Role of β-Adrenoceptor Desensitization in Heart Failure

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Abstract: Heart failure is characterized by left ventricular dysfunction associated with a complex of symptoms that relate to inadequate perfusion of tissues and pulmonary congestion. When the heart is damaged by an insult, compensatory mechanisms mediated through activation of the sympathetic nervous system are involved to stabilize myocardial performance. Although these mechanisms can sustain cardiac function for a short time, chronic activation of sympathetic activity has adverse biological effects.

This review will focus on the changes that occur in the β-adrenergic receptor pathway in the failing heart and will discuss novel approaches to therapy through manipulation of this pathway. Key Words: β-Adrenoceptors—β-Adrenoceptor antagonists—Heart failure

INTRODUCTION

Heart failure is a disease characterized by left ventricular (LV) dysfunction associated with a complex of symptoms that relate to inadequate perfusion of tissues and pulmonary congestion. One of the consequences is the activation of the sympathetic nervous system, which plays a crucial role in adapting circulatory homeostasis to changes in environment. Furthermore, circulating levels of catecholamines are increased in heart failure in proportion to the severity of the disease (69). However, sympathetic hyperactivity can also initiate or accelerate cardiovascular pathology and provoke clinical events in the presence of cardiovascular disease; in fact, patients suffering from heart failure and with plasma levels of norepinephrine have the most unfavorable prognosis (19). These observations have led to the hypotheses that sympathetic activation may play an important role in the progression of heart failure (5,7,53) and that pharmacological interference with this system can produce hemodynamic and clinical benefits (52).
ADRENERGIC RECEPTORS IN THE HEART

Cardiac \( \alpha \)-Adrenoceptors

The heart contains only a small number of \( \alpha \)-adrenoceptors, and the \( \beta:\alpha \) ratio is about 10:1 in the human myocardium (10,68). However, this low number of cardiac \( \alpha \)-adrenoceptors is able to mediate positive inotropic response (27,40). Stimulation of \( \alpha_1 \)-adrenoceptors activates phospholipase C, resulting in an increase in intracellular inositol (1,4,5)-triphosphate and diacylglycerol, which causes an increase in myocyte calcium levels producing a positive inotropic response. In addition, diacylglycerol can activate protein kinase C to stimulate myocardial hypertrophy.

Cardiac \( \beta \)-Adrenoceptors

The primary mechanism in which the mammalian heart rapidly regulates contractility is through the \( \beta \)-adrenoceptor (\( \beta \)AR) pathway. This mechanism is important as a means of responding to neurotransmitter (norepinephrine) or hormone (epinephrine) release. \( \beta \)ARs belong to the large family of G protein-coupled receptors characterized by a typical structure with seven transmembrane domains (33). These receptors contain phosphorylation sites, which serve as targets for protein kinase A, protein kinase C, and \( \beta \)-adrenergic receptor kinases (\( \beta \)ARKs). Three types of \( \beta \)ARs, designated \( \beta_1^- \), \( \beta_2^- \), and \( \beta_3^- \) adrenoceptors, have been cloned from mammalian tissues (22,33). In the heart, the \( \beta_1 \)AR subtype is most abundant, but the \( \beta_2 \) subtype is also present. The receptor site is highly stereospecific, the best fit among catecholamines being obtained with the synthetic agonist isoproterenol (ISO) rather than with the naturally occurring catecholamines, norepinephrine (NE) and epinephrine (E). In the case of \( \beta_1 \)ARs, the order of agonist activity is ISO > E > NE, whereas in the case of \( \beta_2 \)ARs, the order is ISO > E > NE (60).

