC V is primarily localized to the atria of the heart while AC VI is found in both atria and ventricles and is colocalized with β1 adrenergic receptors (β1ARs) [16]. AC is primarily responsible for increasing intracellular production of the second messenger 3′-5′-cyclic adenosine monophosphate, (cAMP) [12,17]. cAMP modulates cardiac contractility via its binding to cAMP-dependent protein kinase (PKA). The catalytic subunit of PKA phosphorylates a range of substrates within the myocyte. In the heart, PKA functions to modulate contractility via its phosphorylation of myocyte proteins including the voltage-gated L-type Ca^{2+} channel, the cardiac ryanodine receptor (RyR2), phospholamban, and troponin I.

L-type Ca^{2+} channels activate RyR to mediate Ca^{2+}-induced Ca^{2+} release (CICR); the primary source of intracellular Ca^{2+} to activate myofilament contraction [18]. Activated L-type Ca^{2+} voltage-dependent channels initiate the inward calcium entry required for CICR [19]. L-type Ca^{2+} channels are located primarily in transverse T-tubules, and in response to an action potential generate a small release of calcium into a cytosolic space known as the diadic cleft that occurs between the opposition of T-tubules with the junctional sarcoplasmic reticulum. This trigger Ca^{2+} activates the large release of Ca^{2+} by the RyR2 to generate what is known as the Ca^{2+} spark [20].

RyR2 is a macromolecular signaling complex located on the junctional sarcoplasmic reticulum (SR). It responds to trigger Ca^{2+} from the L-type Ca^{2+} channel by releasing larger Ca^{2+} stores into the cytoplasm from within the SR, which then activates myofilament contraction. RyR2 can be modulated through phosphorylation by PKA, cGMP-dependent protein kinase (PKG), and Ca^{2+}/calmodulin kinase II (CaMKII) in addition to poly-S-nitrosylation [20–22].

Myocyte relaxation occurs through Ca^{2+} reuptake in the SR via the SR Ca^{2+}-ATPase (SERCA) pump, which is modulated by phospholamban [23]. Phospholamban modulates Ca^{2+} affinity to SERCA2 which regulates the sequestration of cytosolic Ca^{2+} back into the SR [23]. Phospholamban phosphorylation is directly associated with increases in Ca^{2+} affinity for SERCA2