Preface

In recent years, there has been a surge of interest in studies related to the role of a variety of signaling pathways in the control of cardiovascular physiology. Evidence has also accumulated to suggest that an aberration in the signal transduction pathways contributes to the pathophysiology of cardiovascular disease. Several components of the signaling pathways have been identified as potential targets for the development of new therapies of cardiovascular disease. Therefore, this volume has been compiled to highlight the contributions of different signaling systems in modulating normal cardiovascular functions and how a perturbation in these signaling events leads to abnormal cell functions and cardiovascular disorders.

This volume has been divided into five sections dealing with five key signaling pathways regulating different aspects of cardiovascular physiology. The first section describes the role of G-protein-coupled receptor (GPCR) signaling in cardiovascular functions. In this section, Anand-Srivastava has elegantly summarized studies showing that the expression levels of various G-proteins as well as responsiveness of adenylyl cyclase systems to various stimuli such as β-adrenergic receptor (βAR) agonist and vasoactive peptides are defective in various models of hypertension, congestive heart failure (CHF), cardiac hypertrophy, and other diseases. Dent et al. have highlighted studies showing how the alterations in different components of the βAR signaling system contribute to CHF and suggest that βAR blockade could be used as a strategy to treat CHF. Continuing on the same theme, Vacek et al. have reviewed the pathophysiological mechanisms involved in CHF and sudden cardiac death, with an emphasis on the role of homocysteine-induced cross talk between NMDA receptor and GPCRs, while Moolman et al. have elaborated on the contributions of adenosine, cAMP/PKA system as well as p^{38mapk} in eliciting a cardioprotective response during early preconditioning. This section also has two elegant articles on the role of angiotensin II in cardiovascular pathophysiology: Engberding and Grindling and Schaffer and Mozaffari have provided in-depth accounts of various signaling pathways induced by angiotensin II and how the dysregulation of this pathway contributes to heightened growth, proliferation, hypertrophy, and cell survival death responses associated with various cardiovascular abnormalities.

The second section focuses on the role of redox-induced signaling system in cardiovascular biology and complications of diabetes. In this section, Das and Goswami provide experimental evidence supporting a role of redox-regulating proteins in mitigating ischemia-induced oxidative stress and conferring a cardioprotective response, while Turan has demonstrated how an interplay between βAR signaling and redox pathways can modify mechanical performance and energy homeostasis in heart. Additional articles by Anand-Srivastava and Srivastava and by Wu have examined the role of hyperglycemia and methylglyoxal-related advanced glycation end products-induced activation of MAP kinase, PKB, GPCR, G-proteins, adenylyl cyclases, and inflammatory genes in the cardiovascular complications associated with diabetes.

The third section contains articles focused on the regulatory role of growth factor and their receptors in cardiac hypertrophy, vascular remodeling, and therapeutic angiogenesis. In this section, Bouallegue and Srivastava have reviewed the concept of growth factor receptor transactivation as a triggering mechanism to transduce the downstream effects of vasoactive peptides, whereas Calderone has provided a comprehensive analysis of the contributions of peptide growth factors, G_q proteins, and phosphatidylinositol 3-kinase (PI3K)-dependent signaling events in physiological/pathophysiological cardiac hypertrophy. Further, Dixon et al. have elegantly reviewed the role of TGF-β and R-Smad signaling pathways in remodeling of the extracellular matrix in failing hearts, and Luo et al. have demonstrated that activation of MAPK and PI3K may contribute to the pathogenetic mechanism involved in coxsackievirus-induced myocarditis. Two articles in this section by Maulik and Rajalakshmi et al. have provided evidence supporting the use of growth factors such as basic fibroblast growth factors and vascular endothelial growth factors to enhance angiogenesis and vasculogenesis. Finally, Selvakumar and Sharma summarize studies on the characterization and biological significance of *N*-myristoyltransferase (NMT) and its binding proteins which are involved in myristoylation of several signaling proteins, including protein kinases, thereby altering their functions.

The role of calcium in regulating cardiovascular physiology is presented in the fourth section of this volume. House et al. have provided an excellent review on the structure of calmodulin-dependent protein kinase II and its role in the contractility as well as proliferation and migration of VSMC. Banderali et al. have examined in detail the cellular regulation and pharmacological properties of calcium-activated potassium channels and their role in control of vascular tone by endothelium.

The final section of this volume contains articles by Karmazyn et al. and An et al. who have examined in detail the roles of leptin and lipid-induced signaling pathways in the pathogenesis of cardiometabolic syndrome.

Overall, this volume provides a detailed analysis of a wide range of signal transduction systems that mediate hypertrophy, intimal hyperplasia, oxidative damage, contractility, cardiovascular protection, and remodeling. Many components of these signaling pathways are potential targets to develop new therapeutics to treat cardiovascular disorders.

We wish to take this opportunity to thank the contributing authors for their co-operation and sustained interest and the staff at Springer in putting this volume together.

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Chapter 2
β-Adrenoceptor-Linked Signal Transduction Mechanisms in Congestive Heart Failure

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Abstract The cardiac β-adrenoceptor (β-AR)-mediated signal transduction system is composed of β_1- and β_2-ARs, stimulatory (G_s) and inhibitory (G_i) guanine nucleotide binding proteins, adenylyl cyclase (AC), and cAMP-dependent protein kinase (PKA). The activation of β_1- and β_2-ARs is known to increase heart function by promoting Ca^{2+}-movements in cardiomyocytes through the stimulation of G_s-proteins, activation of AC and PKA enzymes, and phosphorylation of the target sites. The activation of PKA increases the phosphorylation of some myofibrillar proteins resulting in cardiac relaxation, whereas PKA-mediated phosphorylation of some nuclear proteins results in cardiac hypertrophy. The activation of β_2-AR has also been shown to affect G_i-proteins, stimulate mitogen-activated protein kinase, and increase protein synthesis by enhancing gene expression. β_1- and β_2-ARs as well as AC are thought to be regulated by PKA- and protein kinase C (PKC)-mediated phosphorylations directly; both PKA and PKC also regulate β-AR indirectly through the involvement of β-AR kinase (βARK), β-arrestins, and $G_{\beta\gamma}$-protein subunits. Differences in the extent of defects in the β-AR signaling system have been identified in different types of heart failure to explain the attenuated response of the failing heart to sympathetic stimulation or catecholamine infusion. A decrease in β_1-AR density, an increase in the level of G_i-proteins, and overexpression of βARK are usually associated with heart failure; however, these changes have been shown to be dependent on the type and stage of heart failure as well as region of the heart. Both local and circulating renin–angiotensin systems, sympathetic nervous system, and endothelial cell function appears to regulate the status of β-AR signal transduction pathway in the failing heart. In this article, we highlight alterations in different components and regulators of the β-AR signal transduction pathway and review the biological basis for altered β-AR-mediated signal transduction in heart failure due to different etiologies as well as discuss the pharmacologic blockade of the β-adrenergic system as an approach for the treatment of congestive heart failure.

