Introduction

The heart is under constant regulation to maintain cardiac output to meet different needs of tissue perfusion under different conditions. Acutely, the regulation is mediated by the sympathetic/β-adrenergic system (SAS) and the vagal/parasympathetic system. The SAS system is activated to exert positive chronotropic, inotropic, and lusitropic effects on the heart when a greater need of cardiac output is imposed. Chronic activation of SAS contributes to the development of cardiac dysfunction and arrhythmias. Although the roles of the SAS system in cardiac physiology and pathophysiology have been studied for decades, many questions remain and new discoveries have been made during the past decade.

SAS and Cardiac Function Regulation in Normal Heart Physiology

Adrenergic agonists, such as epinephrine and norepinephrine are released when the SAS is excited and then bind to the β-adrenergic receptors (β-ARs, including β1 (75%), β2 (25%), the existence of β3-AR in the heart is still in debate). The binding of β-AR agonists dissociates Gβγ from Gαs, which in turn activates the adenylyl cyclase (AC) that catalyzes the production of cyclic-AMP (cAMP) from ATP. Subsequently cAMP activates PKA that phosphorylates multiple targets (AC), the ryanodine receptor (RyR), and troponin I, causing the increase in cardiac contractility (inotropy) and relaxation rate (lusitropy) [1]. In addition, cAMP directly [2] or indirectly via PKA enhances pace making currents in the heart to increased heart rate (chronotropy) [3]. PKA also phosphorylates metabolic enzymes (e.g., phosphorylase kinase) to increase the metabolic rate to match the enhanced demand of energy of the stimulated heart. Lastly, activated PKA is able to regulate gene expression via the activation of cAMP response element binding (CREB) protein, a transcription factor and PKA is able to regulate gene expression via the activation of cAMP signaling pathways. The activation of β-ARs is also able to activate Ca2+-calmodulin-dependent kinases II (CaMKII) through PKA-mediated phosphorylation in a Gi-dependent manner. The β2-AR also couples to PDE4D3 activity to attenuate cAMP signaling [22].

The β-adrenergic signaling can be shut off once the SAS system is not excited by multiple mechanisms: catecholamines in the extracellular milieu can be decreased by metabolism or reuptake by norepinephrine transporter on the sympathetic nerve ends [4]; the β-ARs can be desensitized by PKA or G-protein coupled receptor kinase (GRK)-dependent phosphorylation and internalization [5]. Intracellular cAMP is returned to normal level by cAMP hydrolysis by phosphodiesterases (mainly PDE3 and PDE4) [6]. GRK2 is able to phosphorylate both β1-AR and β2-AR, followed by the binding of arrestin [7], which is able to recruit PDE4 to further limit local cAMP increase [8]. The internalization of β2-AR requires PI3K association with the agonist-bound β2-AR [9]. At last, the PKA-mediated phosphorylation is removed from its target molecules by protein phosphatases (PP1 and PP2A in the heart).

It had been thought β-AR signaling was well studied, but recently it has been demonstrated that cAMP/PKA signaling is far more complex than what we have conceived:

1. β2-AR dually couples to both Gs and Gi [10] and the effects of β2-AR activation can be switched from Gs-PKA to Gi [11] to activate PI3K and Akt, which exerts anti apoptotic effect opposing the proapoptotic effect of β1-AR [12]. In addition, β2-AR stimulation causes ERK1/2 phosphorylation in a Gi-dependent manner. The β2-AR also couples to and regulates Na+/H+ exchanger [13].

2. The cAMP/PKA signaling is compartmentalized spatially by a couple of mechanisms: 1) the adrenergic receptors locate at specific membrane domains such as caveoli, where Acs, PKA and their target molecules are also concentrated [14]. A-protein anchoring proteins (AKAPs) serve as a scaffolding protein to organize a signalosomes comprised of β-AR, AC, PKA, PDEs and LTCC etc [15]. PDEs in close vicinity of AC and PKA limit the local concentration of cAMP.

