Cardiovascular Pharmacology: Open Access
ISSN: 2329-6607

Li et al., Cardiol Pharmacol 2012, 1:1
DOI: 10.4172/2329-6607.1000101

Short Communication Open Access

β-adrenergic System and Cardiac Physiology and Pathophysiology

Ying Li[12], Xiaoying Zhang[2] Yi-zhi Peng[1] and Xiongwen Chen[2]*

[1]*The Third Military Medical University, Chongqing, China*
[2]*Cardiovascular Research Center & Department of Physiology, Temple University School of Medicine, USA*

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 (Ca^{2+}) 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 cAMP response element binding (CREB) protein, a transcription factor and other cAMP response element modulators (e.g., CREM).

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 compartmented 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 Ca^{2+} transients and contractions in a PLCε-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 Ca^{2+}/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 Gαs [35] or PKA [36])

***Corresponding author:** Xiongwen Chen, Cardiovascular Research Center & Department of Physiology, Temple University School of Medicine, USA, Tel: +215-707-3542; Fax: 215-707-5737; E-mail: xchen001@temple.edu

Received November 20, 2012; **Accepted** November 21, 2012; **Published** November 23, 2012

Citation: Li Y, Zhang X, Chen X (2012) β-adrenergic System and Cardiac Physiology and Pathophysiology. Cardiol Pharmacol 1:101. doi:10.4172/2329-6607.1000101

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 Gαs 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 mitigates 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].

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.

References

1. Bers DM (2008) Calcium cycling and signaling in cardiac myocytes. Annu Rev Physiol 70: 23-49.
2. Vinogradova TM, Lyashkov AE, Zhu W, Ruknudin AM, Sirenko S, et al. (2006) High basal protein kinase a-dependent phosphorylation drives rhythmic internal ca2+ store oscillations and spontaneous beating of cardiac pacemaker cells. Circ Res 98: 505-514.
3. Saucerman JJ, McCulloch AD (2006) Cardiac beta-adrenergic signaling: From subcellular microdomains to heart failure. Ann N Y Acad Sci 1080: 348-361.
4. Eisenhofer G (2001) The role of neuronal and extraneuronal plasma membrane transporters in the inactivation of peripheral catecholamines. Pharmacol Ther 91: 35-62.
5. Petrofski JA, Koch WJ (2003) The beta-adrenergic receptor kinase in heart failure. J Mol Cell Cardiol 35: 1167-1174.
6. Osadchii OE (2007) Myocardial phosphodiesterases and regulation of cardiac contractility in health and cardiac disease. Cardiovasc Drugs Ther 21: 171-194.
7. Lefkowitz RJ (1998) G protein-coupled receptors. Iii. New roles for receptor kinases and beta-arrestins in receptor signaling and desensitization. J Biol Chem 273: 18677-18680.
8. Baillie GS, Sood A, McPhee I, Gall I, Perry SJ, et al. (2003) Beta-arrestin-mediated pde4 cAMP phosphodiesterase recruitment regulates beta-adrenoceptor switching from gs to gi. Proc Natl Acad Sci U S A 100: 940-945.
9. Naga Prasad SV, Laporte SA, Chamberlain D, Caron MG, Barak L, et al. (2002) Phosphoinositide 3-kinase regulates β2-adrenergic receptor endocytosis by ap-2 recruitment to the receptor/beta-arrestin complex. J Cell Biol 158: 563-575.
10. Xiao RP, Ji X, Lakatta EG (1995) Functional coupling of the beta 2-adrenoceptor to a pertussis toxin-sensitive g protein in cardiac myocytes. Mol Pharmacol 47: 322-329.
11. Daaka Y, Luttrell LM, Lefkowitz RJ (1997) Switching of the coupling of the beta2-adrenergic receptor to different g proteins by protein kinase a. Nature 390: 88-91.
12. Communal C, Singh K, Sawyer DB, Colucci WS (1999) Opposing effects of β(1)- and β(2)-adrenergic receptors on cardiac myocyte apoptosis: Role of a pertussis toxin-sensitive G protein. Circulation 100: 2210-2212.
13. Jiang T, Steinberg SF (1997) β 2-adrenergic receptors enhance contractility by stimulating HCO3(-)-dependent intracellular alkalinization. Am J Physiol 273: H1044-1047.
14. Balijepalli RC, Foell JD, Hall DD, Hell JW, K AMP TJ (2006) Localization of cardiac l-type ca(2+) channels to a caveolar macromolecular signaling complex is required for β(2)-adrenergic regulation. Proc Natl Acad Sci U S A 103: 7500-7505.
15. Ruehr ML, Russell MA, Bond M (2004) A-kinase anchoring protein targeting of protein kinase a in the heart. J Mol Cell Cardiol 37: 653-665.
16. Kawasaki H, Springett GM, Mochizuki N, Toki S, Nakaya M, et al. (1998) A family of cAMP-binding proteins that directly activate rap1. Science 282: 2275-2279.
17. Dao KK, Teigen K, Kopperud R, Hodneland E, Schwede F, et al. (2006) Epac1 and cAMP-dependent protein kinase holoenzyme have similar AMP affinity, but their cAMP domains have distinct structural features and cyclic nucleotide recognition. J Biol Chem 281: 21500-21511.
18. Oestreich EA, Wang H, Malik S, Kaproth-Joslin KA, Blaxall BC, et al. (2007) Epac-mediated activation of phospholipase C(epsilon) plays a critical role in beta-adrenergic receptor-dependent enhancement of ca2+ mobilization in cardiac myocytes. J Biol Chem 282: 5488-5495.
19. Pereira L, Metrich M, Fernandez-Velasco M, Lucas A, Leroy J, et al. (2007) The c AMP binding protein epac modulates Ca^{2+} sparks by a Ca^{2+}/calmodulin kinase signalling pathway in rat cardiac myocytes. J Physiol 583: 685-694.
20. Mei FC, Qiao J, Tsygankova OM, Meinkoth JL, Quilliam LA, et al. (2002) Differential signaling of cyclic AMP: Opposing effects of exchange protein directly activated by cyclic AMP and cAMP-dependent protein kinase on protein kinase B activation. J Biol Chem 277: 11497-11504.
21. McConnachie G, Langeberg LK, Scott JD (2006) AKAP signaling complexes: Getting to the heart of the matter. Trends Mol Med 12: 317-323.