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Introduction

Activation of the sympathetic nervous system (SNS) (adrenergic system) in response to a variety of stimuli is essential to maintain homeostasis in a constantly changing environment, and in fact is known to regulate myocardial function on a beat–beat or short-term basis (Lamba and Abraham 2000). The physiological and metabolic responses to sympathetic activation are mediated through the action of endogenous catecholamines, norepinephrine (NE) and epinephrine, on adrenoceptors (ARs) (Stiles et al. 1984; Clark and Cleland 2000; Lamba and Abraham 2000). Based on the pharmacological and molecular structure, ARs are divided into two broad classes, α-ARs and β-ARs; however, this review will focus on the β-adrenergic system and its role in the development of congestive heart failure (CHF). Although α-ARs are also altered in CHF, no effort will be made to deal with this issue at this time. It should be mentioned that β-ARs are of three types—β_1-ARs, β_2-ARs, and β_3-ARs—and these differ significantly with respect to the types of cellular responses they mediate (Dhalla et al. 1977; Stiles et al. 1984; Brodde 1991; Lamba and Abraham 2000). Furthermore, it is repertoire and quantity of different β-ARs that determine the overall response of an organ to the circulating catecholamines. Acute changes in cardiac function are controlled predominantly by β-AR intracellular signaling pathways. The signal transduction pathways triggered by agonist occupancy of β-ARs are key regulators of the heart rate, systolic and diastolic function, as well as myocardial metabolism (Lamba and Abraham 2000). However, biology of the β-AR signaling pathway is altered dramatically in CHF (Clark and Cleland 2000) and in fact, adrenergic over-activity is one of the hallmarks of CHF which is associated with a poor prognosis (Clark and Cleland 2000). Initially, increased β-AR signaling allows the heart to adapt quickly to work loads that may vary, allowing the heart to increase its output within a matter of seconds by increasing the pacemaker frequency and myocardial contractility (Lamba and Abraham 2000). Although the adrenergic drive functions as a control mechanism that maintains cardiac performance at an acceptable level, prolonged activation of the SNS exerts a direct adverse action on the heart and produces deleterious peripheral effects (Clark and Cleland 2000). Apart from this classic role in acute regulation of mechanical and electrical functions of the heart, β-ARs may also be involved in long-term control of myocytes including cell survival and apoptosis under various conditions (Communal and Colucci 2005; Weil and Schunkert 2006). With respect to the development of CHF, what amounts to an initially appropriate compensatory adrenergic response to diminished myocardial performance, eventually results in an inappropriate or maladaptive response. Thus, the β-AR signaling mechanisms associated with CHF of different etiologies will be discussed in this article.

β-AR Pharmacology

It is now well known that the positive inotropic action of catecholamines is primarily mediated by their interaction with β-ARs on the cardiac cell surface (Dhalla et al. 1977; Stiles et al. 1984; Brodde 1991). The availability of selective agonists

and antagonists as well as radioligand binding techniques have confirmed the classification of β-AR into β_1-, β_2-, and β_3-ARs (Buxton et al. 1987; Brodde et al. 1989). These have been cloned and the probes derived from these genes have been used to examine the regulation of these receptor proteins (Collins et al. 1981; Tate et al. 1991; Saffitz and Liggett 1992). Such molecular studies have also indicated the existence of a fourth subtype, namely, β_4-ARs. The sequences of β_1- and β_2-AR have a 71% and 54% amino acid identity in the transmembrane domains and in overall sequence, respectively (Searles et al. 1995). The ratio of β_1- to β_2-ARs in the myocardium is about 4:1; this ratio seems to depend on the chamber of the heart as well as species employed for investigation and the type of heart disease. The mammalian heart expresses primarily β_1-ARs (75–85%) and a substantial number of β_2-ARs are also detected in cardiac tissue (Collins et al. 1981; Tate et al. 1991; Saffitz and Liggett 1992). However, the β_2-ARs are mainly expressed in cells such as endothelial cells, fibroblasts, and vascular smooth muscle cells, which are present in the heart. Although the physiological relevance of cardiac β_3-ARs is not well understood, recent evidence suggests that β_3-ARs promote a negative inotropic effect (Tavernier et al. 2003). Since β_3-ARs can modulate relaxation of smooth muscle, the extent to which the β_3-AR-associated negative inotropic effect is direct or secondary to peripheral vasodilation is unknown (Dessy et al. 2004). In contrast, the putative β_4-ARs appear to be akin to β_1- and β_2-ARs in promoting a positive inotropic effect, but their biochemical and pharmacological characteristics are poorly defined (Kohout et al. 2001).

It has been demonstrated that excessive amounts of circulating catecholamines trigger changes in the β-AR system, leading to deterioration of ventricular function (Lamba and Abraham 2000). This is thought to be an adaptive mechanism of the heart to protect compromised myocardium from catecholamine overstimulation. In CHF, due to either idiopathic dilated cardiomyopathy or ischemic heart disease, β_1-ARs selectively undergo downregulation due to uncoupling of the receptors from their respective signaling pathways (Wallukat 2002); these desensitization changes lead to a marked attenuation of the myocardial response to catecholamines. This process of desensitization is initiated by a family of Ser/Thr kinases known as G-protein-coupled receptor kinases (GRKs) that phosphorylate the agonist-coupled G-protein-coupled receptors (GPCRs) (Lamba and Abraham 2000). GPCR desensitization requires not only the kinase activity of GRKs, but also the action of a second protein family, β-arrestins that bind to phosphorylated receptors. β-Arrestin binding subsequently directs the internalization of desensitized GPCRs that can lead to receptor downregulation, or receptor recycling back to the sarcolemmal membrane and stimulation of intracellular signaling pathways (Lamba and Abraham 2000).

Adrenoceptor Signaling in the Heart

The ARs belong to the superfamily of GPCRs, which contain a conserved structure of seven transmembrane α-helices linked by three alternating intracellular and extracellular loops. According to the classic paradigm of GPCR signaling, binding of

the ligand to the receptor induces a sequence of conformational changes that result in its coupling to a heterotrimeric G-protein. Activated G-proteins then dissociate into G_{α} and $G_{\beta\gamma}$ subunits, each capable of modulating the activity of a variety of intracellular effector molecules. Thus, receptors that couple to G stimulatory (G_s) or G inhibitory (G_i) proteins modulate the activity of adenylyl cyclase (AC) to generate the second messenger cAMP and subsequently activate cAMP-dependent protein kinase A (PKA). The α subunit (45 to 52 kDa) of G_s-protein was found to be different from that (39 to 41 kDa) of G_i-protein. Furthermore, ADP ribosylation of the α subunit in G_s-protein is catalyzed by cholera toxin whereas that in G_i-protein is catalyzed by pertussis toxin. Studies at the molecular level for both G_s- and G_i-proteins have revealed that genes for these proteins are not co-regulated (Itoh et al. 1988; Kozasa et al. 1988). On the other hand, G_q-coupled receptors including α-ARs stimulate phospholipase C that in turn generates diacylglycerol and inositol 1,4,5-trisphosphate and activates protein kinase C. The nature of the intracellular response to catecholamine stimulation therefore depends not only on the type of activated receptors and their expression levels, but also on the type of G-proteins they couple to and intracellular pathways activated by the various second messengers. Different isoforms of GRKs (GRK2, GRK3, and GRK5) are known to regulate β-ARs in the heart (Brodde 1991). In fact, GRK2 has been shown to play a critical role in the transition of cardiac hypertrophy to heart failure in transgenic mice overexpressing α_{1B}-ARs (Iaccarino et al. 2001).

