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Catecholamines, Cardiac β -Adrenergic Receptors, and Heart Failure

Robert J. Lefkowitz, MD; Howard A. Rockman, MD; Walter J. Koch, PhD

It is now generally accepted that chronically elevated stimulation of the cardiac β -adrenergic system is toxic to the heart and that such stimulation may contribute to the pathogenesis of congestive heart failure of various causes. Administration of either β -adrenergic agonists or phosphodiesterase inhibitors has been shown to decrease survival of patients with chronic heart failure, even though they produce immediate and long-term hemodynamic benefits.¹ Moreover, in human heart failure, as well as in several animal models, elevated circulating catecholamines lead, via various compensatory mechanisms, to decreased levels and functional activity of cardiac β_1 -adrenergic receptors (β_1 ARs) and thus to marked desensitization of the heart to inotropic β -adrenergic stimulation.²

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These biochemical and physiological changes appear to be mediated by elevated levels of the enzyme β AR kinase1 (β ARK-1, GRK2) in the heart that are invariably associated with dampened responsiveness to catecholamine stimulation.³ β ARK is one of a family of enzymes (G protein-coupled receptor kinases) that phosphorylate β ARs and other G protein-coupled receptors after they have been stimulated, thus leading to their desensitization.⁴ Currently, it is widely believed that these mechanisms protect the heart from the toxic effects of inotropic β -adrenergic support. The recent success of β -blockers in treating chronic heart failure is generally explained by their ability to block the noxious effects of chronic endogenous sympathetic stimulation of the failing heart. In contrast, infusion of β -adrenergic agonists is used solely for short-term and palliative inotropic support.

Given these findings, it is not surprising that there has been little recent interest in therapeutic strategies that aim to facilitate or augment signaling through β -adrenergic-coupled systems in the failing heart. All such approaches, it is generally assumed, must lead to negative consequences for the heart. Such assumptions have gained support from animal studies that demonstrate that even very modest transgenic

overexpression of β_1 ARs in the hearts of mice leads to early and marked cardiomyopathy.⁵ In addition, cardiac transgenic overexpression of the α -subunit of the heterotrimeric G protein G_s also leads to a cardiomyopathic phenotype.⁶ It is against this background that an article in this issue by Liggett et al⁷ highlights several misconceptions and unfounded assumptions about β -adrenergic stimulation of the heart and points the way toward a more rational reconsideration of the potential for manipulating β -adrenergic signaling in the heart for therapeutic gain.

The first widely held erroneous assumption, and the one most directly addressed by Liggett et al, is that β_1 ARs and β_2 ARs are essentially equivalent in their signaling properties and hence in the consequences of their activation. However, in striking contrast to the early cardiomyopathy resulting from even low-level (\approx 5-fold) transgenic overexpression of β_1 ARs in the heart recently reported by Engelhardt et al,⁵ Liggett et al now demonstrate that up to 100-fold overexpression of β_2 ARs in the mouse heart causes significantly increased cardiac contractile force without any cardiomyopathic consequences during the 1-year study period.⁷ (Recall that 1 year is approximately half the normal life span of a mouse.) Only at even higher levels of overexpression (up to 350-fold) were pathological changes observed. Are these results surprising?

In fact, they are not. The first study of transgenic overexpression of a β AR in the mouse heart by Milano et al⁸ reported very high levels of expression of the β_2 AR (up to 200-fold), similar to the higher-expressing lines of Liggett et al. These animals had remarkably elevated contractility unresponsive to further β -adrenergic stimulation. Like the highest-expressing lines of Liggett et al, the inotropic effect in these animals appeared to be due to the constitutive activity of the highly expanded pool of receptors and could not be reduced by conventional β -blockers such as propranolol. These animals still displayed markedly elevated cardiac contractility at 1 year of age and developed mild fibrosis late in life (\geq 1 year),⁹ as would be expected from the dose-response curves for receptor expression now provided by Liggett et al.⁷ The Liggett group also reported a transgenic mouse expressing β_2 ARs at much lower levels of expression (\approx 15-fold). Even at these very low levels, marked potentiation of catecholamine-stimulated inotropy was observed, with no pathological consequences.¹⁰

Other findings also indicate that the consequences of β_1 - and β_2 -adrenergic stimulation in the heart are quite different. Although both receptors classically activate adenylate cyclase via stimulation of G_s , β_2 -receptors can also powerfully stimulate G_i ¹¹ (the myocardial concentrations of which are elevated in CHF). This has at least 2 types of consequences.

