Anti–β_1-adrenergic receptor antibodies and heart failure: causation, not just correlation

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Antibodies specific for the β_1-adrenergic receptor are found in patients with chronic heart failure of various etiologies. From work presented in this issue of the *JCI* (see the related article beginning on page 1419), we can now infer that these antibodies actually contribute to the pathogenesis of chronic heart failure. This commentary discusses mechanisms by which these antibodies may engender cardiomyopathy.

Do anti–β-adrenergic receptor (anti–β-AR) antibodies play a role in the pathogenesis of chronic systolic heart failure (CHF)? This question emerged almost 30 years ago (1), when antibodies with β-adrenergic stimulating (agonist) activity were discovered in the serum of patients with Chagas disease, one of the most common causes of CHF worldwide (2). Since that time, IgGs with agonist activity for the β_1-adrenergic receptor (β_1-AR) have been found in sera not only from patients with Chagas disease, but also from patients with idiopathic dilated cardiomyopathy (3) as well as ischemic (4) cardiomyopathy. Whether these antibodies merely correlate with myocardial inflammation that leads to CHF, result from myocardial inflammation, or actually contribute to the pathogenesis of CHF could not be ascertained — until now. In this issue of the *JCI*, Jahns et al. employed isogenic injections of anti–β_1-AR antiserum in inbred rats to produce a cardiomyopathy that appears to be non-inflammatory (5). In so doing, these authors conclusively demonstrated that agonistic, anti–β_1-AR IgG — by itself — is sufficient to engender the sort of myocardial dysfunction characteristic of CHF. This finding fundamentally advances our understanding of CHF. However, it should not really surprise us, because it represents a logical extension of diverse but congruent investigations conducted over several decades.

To provide historical and mechanistic perspectives for the elegant work of Jahns et al., we address several questions that relate their work to contemporary concepts of β_1-AR pathophysiology: How might IgG activate the β_1-AR, and how could chronic β_1-AR activation result in cardiomyocyte toxicity? What molecular mechanisms regulate the β_1-AR when it is chronically stimulated by IgG or other agonists, and how might these mechanisms affect the pathogenesis of CHF? Lastly, how can these perspectives elucidate the therapeutic efficacy of β-AR antagonists, or "beta blockers," in CHF?

Activation of cardiac β_1-ARs

The β_1-AR constitutes approximately 80% of the cardiac β-AR complement. Like the β_2-AR (with 54% overall homology), the β_1-AR is a seven-membrane–spanning receptor, with three extracellular polypeptide sequences ("loops") connecting the transmembrane α helices (Figure 1). With their intracellular domains, the β-ARs couple to the stimulatory heterotrimeric GTP-binding protein (G_s). Activation of the β_1-AR requires a specific receptor conformation — one that is stabilized by agonist (and, apparently the binding of certain IgGs to the second extracellular loop; ref. 5). It also appears that β_1-AR dimerization (6, 7) may be involved in receptor activation (and may underlie the agonist properties of anti-β_1-AR antibodies observed in CHF patients and rats). Stimulation of β-ARs engenders a cascade of consequent activation: first G_s, then adenylyl cyclase (which forms cAMP), then the cAMP-dependent protein kinase (PKA). Activated PKA subsequently phosphorylates molecules critical for regulating sarcoplasmic $[Ca^{2+}]$ (8) — thereby increasing cardiomyocyte inotropy, chronotropy, and lusitropy. Activation of G_s can also increase L-type Ca^{2+} channel currents directly (9, 10) (Figure 1). Over the last few years, this time-honored scheme has been modified in ways that illuminate the β_1-AR-specific findings of Jahns et al. (5).

Genetic and pharmacologic approaches have demonstrated that the β_1-AR plays the predominant role in mediating cardiac inotropic and chronotropic responses to catecholamines (8). Cardiac preparations from β_1-AR knockout mice fail to augment contractility or their rate of contraction in response to isoproterenol, which stimulates both β_1- and β_2-ARs (11). Remarkably, β_1-AR knockout hearts have almost the same β_2-AR density as cognate wild-type controls, and can demonstrate contractile responses equivalent to controls — when contractility is augmented directly via adenylyl cyclase rather than via β-ARs (11). Even isoproterenol-induced adenylyl cyclase activity in cardiac homogenates is mediated overwhelmingly via the β_1-AR, in a manner disproportionate to the relative densities of β_1- and β_2-ARs (11). The failure of cardiac β_2-ARs to promote cAMP production to a degree commensurate with their expression level may be attributable to a signaling property that the cardiac β_2- and β_1-AR do not share: the ability to activate both the inhibitory heterotrimeric G protein (G_i) and G_s (12, 13). (A β_1-AR subtype-specific intracellular binding protein appears to prevent β_1-AR/G_i coupling [ref. 14].) In human subjects, β_2-AR–selective agonists have been used to augment left ventricular inotropy (15). However, a large fraction of this inotropic effect is mediated by β_1-ARs, and the role of β_2-ARs in this process may be largely to augment norepinephrine release from cardiac sympathetic neurons (15).