β-ARs are most commonly associated with regulation of metabolic pathways and have been described to both inhibit and stimulate AC activity. These GPCRs initiate the production of cAMP with subsequent activation of PKA and thus regulate diverse metabolic and functional events (Homcy et al. 1991). PKA activation is a critical step in mediation of the positive inotropic effect of catecholamines through phosphorylation of L-type Ca^{2+} channels in the sarcolemmal membrane and phospholamban in the sarcoplasmic reticulum to regulate Ca^{2+} movements in the cardiomyocytes. Although the exact mode of coupling G-proteins with AC is not clear, both genetic and biochemical evidence indicate that there are multiple forms of AC with a molecular mass in the range of 120 to 150 kDa (Manolopoulos et al. 1995). Of the nine isoforms of AC, the presence of types II to VII has been detected in cardiac tissue but types V and VI are abundant in the mammalian heart (Yu et al. 1995; Sunahara et al. 1996). The catalytic subunit of AC, which is involved in the formation of cAMP from ATP, is activated by cations such as Mn^{2+} as well as by forskolin whereas other agents such as NaF, Gpp(NH)p, cholera toxin, and pertussis toxin are considered to stimulate the enzyme activity through their interaction with G-proteins. Since different hormones including angiotensin II (Ang II), endothelin I, and NE bind to receptors which are coupled to G_q-proteins, molecular targeting of $G_{q\alpha}$-protein in transgenic mouse models has also shown its involvement in both adaptive and maladaptive responses of the heart to stress (Adams et al. 1998; Dorn and Brown 1999; Sabri et al. 2002). Various studies with transgenic mouse models have revealed that specific overexpression of β_1-ARs, β_2-ARs, G_s-proteins, and AC results in an enhanced cardiac function (Milano et al. 1994; Bond et al. 1995; Xiao et al. 1999).

Recent evidence from cell culture and transgenic mouse models suggest distinct differences between β_1- and β_2-ARs in their ability to modulate the process of apoptosis (Milano et al. 1994; Saito et al. 2000; Morisco et al. 2001; Shizukuda and Buttrick 2002). Expression of these receptors in a double knockout mouse model has revealed that stimulation of β_1-ARs is involved in apoptosis whereas that of β_2-ARs elicits cell survival (Zhu et al. 2001). It appears that overexpression of the human β_1-ARs increases expression of proapoptotic proteins like bax (Bisognano et al. 2000). Also, the proapoptotic influence of the β_1-AR pathway has been attributed to the activation of calcineurin via increased intracellular Ca^{2+} through L-type channels; the activation of calcineurin dephosphorylates Bad, permitting it to heterodimerize with the antiapoptotic proteins Bcl-2 and Bcl-xl (Saito et al. 2000). The differential effect of the β-ARs on the induction of apoptosis may be due to the fact that the β_2-AR coupling to $G_{\alpha i}$ is cardioprotective (Iwai-Kanai and Hasegawa 2004). Interestingly, Zhu et al. (2001) have uncovered a connection between the antiapoptotic effects of β_2-ARs and stimulation of a pertussis toxin-sensitive, phophatidylinositol 3-kinase (PI3K) and Akt-PKB pathway, which may be one of the several antiapoptotic pathways. Overexpression of $G_{s\alpha}$-proteins has been reported to increase heart function and produce apoptosis whereas that for $G_{i\alpha}$-proteins has been shown to attenuate β-AR stimulation (Geng et al. 1999; Janssen et al. 2002). In spite of the complexities of transgenic models and some conflicting results, these experiments have provided evidence that the β_1-AR signal transduction is required for maintaining heart function, but overexpression of any of the components of this system can cause cardiac hypertrophy, apoptosis, and heart dysfunction. In addition to the promotion of apoptosis, production of cytotoxicity via Ca^{2+} overload, and increased free radical generation, adrenergic activation is the major stimulus to pathologic hypertrophy (Wallukat 2002). Thus, in view of the critical role of β-AR signaling pathway in influencing cardiac contractility, any change in the components of this system under pathological conditions can be seen to impair signal transduction mechanisms in the myocardium. However, abnormalities in β-ARs, G-proteins, and AC in failing human hearts appear to depend on the etiology of CHF (Bristow et al. 1991; Bohm et al. 1992; Bristow and Feldman 1992; Steinfath et al. 1992).

Altered β-AR Signaling During Various Cardiac Pathologies

Various pathologic factors such as pressure overload (PO) or volume overload (VO), ischemic reperfusion injury, myocardial infarction, and different types of cardiomyopathies are associated with an excessive stimulation of SNS. This sustained adrenergic drive is not only considered to result in the downregulation of β-AR but is also believed to produce a depression in myocardial reserve, Ca^{2+}-cycling, myocardial energetics, in addition to inducing fetal gene program. All of these abnormalities are considered to contribute toward cardiac dysfunction in CHF. A schematic representation of these events is shown in Figure 2.1. However, this article will be focused

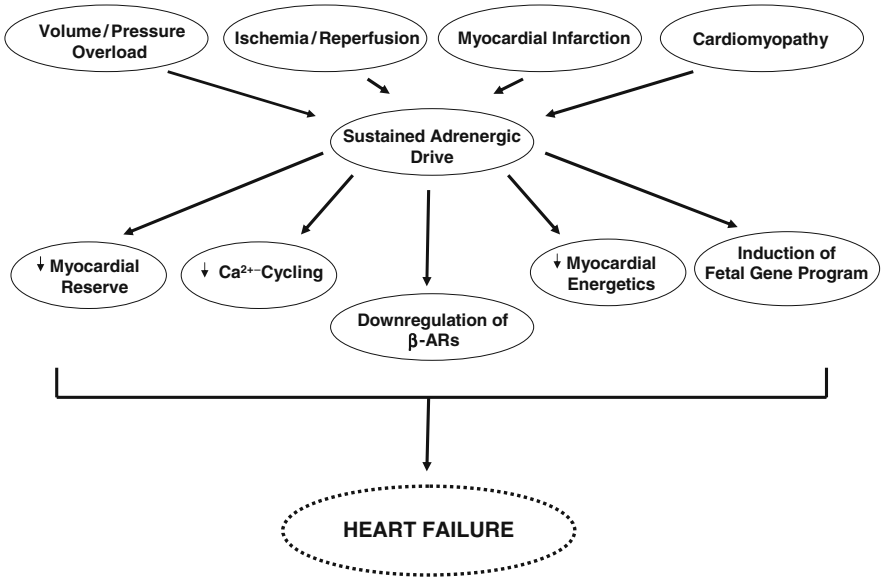

Fig. 2.1 Schematic representation of the mechanisms involved in the development of heart failure due to different etiologies.

on discussion of four components of the β-AR mechanism—β-AR, G-proteins, AC, and PKA—which are known to regulate the major routes of Ca^{2+} entry in the sarcolemmal membrane as well as Ca^{2+}-release from the sarcoplasmic reticular stores in addition to modifying the sensitivity of myofibrils to Ca^{2+} (Figure 2.2). Since changes in β-AR mechanism seem to depend on the type of CHF, it is planned to describe alterations in different components of β-AR systems in different types of heart diseases.