Cardiac G Proteins

The Stimulatory G Protein

G proteins are a superfamily of proteins that bind guanine triphosphate (GTP), a process that is crucial in linking the effect of the first messenger on the receptor to the activity of the membrane-bound enzyme system that produces the second messenger (30). The combination of the \( \beta \)-adrenoceptor, the G-protein complex, and adenylyl cyclase is termed the \( \beta \)-adrenergic system (67). The G protein itself, a heterotrimer composed of Go, G\( \beta \), and G\( \gamma \) subunits, upon receptor stimulation splits into the \( \alpha \)-subunit, which is bound to GTP, and the \( \beta \gamma \) subunit (50). Two different G-protein complexes are involved in \( \beta \)AR signaling, namely, G\( \alpha \) that stimulates and G\( \gamma \) that inhibits activity of adenylyl cyclase (59). The \( \alpha \)-subunit of G\( \alpha \) (G\( \alpha_c \)) combines with GTP and then separates from the other two subunits to enhance activity of adenylyl cyclase. The \( \beta \)- and \( \gamma \)-subunits appear to be linked structurally and in function. In contrast to G\( \alpha \), the GTP-binding protein, G\( \gamma \), is responsible for inhibition of adenylyl cyclase (50). During cholinergic signaling, the muscarinic receptor is stimulated, and GTP binds to the inhibitory \( \alpha \)-subunit, \( \alpha_i \) (49). Dissociation of G\( \alpha \) from the G\( \beta \gamma \) subunits of the G-protein complex leads to inhibition of adenylyl cyclase. Furthermore, G\( \beta \gamma \) subunits can inhibit certain isoforms of adenylyl cyclase by
stimulating GTPase activity, breaking down the active α,-subunit (αs-GTP), so that activation of adenylyl cyclase in response to β-stimulation is reduced.

Another member of the G protein family, Gq, is involved in linking myocardial α-adrenoceptors to the membrane-associated enzyme, phospholipase C.

DEVELOPMENT AND PROGRESSION OF HEART FAILURE

When the heart is damaged by an insult, compensatory mechanisms are activated to stabilize myocardial performance. These mechanisms through increases in heart rate, contractility, volume expansion, and hypertrophy can sustain myocardial function for a short time. However, continued chronic use of these compensatory mechanisms to support the failing heart also has adverse biological effects (Table 1).

CONSEQUENCES OF SYMPATHETIC HYPERACTIVITY

Catecholamine Toxicity

Norepinephrine can exert adverse effects on the cardiovascular system by several independent mechanisms. By increasing cAMP, short-term exposure to norepinephrine can disrupt the structural and functional integrity of cardiac cells (43). Moreover, long-term exposure can induce growth and provoke oxidative stress (54,78), triggering apoptosis (programmed cell death). Both α1- and β1ARs are involved in stimulating cell growth and compromising the viability of the failing heart (23,37,43,78). Sympathetic activation also increases ventricular size and pressure as a consequence of peripheral vasoconstriction and enhanced intravascular volume by impairing salt and water excretion by the kidneys. These effects are mainly α1 mediated (21), and they increase myocardial oxygen demand. At the same time, norepinephrine induces cardiac hypertrophy but restricts the coronary arteries’ blood supply (2,65). Finally, by stimulating β1- and β2ARs, catecholamines increase the heart rate.

Tachycardia affects the oxygen supply-demand relation (34) and worsens the force-frequency relation that is already blunted in the failing heart. Whereas in the normal heart

<table>
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<th>Signaling pathway</th>
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<td>Adrenergic</td>
<td>Increased heart rate, contractility, volume expansion, hypertrophy</td>
<td>Myocyte toxic effects, apoptosis, growth and remodeling, altered gene expression</td>
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<td>Angiotensin II</td>
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<td>Tumor necrosis factor</td>
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<tr>
<td>Stretch/wall stress</td>
<td>Volume expansion, hypertrophy</td>
<td>Apoptosis, growth and remodeling, altered gene expression</td>
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* Adapted from ref. 4.
contractile force is enhanced by an increase in heart rate, the opposite happens in the failing heart (48).

Drugs interfering with the α- and/or βARs can antagonize these deleterious effects. βAR antagonists prevent many of the toxic effects of catecholamines and reverse the structural changes occurring in the failing heart (44,64). They also prolong life in experimental models of heart failure (73). α1AR antagonists can reduce myocardial hypertrophy and cell death (23,43,47,78), but experimental evidence and clinical evidence suggest that α1-blockade alone is insufficient to produce benefits in the treatment of heart failure (17,43,54). In contrast, recent clinical trials have shown that β-blockade is able to improve survival in patients with chronic heart failure (16,45).