Nonstandard abbreviations used: β-adrenergic receptor (β-AR); β_1-adrenergic receptor (β_1-AR); chronic systolic heart failure (CHF); cyclic AMP–dependent protein kinase (PKA); G protein–coupled receptor kinase-2 (GRK2); GRK2 carboxyl-terminal polypeptide (GRK2ct); inhibitory heterotrimeric G protein (G_i); stimulatory heterotrimeric GTP-binding protein (G_s).

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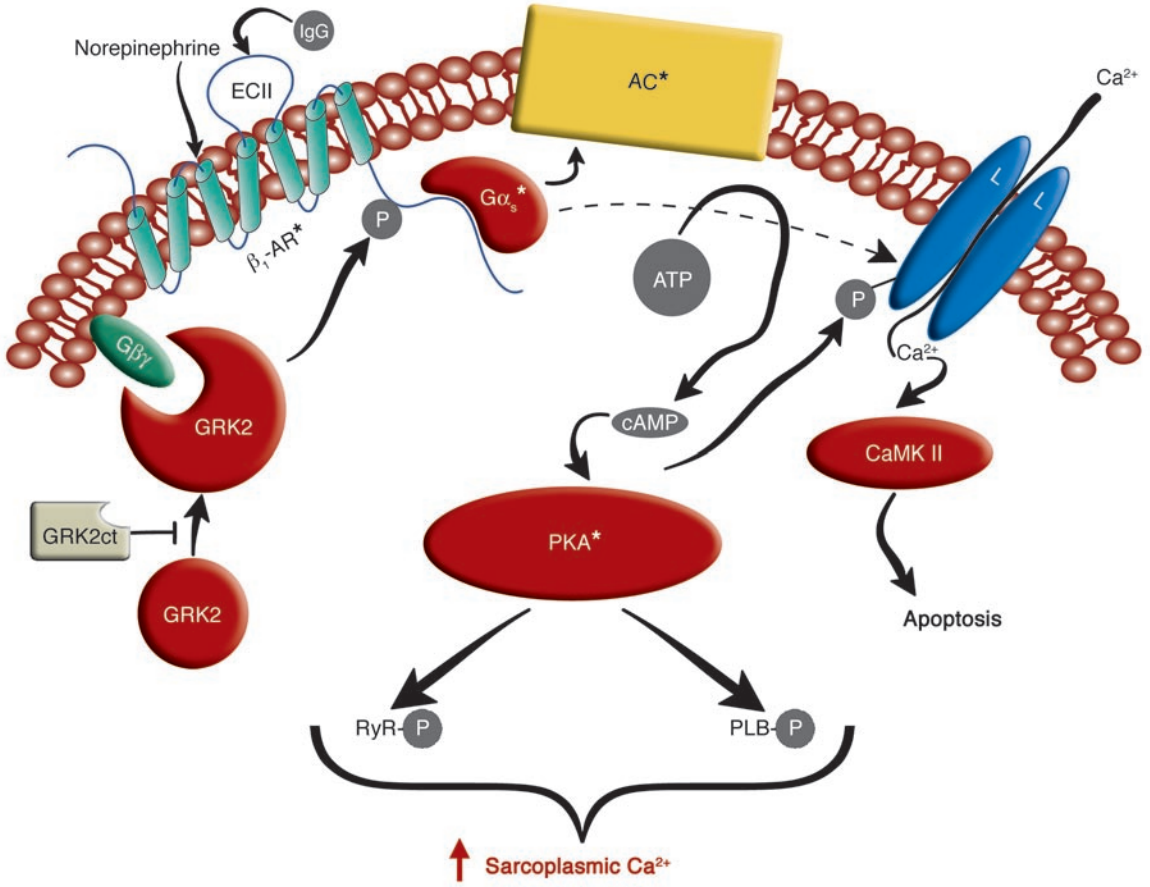