Volume and Pressure Overload Hypertrophy-Induced Changes

Alterations in β_1-AR signaling account for the occurrence of pathologic hypertrophy; this has been shown by reverse remodeling studies using the β-AR blocking agents in the failing human hearts (Frigerio and Roubina 2005). In addition, reversal of fetal gene induction, the molecular hallmark of pathologic hypertrophy, is accompanied by reverse cardiac remodeling in response to β-AR blockers (Lowes et al. 1999). It should be pointed out that cardiac hypertrophy is generally categorized into two broad types: PO-induced hypertrophy and VO-induced hypertrophy. PO occurs in many clinical settings that include hypertension, mitral valve stenosis, and aortic valve stenosis resulting in concentric cardiac remodeling. Thus, an increase in pressure is offset by an increase in the ventricular wall thickness (Carabello 2002). The other type of cardiac hypertrophy due to VO occurs in anemia, heart block, regurgitant mitral or aortic valves, atrial or ventricular septal defects, or other congenital

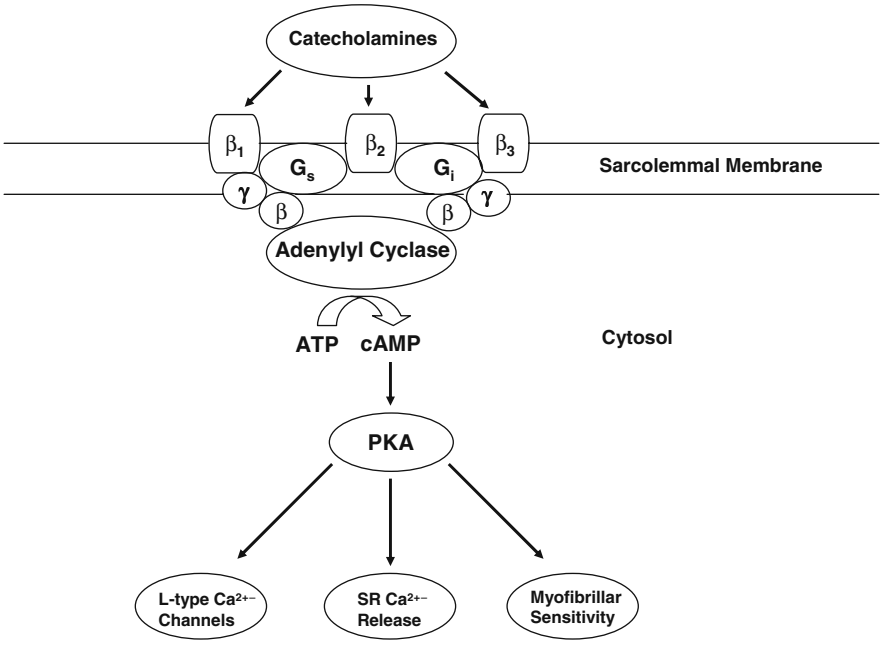

Fig. 2.2 Components of the cardiomyocyte β-adrenergic signaling system and their physiological effects.

diseases, resulting in eccentric cardiac hypertrophy. Dilatation of the left ventricle (LV) chamber occurs via elongation of the surrounding myocytes—the result of sarcomeric replication in series (Carabello 1996). Alterations in β-AR density, AC activity, and G-protein have been identified in cardiac hypertrophy, which normally precedes heart failure due to PO (Galinier et al. 1994; Iaccarino et al. 1999). Further, modification of cardiac AC activities by changes in the G-protein function has been observed in hypertension (Bohm et al. 1993). Changes in the β-AR signaling system have also been shown to be involved in the development of CHF due to both PO and VO. In fact, PO-induced CHF in guinea pigs was associated with an increase in β-AR density without any changes in their affinity (Karliner et al. 1980). A wide variety of changes in the β-AR-linked signal transduction mechanism have also been reported in heart failure induced by rapid pacing and VO (Di Fusco et al. 2000). On the other hand, cardiac hypertrophy and heart failure due to VO induced by aortocaval shunt in rats were associated with hypersensitivity of the myocardium to β-AR stimulation (Wang et al. 2003). We have also shown that the upregulation of the β-AR system as well as changes in the subcellular distribution of regulatory proteins, GRK isoforms, and β-arrestins in the failing hearts due to VO, were partially prevented by treatment of these animals with angiotensin-converting enzyme (ACE) inhibitors and Ang II type 1 receptor (AT_1R) antagonists (Wang et al. 2005). However, such alterations in cardiac hypertrophy and late stages of CHF in this experimental model remain to be examined. Other animal studies of CHF have also

shown myocardial β_1-AR expression and increased GRK activity (Anderson et al. 1999). Importantly, increasing levels of β_1-AR often precede the development of overt clinical CHF and may represent a novel early marker for cardiac dysfunction and a potential target for intervention prior to development of end-stage CHF.

Ischemia-Reperfusion-Induced Changes

An increase in β-AR density and an increase in cAMP formation due to catecholamines have been reported in myocardial ischemia due to coronary occlusion in dogs (Mukherjee et al. 1982). Although increased density of β-ARs was also seen in CHF in dogs, this change was associated with a loss of high affinity for these receptors as well as uncoupling of β-ARs from G-proteins (Maisel et al. 1985, 1987; Freissmuth et al. 1987). Other investigators have also observed an increase in the β-AR density in the ischemic myocardium from dogs and calves and the activities of AC in the absence or presence of different stimulants of G_s-proteins were depressed (Vatner et al. 1988, 1990). On the other hand, no changes in the density of β-ARs and basal AC activity were observed, but a depression in isoproterenol-stimulated AC activity was seen in ischemic or hypoxic dog hearts (Freissmuth et al. 1987; Karliner et al. 1989). Ischemic guinea pig hearts showed an increase and a decrease in the β-AR densities in cell surface and cytoplasmic membranes (Maisel et al. 1985, 1987), respectively, whereas opposite results were obtained upon exposing the neonatal rat cardiomyocytes to hypoxia (Rocha-Singh et al. 1991). The changes in ARs and post-receptor mechanisms including changes in mRNA levels due to ischemia/hypoxia seem to depend on the experimental model employed and the degree as well as duration of the reperfusion injury (Will-Shahab et al. 1991; Bernstein et al. 1992; van den Ende et al. 1994; Ohyanagi et al. 1995). Nonetheless, studies from our laboratory have indicated that the ischemia-reperfusion-induced changes in β-AR signal transduction mechanism in the myocardium are mediated through the generation of oxidative stress (Persad et al. 1997, 1998).

