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β-Adrenergic receptors in the failing heart: the good, the bad, and the unknown

Stephen B. Liggett

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Commentary

One of the most effective means of increasing cardiac output is by activating cardiomyocyte β-adrenergic receptors (βARs). βARs couple primarily to the stimulatory G-protein Gs, which activates adenylyl cyclase; increasing intracellular cAMP levels activate protein kinase A to phosphorylate its substrates troponin I, the L-type Ca2+-channels, and phospholamban (PLB), thus enhancing contractility. In the case of PLB, phosphorylation relieves its inhibition of the sarcoplasmic reticulum Ca2+-ATPase, thereby altering Ca2+ cycling (1). βAR agonists, such as dobutamine, that rapidly increase contractility of the heart have become a mainstay in the acute treatment of decompensated heart failure. This pathway has also been investigated for potential therapies to treat chronic heart failure, but here paradox abounds. In chronic human heart failure and in many animal models of the syndrome, βAR function is, unexpectedly, limited by several molecular mechanisms. These include a decrease in the expression and coupling of the β1AR subtype, a decrease in the coupling of the β2AR subtype, an increase in expression of the inhibitory G protein Gi, an increase in the expression of the βAR kinase (which phosphorylates and desensitizes βARs), and a decrease in expression or function of adenylyl cyclase. Because the consequent decrease in βAR signaling limits energy expenditures in a heart that has little metabolic reserve, this response is generally thought to be adaptive. Indeed, judicious administration […]

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Department of Medicine, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Room G167, Cincinnati, Ohio 45267-0564, USA. Phone: (513) 558-4831; Fax: (513) 558-0835; E-mail: stephen.liggett@uc.edu.

One of the most effective means of increasing cardiac output is by activating cardiomyocyte β-adrenergic receptors (βARs). βARs couple primarily to the stimulatory G-protein G_s, which activates adenylyl cyclase; increasing intracellular cAMP levels activate protein kinase A to phosphorylate its substrates troponin I, the L-type Ca^{2+}-channels, and phospholamban (PLB), thus enhancing contractility. In the case of PLB, phosphorylation relieves its inhibition of the sarcoplasmic reticulum Ca^{2+}-ATPase, thereby altering Ca^{2+} cycling (1). βAR agonists, such as dobutamine, that rapidly increase contractility of the heart have become a mainstay in the acute treatment of decompensated heart failure.

This pathway has also been investigated for potential therapies to treat chronic heart failure, but here paradox abounds. In chronic human heart failure and in many animal models of the syndrome, βAR function is, unexpectedly, limited by several molecular mechanisms. These include a decrease in the expression and coupling of the β_1AR subtype, a decrease in the coupling of the β_2AR subtype, an increase in expression of the inhibitory G protein G_i, an increase in the expression of the βAR kinase (which phosphorylates and desensitizes βARs), and a decrease in expression or function of adenylyl cyclase. Because the consequent decrease in βAR signaling limits energy expenditures in a heart that has little metabolic reserve, this response is generally thought to be adaptive. Indeed, judicious administration of βAR antagonists (β blockers) in chronic heart failure can improve cardiac performance (2). However, because these changes each alter βAR function in different ways, it would be naive to assume that they are all beneficial; some may well be adaptive — acting to oppose the progression of failure — while others are maladaptive. Delineating the mechanisms that uncouple βAR activity from contractility in models of failing ventricular function should provide insight into the critical lesions for adaptive and maladaptive regulation and help identify the most appropriate targets for therapeutic intervention.