3. There is another cAMP sensor, exchange protein directly activated by cAMP (EPAC), in the heart. EPAC1 is highly expressed in the heart but EPAC2 is not [16]. Both PKA and EPAC have similar affinities to cAMP, indicating that EPAC may play a role in normal physiology [17]. EPAC1 seems to play a role in mediating β-AR stimulated increase in myocyte Ca2+ transients and contractions in a PLCg-dependent manner [18]. However, this finding cannot be always repeated and needs further investigation [19]. EPAC activates while PKA suppresses PKB/Akt to affect myocyte survival [20]. Like PKA, EPAC signaling can be spatially and temporally regulated by PDE and AKAP [21]. Both EPAC and PKA promote PDE4D3 activity to attenuate cAMP signaling [22].

4. The β-AR/AC/cAMP/PKA pathway interacts with many other signaling pathways. The activation of β-ARs is also able to activate Ca2+-calmodulin-dependent kinases II (CaMKII) [23] through PKA-dependent mechanism [23] or independent mechanisms [24,25].

SAS Signaling in Cardiac Pathophysiology

Chronic activation of the SAS is a cause for the progression of heart failure (HF) [26,27]. The level of the activation of the SAS system evaluated by the increased blood catecholamine concentration [28] or the nerve activities [29] is closely correlating with the severity of HF [26]. It is believed that enhanced SAS activity is beneficial to maintain the normal hemodynamics initially but gradually causes adverse molecular, cellular and structural remodeling to further weaken the heart [30]. Chronic adrenergic stimulation (e.g., chronic isoproterenol infusion [31,32], sustained high intracellular cAMP concentration [33], and over expression of β-ARs [34] or Gas [35] or PKA [36])...
of the heart in animal models leads to HF. Currently, myocyte death caused by high adrenergic drive is linked to intracellular Ca\textsuperscript{2+} overload and the activation of CaMKII [37-41]. CREB activation by increased intracellular cAMP/PKA activity is involved in cardiac myocyte hypertrophy and apoptosis [42]. Inhibition of CREB reduces cardiac myocyte hypertrophy but promotes cardiomyocyte apoptosis [42]. EPAC activated by elevated cAMP is also able to induced cardiac myocyte hypertrophy via Rac-dependent activation of the calcineurin/NFAT pathway in cardiac myocytes [43].

\textbf{β1-AR} density decreases in failing hearts. \textbf{β2-AR} maintains its density but is uncoupled from Gs, probably due to increased GRK2 and GRK5 activities in HF [44]. Concomitantly, the expression Gs increases in failing hearts [45] and thus uncouples Gas from \textbf{β2-AR}. These changes decrease β-AR stimulation induced cAMP production and eventually the adrenergic responsiveness and exercise tolerance in failing hearts [46]. Currently it has been conceived that the decreased or blunted β-AR-adrenergic response is a protective mechanism to avoid some detrimental effects (e.g., myocyte death) of heightened catecholamines because β-blockers is able to further protect failing hearts [47]. There is polymorphism of β-ARs which could affect the progression of heart disease [48]. In the failing human heart, the coupling of ACs to β-AR is decreased [49,50].

Since chronic SAS activation plays such an important role in HF progression, the blockade of β-ARs has been developed into a standard therapy according to the Guidelines of ACC/AHA [51] and HFSA [52]. Large randomized controlled clinical trials with bisoprolol [53], metoprolol succinate [53] and carvedilol [54] have provided clear evidence of reducing mortality and morbidity and improving CHF symptoms by β-blockers. The efficacy of β-blockers is affected by the etiology (more effective in dilated cardiomyopathy than in ischemic cardiomyopathy [55]) with large patient-to-patient variation probably because of the polymorphism of β-ARs [48]. The cellular and molecular mechanisms of β-blockers are not clearly understood but could be related to lowering the heart rate [56] and normalizing adrenergic responsiveness by restoring β-AR density [57], reducing Gs expression [58] and the early transient activation of GRK2 [59]. On the other hand, β-adrenergic agonists, PDE inhibitors and AC agonists can only be used as acute positive inotropic drugs for stabilizing hemodynamics [60]. Administration of PDE inhibitors for a long term in HF patients increases mortality and morbidity [61,62]. Since β2-AR/Gs activity in heart failure development [71] in animal models of heart failure [72-74]. Most recently, we have shown that PKA inhibition by PKI could be a novel therapy for HF treatment [75].

\textbf{References}