Cardiomyopathy-Induced Changes

The AC activities due to the stimulation of β-receptors and G_s-proteins were increased in adriamycin-induced cardiomyopathy in rabbits (Calderone et al. 1991). On the other hand, no alterations in β-AR density, G-proteins, or AC activities were seen in adriamycin-induced cardiomyopathy in rats (Fu et al. 1991). Depressions in β-ARs and AC activities in the absence or presence of various stimulants were noted in catecholamine-induced cardiomyopathy in rats in addition to an increase and loss of G_i- and G_s-proteins, respectively (Meszaros and Levai 1992; Muller et al. 1993; Zhou et al. 1995). Rats with monocrotaline-induced right heart cardiomyopathy showed depressions in β_1-AR density and AC activities in the presence

of isoproterenol and Gpp(NH)p without any changes in the absence or presence of NaF and forskolin as well as in the β_2-receptor density; these alterations were chamber-specific (Pela et al. 1990; Yoshie et al. 1994). High level of overexpression of β_2-ARs was also found to cause heart failure in a mouse model of cardiomyopathy, which was prevented by expression of GRK2 (Freeman et al. 2001). Overexpression of GRK2 inhibitor of gene-targeted mice was observed to prevent heart failure and improve cardiac function (Rockman et al. 1998). Conflicting results showing either an increase (Ikegaya et al. 1992) or no change (Kessler et al. 1989; Horackova et al. 1991) in β-AR receptor density have also been reported in hamster cardiomyopathy. However, AC activities in the presence of different stimulants as well as the levels of G_s-protein were found to be depressed in the cardiomyopathic hamster hearts (Panagia et al. 1984; Kessler et al. 1989; Ikegaya et al. 1992; Urasawa et al. 1992), but the basal enzyme activity was normal (Panagia et al. 1984; Kessler et al. 1989) and the level of G_i-protein was increased (Urasawa et al. 1992). No alterations in the levels of mRNA encoding G_s-proteins in cardiomyopathic hamsters were detected (Kessler et al. 1989), while information concerning changes in mRNA specific for AC in failing hearts is still lacking. Increased level of G_i-proteins as well as uncoupling of β_1-AR from AC has been suggested to explain the attenuated responses of cardiomyopathic hamster hearts to catecholamines (Witte et al. 1993; Kawamoto et al. 1994). The work carried out in our laboratory has revealed that changes in the β-ARs, AC, and G-proteins are dependent on the stage of CHF in cardiomyopathic hamsters (Sethi et al. 1994).

Myocardial Infarction-Induced Changes

Several investigators have reported a wide variety of alterations in different components of the β-ARs, G-proteins, and AC system in heart dysfunction in failing human heart as well as in various experimental animal models of heart failure (Dhalla et al. 1997; Wang and Dhalla 2000). Some efforts have been made to understand the mechanisms of attenuated responses of failing hearts to catecholamines; these changes are invariably seen in all types of CHF. Both β-AR density and responsiveness to inotropic stimulation are significantly reduced in failing human hearts (Lamba and Abraham 2000). The loss of cardiac β_1-ARs is critical, since this translates to a larger overall percentage of β_2-ARs and emphasizes their distinct signaling properties. A decrease in the density of β-AR was observed in CHF in dogs with pulmonary artery constriction as well as in rats with myocardial infarction (Dhalla et al. 1992). There was no evidence of any change in β-AR density or isoproterenol-stimulated AC activity in heart failure due to myocardial infarction in rats (Hammond et al. 1993) and dogs (Strasser et al. 1990); however, experiments with rats at two stages of myocardial infarction revealed defects in both β-ARs and postreceptor sites associated with attenuated responses to catecholamines (Sethi and Dhalla 1995). Heart dysfunction in rats with nonocclusive coronary artery constriction without any myocardial infarction was associated with depressions in β-AR

density, G_s-protein activity, and isoproterenol-stimulated AC activity (Meggs et al. 1991). CHF due to rapid pacing in dogs was found to decrease β-receptor density, G_s-protein, and AC activity (Marzo et al. 1991; Juneau et al. 1992). Some work employing the molecular biology techniques has shown a decrease in the levels of mRNA specific for β_1-receptors (Bristow and Feldman 1992) and an increase in the levels of mRNA for G_i-protein without any changes in mRNA for G_s-protein in failing human hearts (Eschenhagen et al. 1992).

In spite of the extensive research for identifying defects in the β-AR-mediated signal transduction in failing hearts from patients and experimental animals, several issues remain unresolved. Although marked changes in the pattern of plasma hormones including renin–angiotensin, catecholamines, atrial natriuretic peptide, endothelium-derived relaxing factor as well as endothelin in CHF have been identified (Hodsman et al. 1988; Basu et al. 1996), the exact role of these changes in the genesis of signal transduction abnormalities is far from clear. Some investigators have recently emphasized the importance of local mechanisms such as cardiac renin–angiotensin system (RAS) and NE transport in sympathetic nerve endings in the myocardium, rather than changes in circulating renin–angiotensin and catecholamines, in the development of cardiac dysfunction in heart failure (Bohm et al. 1992, 1995; Yoshikawa et al. 1994; Wollert et al. 1994; Basu et al. 1996; Ganguly et al. 1997). Such local alterations can be seen to explain the differential behavior of the left and right ventricle with respect to changes in adrenergic mechanisms during the development of CHF due to myocardial infarction (Sethi et al. 1997, 1998). Although Yoshida et al. (2001a) failed to observe differences in the isoproterenol-induced response of single cardiomyocytes from left and right ventricles of the 8-week infarcted rats, the concentration (10 nM) of isoproterenol used in this study was too low to elicit any response. Furthermore, the biased selection of single cardiomyocyte employed may have also been another factor for their failure to observe changes. Although Ca^{2+}-handling abnormalities have been reported to occur in hearts failing due to myocardial infarction (Dixon et al. 1990; Afzal and Dhalla 1992; Sethi et al. 2006), the role of these changes in causing an impairment of the signal transduction mechanisms has not been established. In this regard, it should be pointed out that augmented Ca^{2+}-fluxes in the myocardium have been shown to exert a negative regulation of the adrenergic stimulation and the AC activation (Frace et al. 1993; Wang et al. 2002). Furthermore, diltiazem and β-AR antagonists, which are known to regulate Ca^{2+} movements in the myocardium, have been shown to exert beneficial effects with respect to defects in transmembrane signaling due to different pharmacological and pathophysiological interventions (Brodde 1991; Chapados et al. 1992). Likewise, blockade of RAS by ACE inhibitors and AT_1R antagonists was found to prevent changes in β-AR mechanisms in heart failure (Forster et al. 1994; Bohm et al. 1998; Yoshida et al. 2001b; Makino et al. 2003).

Some studies have indicated that alterations in β-AR signal transduction mechanisms were attenuated by different agents, which are known to block β_1-ARs in the heart (Asai et al. 1999; Asano et al. 2001; Liu et al. 2002). In this regard, it should be noted that both SNS and RAS are known to be activated in different types of heart failure. In fact, activation of both SNS (Communal et al. 1998; Iaccarino et al. 1998;

Leineweber et al. 2002) and RAS (Bohm et al. 1998; Bohlender et al. 2001) has been shown to be associated with desensitization of the β-AR mechanisms. Treatment of hypertensive rats with ACE inhibitors and AT_1R antagonists has been reported to normalize the augmented sympathetic activity (K.-Laflamme et al. 1997). Since the activation of RAS was seen before any change in the heart or plasma upon inducing PO (Akers et al. 2000), it appears that the activation of RAS plays a dominant role in changing the sensitivity of failing hearts to β-adrenergic stimulation. Also, we have demonstrated that downregulation of the β-AR G-protein AC system in the LV from the failing heart due to myocardial infarction is attenuated by blockade of the RAS (Sethi et al. 2003). In addition, we have shown that treatment of the infarcted animals with propionyl L-carnitine, a metabolic therapy, not only improved cardiac function but also attenuated defects in the β-adrenergic mechanisms (Sethi et al. 2004). However, whether the desensitization of β-adrenergic mechanisms is due to changes in cardiac gene expression for each of these components, or alterations in the regulatory factors for the β-ARs in the LV of the infarcted animals, remains to be determined. Likewise, nothing is known regarding the molecular mechanisms of hypersensitivity of the right ventricle to catecholamines in the failing hearts due to myocardial infarction.