β-Adrenoceptor Desensitization

βAR signaling can be blunted or “desensitized” by several mechanisms. Receptor downregulation, a mechanism requiring several hours, can be due to a decrease in receptor synthesis or to an increase in receptor sequestration and/or degradation. In addition, β-adrenoceptor mRNA destabilization in response to agonist exposure may occur (62). In contrast to receptor downregulation, a loss of receptor function as a result of uncoupling from the signal-transducing G protein, Gα, can occur rapidly. This process is induced by receptor phosphorylation by protein kinases. The second messengers, cAMP and diacylglycerol, activate protein kinase A and protein kinase C, respectively, that will phosphorylate βARs, leading to a process known as heterologous desensitization. A mechanism of highly specific homologous desensitization of βARs is mediated by members of the family of G protein-coupled receptor kinases (GRKs) (41). A member of this family, GRK2 (commonly known as the β adrenergic receptor kinase 1, βARK1), is expressed in the mammalian heart (38,63). βARK1 phosphorylates agonist-occupied receptors, allowing the interaction with a cytosolic protein β-arrestin, which binds to the receptor and interdicts coupling of Gα to adenylyl cyclase. Increased GRK activity forces the equilibrium of the βARs toward the inactive state, creating a condition of reduced responsiveness to catecholamines (61,62). Increased βARK1 expression and activity are found in human heart failure and could explain why remaining βARs in failing hearts are functionally uncoupled.

β-Adrenergic-Signaling Alterations in the Failing Heart

Downregulation of β1AR gene expression was the first identified molecular defect in the failing human heart (7,12). The original interpretation was that it could affect cardiac function through diminished response to adrenergic signaling (4,7,8). In the failing human heart, there are abnormalities at multiple levels in the βAR pathways. There are also variations in the expression of these abnormalities, depending on the type of cardiomyopathy associated with the systolic dysfunction. For example, downregulation of β1AR occurs in all types of cardiomyopathy that exhibit systolic dysfunction (9). βAR uncoupling, caused by receptor phosphorylation (70), upregulation in Gi (5,9,28), or receptor sequestration, is a universal finding. In addition, there are abnormalities in adenylyl cyclase gene expression in pressure overloaded left (13) or right (5,9) ventricles.

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EFFECT OF β-BLOCKADE ON THE CLINICAL STATUS OF HEART FAILURE

The effect of β-blockade on the clinical status of heart failure has been assessed in several single-center and multicenter placebo-controlled studies. In these studies, the β-adrenoceptor antagonist or placebo was added to preexisting therapy with diuretics, an angiotensin converting enzyme (ACE) inhibitor, and usually digitalis. Clinical status has been assessed by both direct measures (New York Heart Association (NYHA) class and symptom scores) and indirect measures (exercise tolerance and quality of life).

Effects of Selective β₁-Blockade on Symptoms

In single-center placebo-controlled studies, the addition of metoprolol to conventional therapy for 3 to 6 mo produced an improvement in symptoms and exercise tolerance (1,25,29). In multicenter studies, however, results with β₁-adrenoceptor antagonists are more varied. In the Metoprolol in Dilated Cardiomyopathy (MDC) trial, metoprolol improved exercise tolerance, NYHA class, and quality of life at 12 mo (74). In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD), the addition of metoprolol to conventional therapy did not improve exercise tolerance or functional capacity (77). In the Cardiac Insufficiency Bisoprolol study (CIBIS), an improvement in NYHA class was demonstrated. This trial, however, did not evaluate quality of life or exercise tolerance (15).

Effects of Nonselective β₁- and β₂-Blockade on Symptoms

In either single-center (32) or multicenter (11) studies, bucindolol favorably affected cardiac function but did not improve symptoms. In three single-center studies (39,46,51) and four multicenter trials (6,18,20,56), treatment with carvedilol showed an improvement in NYHA class with little effect on exercise tolerance.

