

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

Commentary

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One of the most effective means of increasing cardiac output is by activating cardiomyocyte β -adrenergic receptors (β ARs). β ARs 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). β AR 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, β AR function is, unexpectedly, limited by several molecular mechanisms. These include a decrease in the expression and coupling of the β_1 AR subtype, a decrease in the coupling of the β_2 AR subtype, an increase in expression of the inhibitory G protein G_i , an increase in the expression of the β AR kinase (which phosphorylates and desensitizes β ARs), and a decrease in expression or function of adenylyl cyclase. Because the consequent decrease in β AR signaling limits energy expenditures in a heart that has little metabolic reserve, this response is generally thought to be adaptive. Indeed, judicious administration of β AR antagonists (β blockers) in chronic heart failure can improve cardiac performance (2). However, because these changes each alter β AR 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 β AR 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_2 AR 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_1 AR subtype results in cardiomyopathy with depressed contractile function (5, 6). Such results indicate that although β_1 AR and β_2 AR each couple to G_s , these receptor subtypes must engage distinct signaling pathways. Thus, it appears that β_2 AR, but not the β_1 AR, 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_2 AR can also affect ion flow through the type III Na^+/H^+ exchanger by binding the

the only second messenger that is necessary for adrenergic mediated toxic effects.

As the characterization of these genetically altered mice unfolds, various cross-breeding 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 β AR dysfunction, with other strains that either overexpress the β_2 AR in the heart, express a β AR kinase inhibitor (β ARKct) 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_2 AR 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/ β ARKct mice show normal fractional shortening throughout the 12-month study period. Furthermore, hypertrophy occurs in the HCM/ β_2 AR and HCM/PLB-null mice but not the HCM/ β ARKct 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

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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

in β -myosin heavy chain expression, whereas the most favorable response for atrial natriuretic factor and α -skeletal actin was with the β ARKct-crossed mice. Given that the β ARKct 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 β ARKct animal is that beneficial effects are only found when β ARK levels or activities are increased. Thus, in the muscle-specific *LIM* knockout (19), the HCM mouse, and the calsequestrin overexpression (20) models, β ARK is increased, and in each case, transgenic overexpression of the inhibitor peptide substantially improves function. In contrast, the G_{α_q} overexpressing model of cardiomyopathy, which also displays β AR desensitization, hypertrophy, and marked ventricular dysfunction (21), does not have elevated β ARK levels, and in these cases, ventricular function and β AR responsiveness are not rescued with the β ARK inhibitor (22, 23). Instead, restoration of other dysfunctional components of β AR signaling improves function in vitro or in vivo (23–25).

The β ARKct peptide acts by binding the $\beta\gamma$ subunits that are released from G-protein heterotrimers. $\beta\gamma$ is required for β ARK translocation and thus its ability to phosphorylate β ARs. Since its beneficial effects are seen only in systems that feature elevated kinase activity, it appears that the inhibitory β ARKct peptide acts specifically on this aspect of the pathogenesis. However, other physiologic and biochemical indices of hypertrophy are also improved by β ARKct, and it is intriguing to consider whether blocking $\beta\gamma$ may have effects other than inhibiting β ARK. Indeed, $\beta\gamma$ stimulates tyrosine kinase signaling and phospholipase C activation, which could accelerate hypertrophy. Another consideration is that as cardiac function improves when $\beta\gamma$ signaling is attenuated, β AR function returns as a secondary response. This appears to be the case during β -blocker treatment, as β AR function has

been reported to improve during successful therapy (2). Finally, β ARK 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 β ARK to desensitize other receptors. It should be noted that β_2 AR 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.

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