β-Adrenergic System Blockade

In view of abnormalities in β-AR signal transduction mechanisms during the development of CHF, it is important to discuss the pharmacologic blockade for the β-AR system as an important approach in the treatment of CHF. Over the past 25 years, β-adrenergic blockade has been one of the most successful therapies aimed at attenuating neurohormonal overactivation used in the treatment of patients with CHF (Frigerio and Roubina 2005). β-AR antagonists lead to a decreased risk of death and hospital admission and tend to reverse the adverse effects of prolonged adrenergic stimulation in patients with CHF (Frigerio and Roubina 2005; Chizzola et al. 2006). β-AR blockers for the management of cardiovascular disease are well-established and these agents are widely recommended as important parts of antihypertensive regimens as well as preferred therapies for patients at high risk for coronary heart disease, including those with heart failure. Among three of the most common treatments for heart failure (ACE inhibitors, AT_1 receptor blockers, and β-AR blockers), β-AR blockers have shown a more permanent benefit than that obtained with ACE inhibitors alone. Furthermore, β-AR blockers most likely lower blood pressure and provide target organ protection by mechanisms such as inhibition of RAS, central inhibition of SNS outflow, and slowing of heart rate with a decrease in cardiac output. Efficacy of β-AR blockers appears to be superior to that of ACE inhibitors and AT_1 receptor blockers; however, almost all patients with heart failure enrolled in β-AR blocker clinical trials were already taking ACE inhibitors. Therefore, it is difficult to indicate if β-AR blockade would produce the same results in the absence of RAS antagonism. Recently, the CARMEN (Carvedilol and ACE Inhibitor

Remodeling Mild Heart Failure Evaluation Trial) clinical trial examined the effects of enalapril and carvedilol in patients with mild heart failure (Remme et al. 2004). They found that enalapril alone or carvedilol alone did not cause a significant reduction in LVESV whereas a combined treatment with these agents resulted in a significant reduction in LVESV. In contrast, a previous study comparing carvedilol and captopril showed a significant decrease in LVESV and increased ejection fraction in patients treated with carvedilol only (Khattar et al. 2001).

The three main β-AR blockers that have proven to be of clinical benefit in heart failure are metoprolol, carvedilol, and bisoprolol. These β-AR blockers produce a significant and sustained improvement in ejection fraction and reverse remodeling in addition to reductions in LV sphericity and mitral regurgitation in patients with CHF (Lowes et al. 1999). The newer β-AR blocker used in the treatment of CHF, carvedilol, is a racemic mixture of $R(+)$- and $S(-)$-enantiomers mainly metabolized by cytochrome P (CYP2D6) as well as partially metabolized by CYP1A2 and CYP2C9. Carvedilol is a nonselective β-AR antagonist that leads to systemic arterial vasodilation without reflex tachycardia due to concomitant antagonism of vascular β_1-AR and myocardial β-ARs (DasGupta et al. 1991). Carvedilol is a blocker for β_1-, β_2-, and α_1-ARs raising controversy on whether this type of blocker is superior to selective β_1-AR blockers (Bristow et al. 2003). Therapy of heart failure patients with carvedilol produced a safe and tolerable reduction in heart rate and improved LV function (improved LV systolic shortening fraction and LVEF) within 2 months of treatment. Recent studies have shown that a higher dosage than previously used (75 mg versus 42 mg/day) results in greater benefit in the treatment of heart failure (Chizzola et al. 2006). Carvedilol has also shown to result in improved neuronal adrenergic capture in the myocardial effector cell. Thus, a possible mechanism of action for β-AR antagonists is through improved neuronal reuptake of NE. It is pointed out that AT_1 receptor blockers were found useful in combination with carvedilol in CHF patients (Iwata et al. 2006). Carvedilol is often administered in combination with amiodarone for the treatment of arrhythmias and heart failure (Fukumoto et al. 2005). Many studies have shown a causal relationship between β-AR blockade and reverse remodeling. A small study investigating the effects of metoprolol found that LV function deteriorated after withdrawal of metoprolol in the treatment of heart failure patients and improved LV function after readministration (Waagstein et al. 1989). Furthermore, dose of β-AR blockers has been correlated with the degree of effect on LV volume and ejection fraction (Bristow et al. 1996). Specifically, carvedilol dose was inversely related to mortality (Bristow et al. 1996) and in fact carvedilol therapy and dose were found to be predictors of cardiac size normalization and improved cardiac function. However, the reverse remodeling of the cardiac sympathetic neurons was not associated with an alteration in plasma NE levels. Treatment of heart failure with medication that antagonizes β-ARs tends to reverse the adverse effects of prolonged adrenergic stimuli.

The efficacy of β-AR blockade appears to be superior in achieving reverse remodeling and this is more directly dose-related than that of ACE inhibitors (Frigerio and Roubina 2005). Recently, in a clinical trial examining the effects of metoprolol and atenolol, it was found that patients with heart failure treated with metoprolol

experienced an 88% survival rate; survival rate for patients treated with atenolol was 78% as compared to 48% in control groups. This clearly indicates that metoprolol and atenolol have a favorable effect on the survival rate of patients with CHF. Specifically, metoprolol is considerably more effective than atenolol (Celic et al. 2005). In controlled clinical trials, bisoprolol, carvedilol, and metoprolol exerted favorable effects on survival (CIBIS-II 1999; MERIT-HF Study Group 1999; Patrianakos et al. 2005). Bucindolol had little effect on mortality rates and xamoterol was associated with an increased risk of death (The Xamoterol in Severe Heart Failure Study Group 1990; Domanski et al. 2003).

Nebivolol, a third-generation β_1-AR selective blocker, increases endothelial NO release causing peripheral vasodilation. Nebivolol shows both a high degree of selectivity for β_1-ARs and an ability to stimulate endothelial NO production (Patrianakos et al. 2005). In this study Patrianakos et al. (2005) compared the effects of nebivolol and carvedilol on LV function and exercise capacity in patients with mild to moderate heart failure. It was observed that nebivolol is a safe choice with many beneficial effects on systolic and diastolic LV function and exercise capacity after 1 year of treatment. However, nebivolol produced an initial deterioration in exercise capacity, which was not observed with carvedilol treatment (Patrianakos et al. 2005). Thus, it was concluded that carvedilol produces more favorable effects as compared to nebivolol. The treatment of patients with carvedilol produces a faster effect than nebivolol in terms of improved diastolic dysfunction because of the added antagonism of β_2- and α_1-ARs. The effects of carvedilol may be due to restored Ca^{2+}-homeostasis because chronic adrenergic stimulation has detrimental cardiotoxic effects and causes abnormal Ca^{2+}-handling. This may partially explain the observed diastolic restoration and changes in LV filling pattern (Patrianakos et al. 2005). It should be noted that CHF patients exhibit high body mass index (Horwich et al. 2001; Davos et al. 2003) and treatment with β-AR blockers can further increase total body fat mass and total body fat content (Lainscak et al. 2006).