Effects of β₁-Blockade on the Morbidity and Mortality Rate in Heart Failure

In the MDC study, treatment of nonischemic cardiomyopathy with metoprolol reduced the worsening of heart failure but did not significantly influence the number of deaths (74).

In the RESOLVD trial, metoprolol improved the survival rate in patients with ischemic and nonischemic cardiomyopathy but increased the rate of hospitalization for heart failure (77).

In the CIBIS I study, the addition of bisoprolol (a selective β₁-adrenoceptor antagonist) to conventional therapy was associated with a 34% reduction in the risk of hospitalization for heart failure (15). The CIBIS II study was designed to assess the effect on survival (16). This trial showed a significant reduction in mortality in patients treated with bisoprolol compared with placebo and conventional therapy (Fig. 1) (16). These results have been confirmed by a large-scale randomized placebo-controlled trial (MERIT HF). Treatment once daily with metoprolol CR/XL added to standard therapy improved survival and lowered the risk for sudden death and death from worsening heart failure in patients with mild-to-severe chronic heart failure secondary to left-ventricular systolic dysfunction of ischemic or nonischemic cause (45).
Effects of Combined $\alpha_1$-, $\beta_1$-, and $\beta_2$-Adrenoceptor Antagonists on Morbidity and Mortality in Heart Failure

Since $\alpha_1$-adrenoreceptors contribute to the vasoconstriction and sodium retention in heart failure (21,57,66), drugs that block $\alpha_1$-adrenoceptors can reduce the volume and the pressure of the left ventricle, reducing the risk of worsening heart failure that might otherwise accompany initiation of treatment with $\beta$-adrenoceptor antagonists.

Five different trials have been performed using carvedilol in addition to conventional therapy. In a study performed in Australia and New Zealand, treatment with carvedilol was associated with a reduction in the progression of disease and risk of hospitalization for any reason (3). Survival data in the four U.S. multicenter studies (6,18,20,56) were combined and monitored by a single Data and Safety Monitoring Board (55). Carvedilol therapy was associated with a significant decrease in the risk for death (Fig. 2). The beneficial effect of carvedilol on survival was consistent in all subgroups and was reflected in a decrease in the risk for death from progressive heart failure, as well as in the risk for sudden death. In addition, carvedilol was associated with a reduction in hospitalization for cardiovascular causes. These findings demonstrate how drugs interfering with the adrenergic system can be useful in the treatment of heart failure. Whether $\alpha_1$-adrenoceptor blockade adds to the efficacy of the $\beta$-adrenergic blockade alone is unclear and will require further study.

MECHANISMS OF THE $\beta$-ADRENERGIC BLOCKADE'S BENEFICIAL EFFECTS IN THE FAILING HEART

Since $\beta$-adrenoceptor antagonists are known to depress cardiac function, the use of these agents historically was considered to be contraindicated in patients with compromised ventricular function because of the agents’ short-term adverse effects (26). Recent data have now shown that, in contrast to these adverse short-term changes in ventricular function, the long-term biological action is in most cases beneficial.
Short-Term Hemodynamic Effects

Negative inotropic and chronotropic response and vasoconstriction can depress overall ventricular performance (26,75). These negative consequences may be reduced by starting with low doses of a β-adrenoceptor antagonist followed by a gradual increase.

Long-Term Hemodynamic Effects

Cardiac performance is increased by long-term treatment with β-adrenoceptor antagonists. The most consistent hemodynamic response to long-term β-blockade in patients with heart failure has been an increase in left ventricular ejection fraction (32,39,46,51, 76). The difference between the short-term and long-term effects can be explained by the difference between the short-term and long-term effects of catecholamines on the heart. During short-term treatment, β-adrenoceptor antagonists interfere with the positive inotropic actions of endogenous catecholamines and, thus, cardiac function declines acutely (31). However, during long-term treatment, β-adrenoceptor antagonists antagonize the toxic effects of endogenous catecholamines (24). This action leads to improved cardiac performance, since the recovery of myocardial function is sufficient to overwhelm the short-term cardiodepressant effects of these drugs. Along with the effects on left ventricular contractile function, structural changes involving myocardial remodeling may also account for the long-term benefit of β-adrenoceptor antagonist treatment of heart failure. In fact, in the Australia/New Zealand study, treatment with carvedilol was associated with a reduction in end-diastolic and end-systolic left ventricular diameters (3), supporting the benefits of ventricular remodeling.