22. Dodge-Kafka KL, Soughayer J, Pare GC, Carlisle Michel JJ, Langeberg LK, et al. (2005) The protein kinase a anchoring protein mAKAP coordinates two integrated cAMP effector pathways. Nature 437: 574-578.

23. Maier LS, Bers DM (2002) Calcium, calmodulin, and calcium-calmodulin kinase ii: Heartbeat to heartbeat and beyond. J Mol Cell Cardiol 34: 919-939.

24. Yatani A, Codina J, Imoto Y, Reeves JP, Birnbaumer L, et al. (1987) A G protein directly regulates mammalian cardiac calcium channels. Science 238: 1288-1292.

25. Grimm M, Ling H, Brown JH (2011) Crossing signals: Relationships between beta-adrenergic stimulation and camkii activation. Heart Rhythm 8: 1296-1298.

26. Packer M (1988) Neurohormonal interactions and adaptations in congestive heart failure. Circulation 77: 721-730.

27. Packer M (1995) Evolution of the neurohormonal hypothesis to explain the progression of chronic heart failure. Eur Heart J 16 Suppl F: 4-6.

28. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, et al. (1984) Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 311: 819-823.

29. Leimbach WN Jr, Wallin BG, Victor RG, Aylward PE, Sundlof G, et al. (1986) Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. Circulation 73: 913-919.

30. Francis GS, McDonald KM, Cohn JN (1993) Neurohumoral activation in preclinical heart failure. Remodeling and the potential for intervention. Circulation 87: IV90-96.

31. Colucci WS (1998) The effects of norepinephrine on myocardial biology: Implications for the therapy of heart failure. Clin Cardiol 21: I20-I24.

32. Communal C, Singh K, Pimentel DR, Colucci WS (1998) Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the beta-adrenergic pathway. Circulation 98: 1329-1334.

33. Movsesian MA, Bristow MR (2005) Alterations in cAMP-mediated signaling and their role in the pathophysiology of dilated cardiomyopathy. Curr Top Dev Biol 68: 25-48.

34. Engelhardt S, Hein L, Wiesmann F, Lohse MJ (1999) Progressive hypertrophy and heart failure in beta1-adrenergic receptor transgenic mice. Proc Natl Acad Sci U S A 96: 7059-7064.

35. Iwase M, Uechi M, Vatner DE, Asai K, Shannon RP, et al. (1997) Cardiomyopathy induced by cardiac Gs alpha overexpression. Am J Physiol 272: H585-589.

36. Antos CL, Frey N, Marx SO, Reiken S, Gaburjakova M, et al. (2001) Dilated cardiomyopathy and sudden death resulting from constitutive activation of protein kinase a. Circ Res 89: 997-1004.