β-AR blockers differ with respect to many pharmacologic properties in β_1/β_2-AR selectivity, intrinsic sympathomimetic activity, and vasodilatory capabilities (Weber 2005). The β-AR blocker class is divided into three generations of antagonists. The first-generation β-AR blockers, such as propanolol, exert blockade on both β_1- and β_2-receptors equally and are therefore termed nonselective β-AR blockers (Weber 2005). The second-generation β-AR blockers (metoprolol, bisoprolol, and atenolol) have a higher affinity binding to β_1-receptors and are referred to as selective β-AR blockers. At higher doses, these selective β-AR blockers may exert some inhibition of β_2-AR as well (Weber 2005). The third-generation β-AR blockers differ from the previous two in their vasodilatory activity. In this class, there are β-AR blockers such as labetalol, which is nonselective with a higher affinity for the β_1-receptor than for the β_2-receptors, whereas carvedilol is a β_1 selective blocker but becomes less selective at higher doses (Weber 2005). Bucindolol, also a third-generation β-AR blocker, is completely nonselective for all ARs. These three third-generation β-AR blockers provide some vasodilatory action through blockade of the α_1-AR thereby regulating endothelial function and vasoconstriction in peripheral blood vessels. The newest β-AR blocker, nebivolol, is a third-generation

blocker that has higher β_1-AR selectivity compared with other β-AR blockers in addition to its vasodilatory effects (Weber 2005). Some β-AR blockers (acebutol, penbutolol, pindolol) are capable of both stimulating β-ARs as well as opposing the transmission of SNS signaling. This combination has been shown to attenuate the decreases in heart rate and cardiac output and increases in peripheral vascular resistance associated with β-AR blockade (Weber 2005).

Conclusions

A detailed analysis of the existing literature reveals that changes in β-ARs, G-proteins, and AC depend on the type and stage of heart disease as well as area of the heart and the type of membrane preparations from failing hearts employed for investigations (Pela et al. 1990; Persad et al. 1997; Rockman et al. 1998). The results on β-AR mechanisms in different experimental models as well as in patients with heart failure support the view that alterations in this system depend on the underlying type of the disease (Matsuda et al. 2000; Sayar et al. 2000; Wallukat 2002; Leineweber et al. 2003). The ARs, G-proteins, and AC systems are either unchanged, upregulated, or downregulated in failing myocardium. Furthermore, alterations may occur in one component of the system without changes in the others; such a discrepancy in results seems to depend on the type and stage of the heart disease. Although most of the work in this field has been carried out on myocardial tissues from patients with heart disease (Schotten et al. 2000), it should be recognized

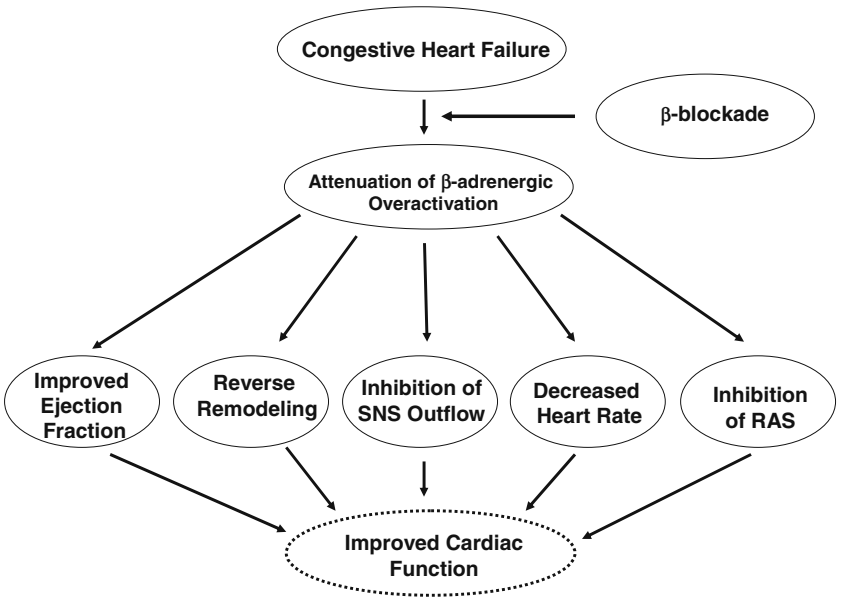

Fig. 2.3 The beneficial mechanisms of action due to β-blockade in congestive heart failure.

that all of these patients were on different cardiac drugs, and thus the results are difficult to interpret in terms of pathophysiological changes in CHF. Nonetheless, it is evident from the foregoing discussion that cardiac dysfunction in patients with CHF is improved upon the blockade of β-AR. This beneficial effect is primarily due to the reduction of the β-adrenergic overdrive which results in reversal of cardiac remodeling, depression in heart rate, and decrease in the overactivity of RAS (Figure 2.3).

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References

Adams, J.W., Sakata, Y., Davis, M.G., Sah, V.P., Wang, Y., Liggett, S.B., Chien, K.R., Brown, J.H., and Dorn, G.W., 2nd. 1998. Enhanced $G_{\alpha q}$ signaling: a common pathway mediates cardiac hypertrophy and apoptotic heart failure. Proc. Natl. Acad. Sci. USA 95:10140–10145.

Afzal, N., and Dhalla, N.S. 1992. Differential changes in left and right ventricular SR calcium transport in congestive heart failure. Am. J. Physiol. Heart Circ. Physiol. 262:H868–H874.

Akers, W.S., Cross, A., Speth, R., Dwoskin, L.P., and Cassis, L.A. 2000. Renin-angiotensin system and sympathetic nervous system in cardiac pressure-overload hypertrophy. Am. J. Physiol. Heart Circ. Physiol. 279:H2797–H2806.

Anand-Srivastava, M.B., de Champlain, J., and Thibault, C. 1993. DOCA-salt hypertensive rat hearts exhibit altered expression of G-proteins. Am. J. Hypertens. 6:72–75.

Anderson, K.M., Eckhart, A.D., Willette, R.N., and Koch, W.J. 1999. The myocardial β-adrenergic system in spontaneously hypertensive heart failure (SHHF) rats. Hypertension 33:402–407.

Asai, K., Yang, G.P., Geng, Y.J., Takagi, G., Bishop, S., Ishikawa, Y., Shannon, R.P., Wagner, T.E., Vatner, D.E., Homcy, C.J., and Vatner, S.F. 1999. β-adrenergic receptor blockade arrests myocyte damage and preserves cardiac function in the transgenic $G_{s\alpha}$ mouse. J. Clin. Invest. 104:551–558.

Asano, K., Zisman, L.S., Yoshikawa, T., Headley, V., Bristow, M.R., and Port, J.D. 2001. Bucindolol, a nonselective β_1- and β_2-adrenergic receptor antagonist, decreases β-adrenergic receptor density in cultured embryonic chick cardiac myocyte membranes. J. Cardiovasc. Pharmacol. 37:678–691.

Basu, S., Sinha, S.K., Shao, Q., Ganguly, P.K., and Dhalla, N.S. 1996. Neuropeptide Y modulation of sympathetic activity in myocardial infarction. J. Am. Coll. Cardiol. 27:1796–1803.

Bernstein, D., Doshi, R., Huang, S., Strandness, E., and Jasper, J.R. 1992. Transcriptional regulation of left ventricular β-adrenergic receptors during chronic hypoxia. Circ. Res. 71:1465–1471.