Effect of β-Adrenoceptor Antagonists on the βAR Signaling Pathway

As mentioned earlier, in addition to activation of cellular responses, β-agonist binding to receptor initiates mechanisms to promote the antithetical pathway of homologous
desensitization to decrease agonist-dependent signaling. Triggering the desensitization process is the phosphorylation of intracellular residues within the activated receptor by GRKs (36,42). One interpretation for these changes is that they are partially adaptive, serving to withdraw the heart from harmful excessive β-adrenergic stimulation (24). Another interpretation is that these changes that begin as an adaptive mechanism to buffer the negative effect of chronic exposure to increased catecholamines become, over time, maladaptive.

GRK-mediated desensitization of βARs appears to be extremely important not only in the normal regulation of cardiac function but also in the presence of disease. βARK1 appears to be the primary GRK involved in regulating βARs in the heart. In fact, an increase in βARK1 expression and activity has been found in several cardiovascular diseases, including human congestive heart failure (14,58,70,71,72). Our findings in transgenic mice that overexpress different members of the GRK family demonstrate how the upregulation of βARK1 in the diseased heart could markedly alter βAR function through receptor desensitization (14,38,63).

In a recent study, chronic infusion of isoproterenol for 14 d in normal mice produced myocardial hypertrophy, which was accompanied by impaired βAR signaling (35). Interestingly, βAR uncoupling appeared to be due to increased expression of βARK1, as both the mRNA and protein level were significantly elevated, which translated into enhanced myocardial GRK activity (35). The chronic infusion of atenolol (a selective β1AR antagonist) or carvedilol (α1-, β1-, and β2AR antagonist) led to the selective decrease of βARK1 expression, resulting in enhanced βAR signaling (35). Obtaining the same results with either atenolol or carvedilol suggests that addition of β-adrenoceptor antagonists can improve β-adrenergic signaling in the heart.

In our laboratory, we tested the hypothesis that βARK1 inhibition can improve cardiac function in heart failure. With the use of gene-targeting technology, a mouse model of heart failure was developed that contained a peptide inhibitor of βARK1 (61). In that study we found the striking finding that overexpression of a βARK1 inhibitor prevented the development of cardiomyopathy in a model of heart failure (61). The complete restoration to a normal cardiac phenotype was associated with inhibition of βARK1 activity and suggests a potential novel therapeutic approach to heart failure (61).

CONCLUSIONS

A hallmark of chronic heart failure is activation of the sympathetic nervous system. This early adaptive response over time becomes maladaptive, with elevated levels of circulating catecholamines being associated with a worse prognosis. Sympathetic hyperactivity can initiate or accelerate cardiovascular pathology and provoke clinical events in the presence of cardiovascular disease. In the past, use of β-adrenoceptor antagonists was considered absolutely contraindicated in patients with heart failure because of their negative inotropic and chronotropic activity. It is now clear from experimental studies and several large clinical trials that β-adrenoceptor antagonists can be an important therapeutic intervention for this disease. One of the mechanisms proposed for the beneficial effect of β-adrenoceptor antagonists is antagonism of the adverse effects of excessive catecholamine stimulation on the failing heart. βAR desensitization by βARK1 is increased in human heart failure. A reciprocal regulation of myocardial βARK1 expression by

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β-adrenoceptor stimulation and blockade has been recently demonstrated, providing new insights for the effectiveness of β-adrenoceptor antagonists in the treatment of heart failure. Studies from our laboratory in gene-targeted mice have shown that addition of a βARK1 inhibitor can prevent the development of heart failure, and they suggest that reversal of chronic βAR desensitization may be beneficial. Novel therapeutic strategies that aim to modulate βAR signaling in the presence of chronic β-adrenoceptor antagonist therapy may become an important adjunct in the treatment of patients with chronic heart failure.

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