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First, it limits the extent of the contractile response to overexpressed β 2ARs, as in the animals reported by Milano et al⁸ (because G_i inhibits adenylate cyclase). Only when G_i proteins were inactivated by pertussis toxin treatment did these transgenically overexpressed β 2ARs fully stimulate contractility.¹¹ Second, activation of G_i has the potential to couple these receptors to other important signaling pathways, such as the MAP kinases.¹² Cardiac β 1ARs and β 2ARs have also been shown to differ in their effects on contraction, cytosolic Ca^{2+} concentrations, and Ca^{2+} currents in isolated rat ventricular cells.¹³

That β 1ARs and β 2ARs should display distinctly different signaling patterns is predictable from their molecular structures. Both are heptahelical or 7-membrane-span receptors. Greatest amino acid identity is present in the transmembrane regions ($\approx 71\%$), which determine the specificity of ligand binding.¹⁴ However, the cytoplasmic regions of the receptors, which interact with other cellular proteins to mediate various signaling events, are considerably more divergent.¹⁴ In fact, Liggett et al have previously called attention to polyproline stretches present in the third cytoplasmic loop of β 1ARs but not β 2ARs.¹⁵ Swapping of this region between the β 1ARs and β 2ARs significantly altered their signaling properties.¹⁵ Moreover, we recently identified a novel family of the SH₃ domain containing proteins that interact with the β 1ARs (and not the β 2ARs) via this region.¹⁶ Distinctly different proteins also interact with the β 1ARs and β 2ARs via protein interaction domains called PDZ domains that bind to the divergent last 4 amino acid residues of the carboxy-terminal tails of these receptors.¹⁷

Recent studies have increasingly implicated the process of apoptosis, or programmed cell death, in the development of cardiomyopathy and heart failure.¹⁸ In vitro experiments with isolated cardiac myocytes,^{19,20} as well as in vivo experiments with knockout mice lacking either β 1AR, β 2AR, or both (A.J. Patterson, B.K. Kobilka, personal communication, 1999), indicate that chronic catecholamine stimulation induces apoptosis or sudden death, respectively. However, these responses appear to be initiated by β 1ARs, whereas β 2AR stimulation either has no effect or may even be protective.^{19,20} Thus, although both receptors are present in cardiac myocytes and mediate inotropic effects, the toxic effect of β -adrenergic stimulation appears to be mediated largely, if not exclusively, by the β 1AR.

Another recent line of research relevant to issues raised in the article by Liggett et al concerns the consequences of lowering the elevated levels of cardiac β ARK-1 activity generally found in human heart failure or in animal models of the disease. Lowering of β ARK-1 activity in the heart presumably would enhance signaling through not only β ARs but other G protein-coupled receptors as well. As shown in animal models of several cardiac disorders, cardiac β ARK-1 levels rise early, before marked cardiac deterioration and desensitization occur, presumably in response to the increased sympathetic stimulation that accompanies heart failure.²¹ Moreover, 3-fold transgenic overexpression of β ARK in the mouse heart (a level comparable to that observed in heart failure) reproduces the marked biochemical and physi-

ological desensitization to β -adrenergic stimulation observed in heart failure.²²

What are the physiological effects of lowering cardiac β ARK activity? One approach lowered β ARK activity by transgenic overexpression of an inhibitory peptide derived from the carboxy-terminus of β ARK. This peptide blocks the interaction of endogenous β ARK with $G_{\beta\gamma}$, preventing agonist-induced translocation of the enzyme to the plasma membrane.²² A second approach was to knock out a single β ARK allele by homologous recombination.²³ In both models, reduction in myocardial β ARK activity increased basal and isoproterenol-stimulated myocardial contractility in vivo. When these 2 mouse lines were crossed to produce animals with even lower myocardial β ARK-1 activity, contractility rose even more.²³ These data suggest that β ARK-1-mediated desensitization of β ARs and perhaps other G protein-coupled receptors acts as a brake on myocardial contractility. Of course, other, as yet undefined, activities of β ARK might also be involved. Animals with reduced cardiac β ARK activity and increased myocardial contractility have normal life spans, with no cardiac pathological conditions detectable at any point.²²

Therapeutic Implications

The observations summarized above, indicating that increased β 2AR activity or reduction in β ARK levels can improve myocardial performance without noxious effects on the heart, call into question the widely held notion that any maneuver that chronically augments β -adrenergic signaling in the heart will have deleterious consequences. They also immediately suggest several novel therapeutic strategies for the treatment of heart failure, some of which are currently being tested in animal models.