Toward this end, a number of transgenic and gene ablation mice have been created, in which various components of the pathway are amplified or missing. These studies have yielded some intriguing results. For example, a low level of β_2AR overexpression in the hearts of transgenic mice is well tolerated, with persistent enhancement of ejection fraction and absence of histopathological findings (3, 4). In contrast, low-level overexpression of the β_1AR subtype results in cardiomyopathy with depressed contractile function (5, 6). Such results indicate that although β_1AR and β_2AR each couple to G_s, these receptor subtypes must engage distinct signaling pathways. Thus, it appears that β_2AR, but not the β_1AR, can couple to the inhibitory G-protein, G_i, which may lead to an attenuated cAMP response (7) or to the activation of other, less-well-defined pathways (8). β_2AR can also affect ion flow through the type III Na^+/H^+ exchanger by binding the Na^+/H^+ exchanger regulatory factor (9). Recent studies (10) also indicate that the two subtypes have different distributions within membrane microdomains of the myocyte, which may be another critical distinction. Interestingly, overexpression of adenylyl cyclase types V and VI in transgenic mouse hearts results in enhanced ventricular performance without apparent deleterious effects (11, 12), suggesting that cAMP alone may not be the only second messenger that is necessary for adrenergic mediated toxic effects.

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As the characterization of these genetically altered mice unfolds, various crossbreeding experiments are being carried out between mouse models of cardiomyopathy and other transgenic or knockout lines, in hopes of correcting specific aspects of the deranged signaling seen in the various models. In this issue of the *JCI*, Freeman et al. (13) report on the outcomes of altering three components of the signal transduction pathway in a mouse model of hypertrophic cardiomyopathy (HCM). HCM mice overexpress a modified myosin heavy chain, which results in hypertrophy followed by ventricular dilatation, depressed fractional shortening and exercise intolerance (14, 15). Freeman et al. (13) crossbred these mice, which show evidence of βAR dysfunction, with other strains that either overexpress the β_2AR in the heart, express a βAR kinase inhibitor (βARKct) in the heart, or are genetically ablated for PLB (PLB-null). Previous studies, confirmed here, showed that these perturbations each lead to enhanced contractility (16–18). However, their effects on the course of ventricular failure in the HCM mice were quite different. The HCM/β_2AR mice initially show enhanced systolic function over that of nontransgenics, but by 8 months, the fractional shortening of their cardiac muscles is reduced, and half of the mice are dead. In contrast, HCM/PLB-null mice and HCM/βARKct mice show normal fractional shortening throughout the 12-month study period. Furthermore, hypertrophy occurs in the HCM/β_2AR and HCM/PLB-null mice but not the HCM/βARKct mice. The expression profiles of three hypertrophy related genes, β-myosin heaving chain, atrial natriuretic factor, and α-skeletal actin also differ in the groups. Normal expression of these genes is not found in any of the crossbred mice, but PLB-null–crossed mice showed the greatest improvement

in β-myosin heavy chain expression, whereas the most favorable response for atrial natriuretic factor and α-skeletal actin was with the βARKct-crossed mice. Given that the βARKct mice also show no evidence of myocardial hypertrophy, as assessed by heart-to-body weight ratios, it appears that expression of this peptide had the most favorable chronic effects of the crosses, within the context of the HCM phenotype.

A consistent finding in these types of crossbreeding experiments with the βARKct animal is that beneficial effects are only found when βARK levels or activities are increased. Thus, in the muscle-specific *LIM* knockout (19), the HCM mouse, and the calsequestrin overexpression (20) models, βARK is increased, and in each case, transgenic overexpression of the inhibitor peptide substantially improves function. In contrast, the $G_{\alpha q}$ overexpressing model of cardiomyopathy, which also displays βAR desensitization, hypertrophy, and marked ventricular dysfunction (21), does not have elevated βARK levels, and in these cases, ventricular function and βAR responsiveness are not rescued with the βARK inhibitor (22, 23). Instead, restoration of other dysfunctional components of βAR signaling improves function in vitro or in vivo (23–25).

