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 epinephrines and norepinephrines 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 in cardiac myocytes: the L-type calcium (Ca2+) channel (LTCC), the phospholamban (PLB), 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 the SAS system and the vagal/parasympathetic system. The SAS 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.

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of the heart in animal models leads to HF. Currently, myocyte death caused by high adrenergic drive is linked to intracellular Ca\(^{2+}\) 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].

β1-AR density decreases in failing hearts. β2-AR maintains its density but is uncoupled from Gs, probably due to increased GRK2 and GRK5 activities in HF [44]. Concomitantly, the expression Gi is increased in failing hearts [45] and thus uncouples Gas from 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-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 Gi 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/Gi activation protects myocytes from apoptosis through a PI3K/ Akt-dependent mechanism, the co-application of β1-blockers with β2-agonist has been explored and shown predicted protection effect in HF animal models [63,64]. In addition, Gi activation exerts anti arrhythmia effect [65,66]. Despite that, to date, there is no clinical trial adopting this strategy because early clinical trials with a β2-AR agonist, fenoterol, were not successful. GRK inhibition is also studied for potential treatment of HF aiming to restore the blunted adrenergic response [67,68]. Inhibiting GRK2 [69,70] or disrupting PI3K/GRK2 interaction with βARKct has been shown to prolong survival, attenuate cardiac hypertrophy and apolipoprotein C ejection fraction and attenuates the progression of heart failure [71] in animal models of heart failure [72-74]. Most recently, we have shown that PKI inhibition by PKI could be a novel therapy for HF treatment [75].

Conclusion

Since the SAS plays such important roles in cardiac physiology and pathophysiology, further studies to elucidate the novel aspects of this system and targeting novel molecules for heart disease prevention and treatment are warranted.