β 2-Adrenergic Receptors

Can overexpression of β 2ARs (a possible future target of gene therapy) improve cardiac performance in the setting of heart failure without causing negative effects? The question is being approached in several ways. One is to cross animals overexpressing β 2ARs in the heart with genetically engineered lines of mice that develop heart failure.^{24,25} An important caveat in this approach is that, as described above, many of the lines of transgenic β AR-overexpressing mice described thus far express the receptors at extraordinarily high levels, well beyond the therapeutic window delineated by Liggett et al.⁷ In fact, when a transgenic animal model of hypertrophic cardiomyopathy with heart failure (overexpression of the α -subunit of the heterotrimeric G protein G_q) was made to coexpress the β 2AR at relatively low levels, improved myocardial performance was observed, whereas at higher levels, deterioration was observed.²⁵ Very high levels of transgenic β 2AR overexpression did not improve another genetic mouse model of heart failure (MLP knockout).²⁴ However, as delineated by Liggett et al, such studies need to be performed in the future with much lower levels of β 2AR expression.

Another approach has been to transfer the β 2AR with adenoviral vectors. Enhanced function of cultured cardiac myocytes isolated from failing rabbit hearts has been achieved via gene transfer, leading to expression levels

≈15-fold above normal.²⁶ In addition, by use of a catheter-based technique for delivery of an adenovirus containing the human β_2 AR transgene to the rabbit coronary circulation *in vivo*²⁷ or by delivering the β_2 AR virus to heterotopically transplanted rat hearts, global myocardial expression of receptor was achieved at levels 5- to 10-fold above normal.²⁸ Strikingly, this was sufficient to raise basal and isoproterenol-stimulated cardiac contractility. These studies underscore the potential feasibility of a gene therapy approach with β_2 ARs. They also highlight an apparently broad therapeutic window, because at least 10- to 20-fold higher levels of transgenic overexpression than were functionally effective in these adenoviral studies in rat and rabbit were necessary to observe any chronic cardiotoxicity.

β ARK Inhibition

Transgenic overexpression of a β ARK inhibitor peptide largely reverses the impaired cardiac performance in both the MLP knockout mouse²⁴ and the calsequestrin-overexpression mouse models of heart failure.²⁹ In the latter model, not only is cardiac function improved but survival time is approximately doubled with the β ARK inhibitor peptide. In both cases, the markedly blunted β -adrenergic responsiveness of the heart is reversed and the elevated β ARK levels are lowered toward normal. In another example, the blunted cardiac response to isoproterenol and elevated cardiac β ARK activity in transgenic mice overexpressing β ARK in the heart are both reversed when these animals are mated with mice expressing the β ARK inhibitor peptide in the heart.³⁰ These results directly demonstrate that the ability of the β ARK inhibitor to increase cardiac responsiveness to catecholamines (endogenous and exogenous) is, in fact, associated with its ability to inhibit the enzyme *in vivo*.

In vitro, adenovirus-mediated transfer of the β ARK inhibitor peptide into cardiac myocytes derived from rabbits previously paced into ventricular failure has also been shown to restore β -adrenergic-responsive cAMP accumulation to normal.²⁶ A caveat to the interpretation of these studies, however, is that the β ARK inhibitor peptide works by blocking $G_{\beta\gamma}$ interaction with the enzyme. Because $G_{\beta\gamma}$ undoubtedly plays a variety of other signaling roles in the heart, the possibility remains that the β ARK inhibitor peptide in fact has activities unrelated to β ARK inhibition.

One case in which β ARK inhibition has not reversed deteriorating cardiac function is the previously mentioned G_{α_q} -overexpressing mouse with hypertrophy and heart failure.²⁵ However, it should be noted that unlike the other models cited, and in fact most cases of human heart failure, these animals do not display elevated cardiac β ARK activity or downregulated cardiac β ARs.