37. Zhu WZ, Wang SQ, Chakir K, Yang D, Zhang T, et al. (2003) Linkage of beta1-adrenergic stimulation to apoptotic heart cell death through protein kinase a-independent activation of ca2+/calmodulin kinase ii. J Clin Invest 111: 617-625.

38. Yang Y, Zhu WZ, Joiner ML, Zhang R, Oddis CV, et al. (2006) Calmodulin kinase ii inhibition protects against myocardial cell apoptosis in vivo. Am J physiol Heart circ physiol 291: H3065-3075.

39. Zhang R, Khoo MS, Wu Y, Yang Y, Grueter CE, et al. (2005) Calmodulin kinase ii inhibition protects against structural heart disease. Nat Med 11: 409-417.

40. Grueter CE, Colbran RJ, Anderson ME (2007) CaMKII, an emerging molecular driver for calcium homeostasis, arrhythmias, and cardiac dysfunction. J Mol Med 85: 5-14.

41. Chen X, Zhang X, Kubo H, Harris DM, Mills GD, et al. (2005) Ca^{2+} influx-induced sarcoplasmic reticulum ca2+ overload causes mitochondrial-dependent apoptosis in ventricular myocytes. Circ Res 97: 1009-1017.

42. Tomita H, Nazmy M, Kajimoto K, Yehia G, Molina CA, et al. (2003) Inducible cAMP early repressor (icer) is a negative-feedback regulator of cardiac hypertrophy and an important mediator of cardiac myocyte apoptosis in response to beta-adrenergic receptor stimulation. Circ Res 93: 12-22.

43. Morel E, Marcantoni A, Gastineau M, Birkedal R, Rochais F, et al. (2005) cAMP-binding protein epac induces cardiomyocyte hypertrophy. Circ Res 97: 1296-1304.

44. Hata JA, Williams ML, Koch WJ (2004) Genetic manipulation of myocardial beta-adrenergic receptor activation and desensitization. J Mol Cell Cardiol 37: 11-21.

45. Neumann J, Schmitz W, Scholz H, von Meyerinck L, Doring V, et al. (1988) Increase in myocardial Gi-proteins in heart failure. Lancet 2: 936-937.

46. Feldman AM (2002) Adenylyl cyclase: A new target for heart failure therapeutics. Circulation 105: 1876-1878.

47. Lohse MJ, Engelhardt S, Eschenhagen T (2003) What is the role of beta-adrenergic signaling in heart failure? Circ Res 93: 896-906.

48. Azuma J, Nonen S (2009) Chronic heart failure: Beta-blockers and pharmacogenetics. Eur J Clin Pharmacol 65: 3-17.

49. Klapholz M (2009) Beta-blocker use for the stages of heart failure. Mayo Clin Proc 84: 718-729.

50. Tevaearai HT, Koch WJ (2004) Molecular restoration of beta-adrenergic receptor signaling improves contractile function of failing hearts. Trends Cardiovasc Med 14: 252-256.

51. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, et al. (2005) Acc/aha 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the american college of cardiology/american heart association task force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure): Developed in collaboration with the american college of chest physicians and the international society for heart and lung transplantation: Endorsed by the heart rhythm society. Circulation 112: e154-235.

52. Heart Failure Society of America (2006) Executive summary: Hfsa 2006 comprehensive heart failure practice guideline. J Card Fail 12: 10-38.

53. (1999) The cardiac insufficiency bisoprolol study II (CIBIS-II): A randomised trial. Lancet 353: 9-13.

54. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, et al. (1996) The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol heart failure study group. N Engl J Med 334: 1349-1355.

55. Yamada T, Fukunami M, Ohmori M, Iwakura K, Kumagai K, et al. (1993) Which subgroup of patients with dilated cardiomyopathy would benefit from long-term beta-blocker therapy? A histologic viewpoint. J Am Coll Cardiol 21: 628-633.

56. Mason RP, Giles TD, Sowers JR (2009) Evolving mechanisms of action of beta blockers: Focus on nebivolol. J Cardiovasc Pharmacol 54:123-128.

57. Brodde OE (2007) Beta-adrenoceptor blocker treatment and the cardiac beta-adrenoceptor-g-protein(s)-adenylyl cyclase system in chronic heart failure. Naunyn Schmiedebergs Arch Pharmacol 374: 361-372.

58. Sigmund M, Jakob H, Becker H, Hanrath P, Schumacher C, et al. (1996) Effects of metoprolol on myocardial beta-adrenoceptors and Gi alpha-proteins in patients with congestive heart failure. Eur J Clin Pharmacol 51:127-132.