Figure 1
Schema for β_1-AR–mediated cardiomyocyte stimulation and β_1-AR desensitization. The seven-membrane-spanning β_1-AR is stimulated by the physiologic agonist norepinephrine or by IgG specific for the receptor's second extracellular loop (ECII) (in CHF subjects). The stimulated β_1-AR then activates the heterotrimeric G_s, which dissociates into its $G\alpha_s$* and $G\beta\gamma$ substituents. The $G\alpha_s$* activates both adenylyl cyclase (AC), which catalyzes cAMP formation, and the L-type calcium channel (L), which then permits Ca^{2+} to enter the cardiomyocyte. This Ca^{2+} can both augment contractility and, on a slower time scale, promote cardiomyocyte apoptosis by activating Ca^{2+}/calmodulin kinase II (CaMK II). The cAMP produced by adenylyl cyclase activates PKA, which subsequently phosphorylates (P) numerous substrates important to sarcoplasmic [Ca^{2+}] regulation: the L-type Ca^{2+} channel, the ryanodine receptor (RyR), and phospholamban (PLB). The net effect of this activity in the short term is to augment sarcoplasmic [Ca^{2+}] and contractility. (In the long term, this activity engenders cardiomyocyte toxicity.) The activated β_1-AR is desensitized when it is phosphorylated by PKA (not shown) and by GRK2, the cellular expression of which increases with chronic β_1-AR stimulation. Translocation of GRK2 from the sarcoplasm to the sarcolemma requires $G\beta\gamma$ subunits, and this translocation is inhibited when GRK2ct is expressed heterologously in cardiomyocytes. Asterisks denote activated proteins.

Excessive β_1-AR activation yields cardiomyocyte toxicity

Excessive isoproterenol stimulation has long been known to produce cardiomyocyte toxicity, myocardial scarring, and CHF (16, 17). More recently, chronic administration of submaximal isoproterenol doses has also been shown to produce cardiomyopathy, independent of myocardial scarring (18). That this isoproterenol-induced cardiomyopathy results primarily from β_1-AR activation can be inferred from the β_1-AR knockout mouse studies discussed above (11), as well as from a host of in vitro studies with rodent cardiomyocytes (13, 19). Further evidence that chronic β_1-AR hyperstimulation causes cardiomyocyte toxicity has emerged from studies with transgenic mice displaying modest (~15-fold), cardiac-specific overexpression of the β_1-AR: these mice not only possessed enhanced β_1-AR activity, but also developed cardiomyopathy by age 4–9 months (20). In contrast, transgenic mice overexpressing the β_2-AR at higher absolute levels failed to develop any cardiomyopathy by this age (21).

The particular signaling pathways responsible for β_1-AR–induced cardiomyocyte toxicity remain somewhat enigmatic. Increasing cardiomyocyte PKA activity by as little as 2.4-fold can engender CHF (22), and cardiomyocyte overexpression of $G\alpha_s$ engenders CHF (23). However, overexpression of adenylyl cyclase type VI (which also augments cardiomyocyte cAMP levels) not only avoids CHF but also can alleviate CHF in the $G\alpha_q$-overexpressing mouse (24). In addition, β_1-AR–promoted cardiomyocyte apoptosis can result from Ca^{2+}/calmodulin-dependent protein kinase activity, independently from the PKA pathway (19). The diverse studies delineating molecular mechanisms responsible for β_1-AR–promoted cardiomyocyte toxicity have been reviewed recently (8). In light of these data, it is intriguing that levels of plasma norepinephrine (which activates the β_1-AR, like the anti-β_1-AR IgG of Jahns et al. [ref. 5]) have been directly and independently associated with CHF mortality in human subjects (25).

Regulatory mechanisms for subduing the β_1-AR signaling system

In the face of persistent β_1-AR hyperstimulation (either in CHF or experimental systems), both receptor-based and non-receptor counter-regulatory mechanisms are engaged in the cardiomyocyte — perhaps to bridle cellular toxicity. These mechanisms result in approximately 50% downregulation of the β_1-AR itself (26) (through mechanisms that appear to involve PI3K [ref. 27]), a decrease in adenylyl cyclase activity, and upregulation of the multifunctional G_i (which can inhibit adenylyl cyclase) (23). In addition, myocardium from CHF patients demonstrates a two- to threefold upregulation of G protein–coupled receptor kinase-2 (GRK2) (26), which phosphorylates and desensitizes the β_1-AR (28, 29). This upregulation of GRK2 even precedes the onset of left ventricular failure in mice with transgenic myocardial overexpression of calsequestrin (30). Although these "desensitizing" mechanisms are insufficient to prevent CHF, some of them may, paradoxically, contribute to CHF pathophysiology. Perhaps the most thoroughly studied of these cases is the role of GRK2.