Taken together, these results suggest that inhibition of cardiac β ARK activity, either by gene transfer or more directly by the development of suitable inhibitor drugs, may represent a novel approach to the treatment of heart failure. The concern about such an approach has stemmed from the notion that elevated myocardial β ARK levels and the resulting desensitization of cardiac β ARK are purely protective mechanisms. Abrogation of such compensatory mechanisms, it has been reasoned, would surely only worsen the physio-

logical deterioration caused by excess catecholamine stimulation. However, as demonstrated above, when this notion is directly tested in animal models, it is found not to be so. Inhibition of elevated β ARK activity by blockade of $G_{\beta\gamma}$ interactions in several animal models of heart failure leads to reversal of desensitization and improved cardiac performance and longevity.^{24,29} These findings, in turn, suggest that elevated β ARK activity and desensitization are, at least in some respects, maladaptive in the failing heart. Thus, the best strategy for developing potentially useful β ARK inhibitors may be to target the $G_{\beta\gamma}$ - β ARK interaction.

How can one reconcile a potential role for augmentation of β_2 AR signaling or for β ARK inhibition in heart failure with the well-established findings that β -adrenergic agonist therapy, although of short-term benefit, does not improve long-term outcomes¹ and with the recent success of β -blocker³¹ therapy for heart failure? The answer appears to lie in the very different consequences of each of these means of augmenting β -adrenergic stimulation of the heart. Chronic catecholamine (agonist) stimulation of the heart demonstrably has deleterious effects, which appear to be mediated largely via β_1 ARs. The concept of inotropic gene therapy with β_2 ARs appears to circumvent these negative effects by engaging a distinct portfolio of signaling pathways that lack the apoptotic and perhaps some of the arrhythmogenic potential of β_1 AR stimulation.

Inhibitors of β ARK increase contractility in several animal models of heart failure without any evidence of pathological consequences even over very long periods.^{24,29} This is in striking contrast to the effects of chronic stimulation of β_1 ARs⁵ or G_{sa} .⁶ This may be due to facilitation of cardiac support mediated by the normal ebb and flow of endogenous catecholamines (which is blocked by desensitization in heart failure) and perhaps by other, as yet unspecified, endogenous G protein-coupled receptor agonists (β ARK activity is not limited to β ARs).⁴ It is striking that β ARK inhibition shares with other pharmacological therapies known to improve heart failure (eg, β -blockers) the ability to normalize or remodel signaling through the cardiac β -adrenergic system by reducing desensitization, lowering cardiac GRK activity,³² enhancing catecholamine sensitivity, and raising levels of β_1 ARs. Thus, it is plausible that the salutary effects of β -blockers in chronic treatment of heart failure may be due, at least in part, to their demonstrated ability to reduce the elevated levels of myocardial β ARK.

With recent landmark trials showing beneficial effects of β -blockers in the treatment of chronic heart failure,³³ it is natural to ask why anyone would want to augment β AR signaling with a β ARK inhibitor. However, given the experimental data showing the remarkable salutary effects of the β ARK inhibitory peptide on reversing β AR desensitization, it becomes apparent that β -blocker therapy and β ARK inhibition may in fact be complementary therapeutic modalities. For example, whereas treatment with β -blockers will antagonize the catecholamine toxicity associated with heart failure, β ARK inhibition will act to preserve normal β AR-G protein coupling in times of need, such as during exercise and periods of stress. Thus, there are likely to be major differences between the deleterious effects of chronic β AR stimulation

and the potentially beneficial effects of intermittent β AR stimulation.

Twenty years ago, the idea that β -adrenergic antagonists could be used as therapeutic agents to treat heart failure was viewed as quite heretical, even though clinical data to support this were already emerging.³⁴ Almost 2 decades was necessary to reverse the well-established, although erroneous, conventional wisdom on this point and bring these drugs into the therapeutic armamentarium for the treatment of heart failure. Given the rapid pace of current experimental efforts, a much more rapid assessment of β_2 AR augmentation and β ARK inhibition as novel therapeutic modalities in heart failure seems likely. Testing of the latter therapeutic target would be greatly facilitated by the development of small-molecule inhibitors of the β ARK-G $_{\beta\gamma}$ interaction.

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