59. Leineweber K, Rohe P, Beilfuss A, Wolf C, Sporkmann H, et al. (2005) G-protein-coupled receptor kinase activity in human heart failure: Effects of beta-adrenoceptor blockade. Cardiovasc Res 66: 512-519.

60. Milfred-LaForest SK, Shubert J, Mendoza B, Flores I, Eisen HJ, et al. (1999) Tolerability of extended duration intravenous milrinone in patients hospitalized for advanced heart failure and the usefulness of uptitration of oral angiotensin-converting enzyme inhibitors. Am J Cardiol 84: 894-899.

61. Feldman AM, Bristow MR, Parmley WW, Carson PE, Pepine CJ, et al. (1993) Effects of vesnarinone on morbidity and mortality in patients with heart failure. Vesnarinone study group. N Engl J Med 329: 149-155.

62. Nony P, Boissel JP, Lievre M, Leizorovicz A, Haugh MC, et al. (1994) Evaluation of the effect of phosphodiesterase inhibitors on mortality in chronic heart failure patients. A meta-analysis. Eur J Clin Pharmacol 46:191-196.

63. Xiao RP, Zhu W, Zheng M, Chakir K, Bond R, et al. (2004) Subtype-specific beta-adrenoceptor signaling pathways in the heart and their potential clinical implications. Trends Pharmacol Sci 25: 358-365.

64. Ahmet I, Krawczyk M, Heller P, Moon C, Lakatta EG, et al. (2004) Beneficial effects of chronic pharmacological manipulation of beta-adrenoreceptor subtype signaling in rodent dilated ischemic cardiomyopathy. Circulation 110: 1083-1090.

65. Eschenhagen T, Mende U, Diederich M, Hertle B, Memmesheimer C, et al. (1996) Chronic treatment with carbachol sensitizes the myocardium to c AMP-induced arrhythmia. Circulation 93: 763-771.

66. Grimm M, Gsell S, Mittmann C, Nose M, Scholz H, et al. (1998) Inactivation

of (gialpha) proteins increases arrhythmogenic effects of beta-adrenergic stimulation in the heart. J Mol Cell Cardiol 30: 1917-1928.

67. Pleger ST, Boucher M, Most P, Koch WJ (2007) Targeting myocardial beta-adrenergic receptor signaling and calcium cycling for heart failure gene therapy. J Card Fail 13: 401-414.

68. Vinge LE, Raake PW, Koch WJ (2008) Gene therapy in heart failure. Circ Res 102: 1458-1470.

69. Raake PW, Zhang X, Vinge LE, Brinks H, Gao E, et al. (2012) Cardiac G-protein-coupled receptor kinase 2 ablation induces a novel ca2+ handling phenotype resistant to adverse alterations and remodeling after myocardial infarction. Circulation 125: 2108-2118.

70. Raake PW, Vinge LE, Gao E, Boucher M, Rengo G, et al. (2008) G protein-coupled receptor kinase 2 ablation in cardiac myocytes before or after myocardial infarction prevents heart failure. Circ Res 103: 413-422.

71. Akhter SA, Eckhart AD, Rockman HA, Shotwell K, Lefkowitz RJ, et al. (1999) *In vivo* inhibition of elevated myocardial beta-adrenergic receptor kinase activity in hybrid transgenic mice restores normal beta-adrenergic signaling and function. Circulation 100: 648-653.

72. Nienaber JJ, Tachibana H, Naga Prasad SV, Esposito G, Wu D, et al. (2003) Inhibition of receptor-localized pi3k preserves cardiac beta-adrenergic receptor function and ameliorates pressure overload heart failure. J Clin Invest 112: 1067-1079.

73. Perrino C, Naga Prasad SV, Schroder JN, Hata JA, Milano C, et al. (2005) Restoration of beta-adrenergic receptor signaling and contractile function in heart failure by disruption of the betaark1/phosphoinositide 3-kinase complex. Circulation 111: 2579-2587.

74. Tachibana H, Naga Prasad SV, Lefkowitz RJ, Koch WJ, Rockman HA (2005) Level of beta-adrenergic receptor kinase 1 inhibition determines degree of cardiac dysfunction after chronic pressure overload-induced heart failure. Circulation 111: 591-597.

75. Zhang X, Szeto C, Gao E, Tang M, Jin J, et al. (2012) Cardiotoxic and cardioprotective features of chronic β-adrenergic signaling. Circ Res.