The βARKct peptide acts by binding the βγ subunits that are released from G-protein heterotrimers. βγ is required for βARK translocation and thus its ability to phosphorylate βARs. Since its beneficial effects are seen only in systems that feature elevated kinase activity, it appears that the inhibitory βARKct peptide acts specifically on this aspect of the pathogenesis. However, other physiologic and biochemical indices of hypertrophy are also improved by βARKct, and it is intriguing to consider whether blocking βγ may have effects other than inhibiting βARK. Indeed, βγ stimulates tyrosine kinase signaling and phospholipase C activation, which could accelerate hypertrophy. Another consideration is that as cardiac function improves when βγ signaling is attenuated, βAR function returns as a secondary response. This appears to be the case during β-blocker treatment, as βAR function has been reported to improve during successful therapy (2). Finally, βARK phosphorylates multiple G protein–coupled receptors, so the phenotypic improvement in animals expressing the inhibitory peptide may be explained in part by the ability of βARK to desensitize other receptors. It should be noted that β_2AR overexpression (23) and PLB ablation (26, 27) have improved a number of phenotypic characteristics of other models of cardiomyopathy. A coherent picture of how interdiction at these various points in the pathway can sometimes afford qualitatively similar rescue is still lacking.

Looking ahead to human therapy, because the strategy employed will surely depend on the etiology of the failure and the need for acute or chronic therapy, crossbreeding experiments like those of Freeman et al. (13) are crucial to identify strategies to pursue (or avoid) for the clinical modification of heart failure. However, understanding how these approaches achieve their effects will ultimately provide the greatest impetus for developing new genetic or pharmacologic therapies for human heart failure.