Relieving excessive β_1-AR desensitization

Inhibition of cardiomyocyte GRK2 activity has been shown to ameliorate CHF in several mouse models, including deficiency of muscle LIM protein (31) and myocardial calsequestrin overexpression (32). GRK2 inhibition in these studies was achieved by transgenic myocardial overexpression of a polypeptide that comprises the carboxyl-terminal third of GRK2. This molecule, termed GRK2ct, inhibits GRK2 activity on receptors by binding to the heterotrimeric G protein $\beta\gamma$ subunits required for GRK2 recruitment to the receptors (33) (Figure 1). Because "GRK2ct therapy" presumably does not alter the fundamental cardiomyocyte problems leading to myocardial dysfunction in these mouse models, its success points to the possibility that CHF-related enhancement of cardiomyocyte GRK2 activity may itself be maladaptive, and contribute to the pathogenesis of CHF. Remarkably, GRK2ct-expressing myocardium demonstrates attenuation of CHF-related GRK2 upregulation (31), β_1-AR downregulation (31), and β_1-AR/adenylyl cyclase desensitization (31, 32). In interpreting these data, however, it is important to note that GRK2ct binds a large variety of $G\beta\gamma$ subunits as well as phosphatidylinositol 3,5-bisphosphate (33). These binding activities could, beyond inhibiting GRK2, also contribute to the effects observed with GRK2ct (27, 34).

β-AR antagonists: possible mechanisms underlying therapeutic efficacy

Improvements in myocardial contractility, exercise tolerance, and mortality have been observed in CHF patients treated chronically with the β-AR antagonists metoprolol, bisoprolol, and carvedilol (35). This clinical improvement cannot depend upon reversal of β_1-AR downregulation, since carvedilol does not promote such a reversal (35). Moreover, this clinical improvement seems unlikely to be mediated through β_1-ARs at all, since it can be observed under conditions precluding agonist stimulation of β_1-ARs (36). However, probably because it diminishes toxic hyperstimulation of the β_1-AR by elevated sympathetic tone, prolonged β-AR antagonist therapy reduces cardiomyocyte apoptosis in CHF (37) and effects a partial recovery of CHF-associated derangements in gene expression (38, 39) and PKA-mediated hyperphosphorylation of proteins (40, 41), including those constituting the signaling and Ca^{2+}-handling machinery downstream of the β_1-AR. These "receptor-distal" mechanisms can enhance myocardial performance despite ongoing β-AR antagonist occupancy (36).

As a specific example of how mechanisms distal to the receptors can affect cardiomyocyte function, let us again consider the role of GRK2 in CHF. Bisoprolol (42) and carvedilol (43) have been used in animals to reduce GRK expression. (We should note that bisoprolol was used by Jahns et al. to abolish the adenylyl cyclase response to anti–β_1-AR IgG [ref. 5].) Because GRK2 can desensitize a multitude of heptahelical receptors (33), reduced GRK2 levels could enhance signal transduction, and thus inotropy, evoked by heptahelical receptors other than the (antagonist-occupied) β_1-AR, such as endothelin receptors (44). From the perspective of this hypothesis, it is intriguing that metoprolol and GRK2ct reduced calsequestrin-associated cardiomyopathy in a synergistic manner (32).

Perspectives

From decades of CHF investigations, we should indeed have expected that agonistic, anti–β_1-AR antibodies *would* promote the development of heart failure. Now that Jahns et al. have provided an important proof of principle (5), we have another excellent reason to increase the clinical use of β-AR antagonist therapy in CHF of all causes. Whether immunoadsorption of anti–β_1-AR antibodies (45) will provide CHF patients with benefits beyond those obtainable from β-AR antagonists alone, however, remains to be determined.

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Dissecting the functional role of different isoforms of the L-type Ca^{2+} channel

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There currently exist a great number of different mouse lines in which the activity of a particular gene of interest has been inactivated or enhanced. However, it is also possible to insert specific mutations in a gene so that the pharmacological sensitivity of the gene product is altered. An example of such an approach shows how the abolition of the sensitivity of an L-type Ca^{2+} channel isoform to dihydropyridines allows the investigation of the physiological role of these channels in different tissues (see the related article beginning on page 1430).

Nonstandard abbreviations used: dihydropyridine (DHP); L-type Ca^{2+} channel (LTCC).

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The LTCC family

L-type Ca^{2+} channels (LTCCs) are formed by different pore-forming $\alpha 1$ subunit isoforms named $Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, and $Ca_v1.4$ associated to auxiliary subunits ($\alpha 2$-δ, β, and γ) (1). The common pharmacological hallmark of all native and recombinant LTCCs is their sensitivity to dihydropyridines (DHPs). However, the small differences among the LTCC $\alpha 1$ isoforms in their affinity for DHPs (agonists and antagonists) have limited the study of the functional role of these channels in various tissues, including the cardiovascular system, the brain, and the endocrine glands.

In this issue of the *JCI*, Sinnegger-Brauns and coworkers report that they have developed a new mouse model resulting from a knock-in mutation of the $Ca_V1.2$ voltage-dependent LTCC subunit which abolishes the sensitivity of the channel to DHP (referred to herein as the $Ca_V1.2DHP^{-/-}$ mouse) (see Figure 1) (2). Since $Ca_v1.2$ is