1. Brittsan, A.G., and Kranias, E.G. 2000. Phospholamban and cardiac contractile function. *J. Mol. Cell. Cardiol.* **32**:2131–2139.
2. Bristow, M.R. 2000. Mechanistic and clinical rationales for using beta-blockers in heart failure. *J. Card. Fail.* **6**:8–14.
3. Turki, J., Pak, J., Green, S., Martin, R., and Liggett, S.B. 1995. Genetic polymorphisms of the β_2-adrenergic receptor in nocturnal and non-nocturnal asthma: evidence that Gly16 correlates with the nocturnal phenotype. *J. Clin. Invest.* **95**:1635–1641.
4. Liggett, S.B., et al. 2000. Early and delayed consequences of β_2-adrenergic receptor overexpression in mouse hearts. *Circulation.* **101**:1707–1714.
5. Engelhardt, S., Hein, L., Wiesmann, F., and Lohse, M.J. 1999. Progressive hypertrophy and heart failure in beta1-adrenergic receptor transgenic mice. *Proc. Natl. Acad. Sci. USA.* **96**:7059–7064.
6. Bisognano, J.D., et al. 2000. Myocardial-directed overexpression of the human beta(1)-adrenergic receptor in transgenic mice. *J. Mol. Cell. Cardiol.* **32**:817–830.
7. Tepe, N.M., and Liggett, S.B. 2000. Functional receptor coupling to G_i is a mechanism of agonist-promoted desensitization of the β_2-adrenergic receptor. *J Recept. Signal Transduct. Res.* **20**:75–85.
8. Daaka, Y., Luttrell, L.M., and Lefkowitz, R.J. 1997. Switching of the coupling of the β_2-adrenergic receptor to different G proteins by protein kinase A. *Nature.* **390**:88–91.
9. Hall, R.A., et al. 1998. The β_2-adrenergic receptor interacts with the Na^+/H^+-exchanger regulatory factor to control Na^+/H^+ exchange. *Nature.* **392**:626–630.
10. Rybin, V.O., Xu, X., Lisanti, M.P., and Steinberg, S.F. 2000. Differential targeting of beta-adrenergic receptor subtypes and adenylyl cyclase to cardiomyocyte caveolae. A mechanism to functionally regulate the cAMP signaling pathway. *J. Biol. Chem.* **275**:41447–41457.
11. Tepe, N.M., et al. 1999. Altering the receptor-effector ratio by transgenic overexpression of type V adenylyl cyclase: enhanced basal catalytic activity and function without increased cardiomyocyte β-adrenergic signalling. *Biochemistry.* **38**:16706–16713.
12. Gao, M.H., et al. 1999. Adenylylcyclase increases responsiveness to catecholamine stimulation in transgenic mice. *Circulation.* **99**:1618–1622.
13. Freeman, K., et al. 2001. Alterations in cardiac adrenergic signaling and calcium cycling differentially affect the progression of cardiomyopathy. *J. Clin. Invest.* **107**:967–974.
14. Vikstrom, K.L., Factor, S.M., and Leinwand, L.A. 1996. Mice expressing mutant myosin heavy chains are a model for familial hypertrophic cardiomyopathy. *Mol. Med.* **2**:556–567.
15. Freeman, K., et al. 2001. Progression from hypertrophic to dilated cardiomyopathy in mice that express a mutant myosin transgene. *Am. J. Physiol. Heart Circ. Physiol.* **280**:H151–H159.
16. Milano, C.A., et al. 1994. Enhanced myocardial function in transgenic mice overexpressing the β_2-adrenergic receptor. *Science.* **264**:582–586.
17. Koch, W.J., et al. 1995. Cardiac function in mice overexpressing the β-adrenergic receptor kinase or a βARK inhibitor. *Science.* **268**:1350–1353.
18. Luo, W., et al. 1994. Targeted ablation of the phospholamban gene is associated with markedly enhanced myocardial contractility and loss of β-agonist stimulation. *Circ. Res.* **75**:401–409.
19. Rockman, H.A., et al. 1998. Expression of a beta-adrenergic receptor kinase 1 inhibitor prevents the development of myocardial failure in gene-targeted mice. *Proc. Natl. Acad. Sci. USA.* **95**:7000–7005.
20. Harding, V., Jones, L., Lefkowitz, R.J., Koch, W.J., and Rockman, H.A. 2001. Cardiac βARK1 inhibition prolongs survival and augments β blocker therapy in a mouse model of severe heart failure. *Proc. Natl. Acad. Sci. USA.* In press.
21. D'Angelo, D.D., et al. 1997. Transgenic Gαq overexpression induces cardiac contractile failure in mice. *Proc. Natl. Acad. Sci. USA.* **94**:8121–8126.
22. Dorn, G.W.I., Tepe, N.M., Wu, G., Yatani, A., and Liggett, S.B. 2000. Mechanisms of impaired β-adrenergic receptor signaling in $G_{\alpha q}$-mediated cardiac hypertrophy and ventricular dysfunction. *Mol. Pharmacol.* **57**:278–287.
23. Dorn, G.W., II., Tepe, N.M., Lorenz, J.N., Koch, W.J., and Liggett, S.B. 1999. Low- and high-level transgenic expression of β_2-adrenergic receptors differentially affect cardiac hypertrophy and function in $G_{\alpha q}$-overexpressing mice. *Proc. Natl. Acad. Sci. USA.* **96**:6400–6405.
24. Tepe, N.M., and Liggett, S.B. 1999. Transgenic replacement of type V adenylyl cyclase identifies a critical mechanism of β-adrenergic receptor dysfunction in the $G_{\alpha q}$ overexpressing mouse. *FEBS Lett.* **458**:236–240.
25. Roth, D.M., et al. 1999. Cardiac-directed adenylyl cyclase expression improves heart function in murine cardiomyopathy. *Circulation.* **99**:3099–3102.
26. Minamisawa, S., et al. 1999. Chronic phospholamban-sarcoplasmic reticulum calcium ATPase interaction is the critical calcium cycling defect in dilated cardiomyopathy. *Cell.* **99**:313–322.
27. Sato, Y., et al. 2001. Rescue of contractile parameters and myocyte hypertrophy in calsequestrin overexpressing myocardium by phospholamban ablation. *J. Biol. Chem.* In press.