Bisognano, J.D., Weinberger, H.D., Bohlmeyer, T.J., Pende, A., Raynolds, M.V., Sastravaha, A., Roden, R., Asano, K., Blaxall, B.C., Wu, S.C., Communal, C., Singh, K., Colucci, W., Bristow, M.R., and Port, D.J. 2000. Myocardial-directed overexpression of the human β_1-adrenergic receptor in transgenic mice. J. Mol. Cell. Cardiol. 32:817–830.

Bohlender, J., Hildenbrand, U., Wagner, K.D., Gunther, J., Hempel, P., Schlegel, W.P., Luft, F.C., Krause, E.G., and Bartel, S. 2001. Myocardial adrenergic dysfunction in rats with transgenic, human renin-dependent hypertension. J. Hypertens. 19:1453–1463.

Bohm, M., Gierschik, P., and Erdmann, E. 1992. Quantification of $G_{i\alpha}$-proteins in the failing and nonfailing human myocardium. Basic Res. Cardiol. 87:37–50.

Bohm, M., Gierschik, P., Knorr, A., Schmidt, U., Weismann, K., and Erdmann, E. 1993. Cardiac adenylyl cyclase, β-adrenergic receptors, and G proteins in salt-sensitive hypertension. Hypertension 22:715–727.

Bohm M., La Rosee, K., Schwinger, R.H., and Erdmann, E. 1995. Evidence for reduction of norepinephrine uptake sites in the failing human heart. J. Am. Coll. Cardiol. 25:146–153.

Bohm, M., Zolk, O., Flesch, M., Schiffer, F., Schnabel, P., Stasch, J.P., and Knorr A. 1998a. Effects of angiotensin II type 1 receptor blockade and angiotensin-converting enzyme inhibition on cardiac β-adrenergic signal transduction. Hypertension 31:747–754.

Bohm, M., Ettelbruck, S., Flesch, M., van Gilst, W.H., Knorr, A., Maack, C., Pinto, Y.M., Paul, M., Teisman, A.C., and Zolk, O. 1998b. β-adrenergic signal transduction following carvedilol treatment in hypertensive cardiac hypertrophy. Cardiovasc. Res. 40:146–155.

Bond, R.A., Leff, P., Johnson, T.D., Milano, C.A., Rockman, H.A., McMinn, T.R., Apparsundaram, S., Hyek, M.F., Kenakin, T.P., and Allen, L.F. 1995. Physiological effects of inverse agonists in transgenic mice with myocardial overexpression of the β_2-adrenoceptor. Nature 374:272–276.

Bristow, M.R., and Feldman, A.M. 1992. Changes in the receptor-G protein-adenylyl cyclase system in heart failure from various types of heart muscle disease. Basic Res. Cardiol. 87:15–35.

Bristow, M.R., Anderson, F.L., Port, J.D., Skerl, L., Hershberger, R.E., Larrabee, P., O'Connell, J.B., Renlund, D.G., Volkman, K., Murray, J., et al. 1991. Differences in β-adrenergic neuroeffector mechanisms in ischemic versus idiopathic dilated cardiomyopathy. Circulation 84:1024–1039.

Bristow, M.R., Gilbert, E.M., Abraham, W.T., Adams, K.F., Fowler, M.B., Hershberger, R.E., Kubo, S.H., Narahara, K.A., Ingersoll, H., Krueger, S., Young, S., and Shusterman, N. 1996. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation 94:2807–2816.

Bristow, M.R., Feldman, A.M., Adams, K.F., Jr., and Goldstein, S. 2003. Selective versus nonselective β-blockade for heart failure therapy: are there lessons to be learned from the COMET trial? J. Card. Fail. 9:444–453.

Brodde, O.E. 1991. Pathophysiology of the β-adrenoceptor system in chronic heart failure: consequences for treatment with agonists, partial agonists or antagonists? Eur. Heart J. 12 Suppl. F:54–62.

Brodde, O.E., Zerkowski, H.R., Doetsch, N., Motomura, S., Khamssi, M., and Michel, M.C. 1989. Myocardial β-adrenoceptor changes in heart failure: concomitant reduction in β_1- and β_2-adrenoceptor function related to the degree of heart failure in patients with mitral valve disease. J. Am. Coll. Cardiol. 14:323–331.

Buxton, B.F., Jones, C.R., Molenaar, P., and Summers, R.J. 1987. Characterization and autoradiographic localization of β-adrenoceptor subtypes in human cardiac tissues. Br. J. Pharmacol. 92:299–310.

Calderone, A., de Champlain, J., and Rouleau, J.L. 1991. Adriamycin-induced changes to the myocardial β-adrenergic system in the rabbit. J. Mol. Cell. Cardiol. 23:333–342.

Carabello, B.A. 1996. Models of volume overload hypertrophy. J. Card. Fail. 2:55–64.

Carabello, B.A. 2002. Concentric versus eccentric remodeling. J. Card. Fail. 8:S258–S263.

Celic, V., Pencic, B., Dekleva, M., Dimkovic, S., and Kocijancic, M. 2005. [Metoprolol and atenolol in mild-to-moderate chronic heart failure: comparative study]. Srp. Arh. Celok. Lek. 133:242–247.

Chapados, R.A., Gruver, E.J., Ingwall, J.S., Marsh, J.D., and Gwathmey, J.K. 1992. Chronic administration of cardiovascular drugs: altered energetics and transmembrane signaling. Am. J. Physiol. Heart Circ. Physiol. 263:H1576–H1586.

Chizzola, P.R., de Freitas, H.F.G., Marinho, N.V.S., Mansur, J.A., Meneghetti, J.C., and Bocchi, E.A. 2006. The effect of β-adrenergic receptor antagonism in cardiac sympathetic neuronal remodeling in patients with heart failure. Int. J. Cardiol. 106:29–34.

CIBIS-II Investigators and Committees. 1999. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 353:9–13.

Clark, A.L., and Cleland, J.G.F. 2000. The control of adrenergic function in heart failure: therapeutic intervention. Heart Fail. Revi. 5:101–114.

Collins, S., Caron, M.G., and Lefkowitz, R.J. 1991. Regulation of adrenergic receptor responsiveness through modulation of receptor gene expression. Annu. Rev. Physiol. 53:497–508.

Communal, C., and Colucci, W.S. 2005. The control of cardiomyocyte apoptosis via the β-adrenergic signaling pathways. Arch. Mal. Coeur Vaisse 98:236–241.

Communal, C., Singh, K., Pimental, D.R., Colucci, W.S. 1998. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the beta-adrenergic pathway. Circulation 98: 1329–1334.

DasGupta, P., Broadhurst, P., and Lahiri, A. 1991. The effects of intravenous carvedilol, a new multiple action vasodilatory β-blocker, in congestive heart failure. J. Cardiovasc. Pharmacol. 18:S12–S16.

Davos, C.H., Doehner, W., Rauchhaus, M., Cicoira, M., Francis, D.P., Coats, A.J., Clark, A.L., and Anker, S.D. 2003. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. J. Card. Fail. 9:29–35.

Dessy, C., Moniotte, S., Ghisdal, P., Havaux, X., Noirhomme, P., and Balligand, J.L. 2004. Endothelial β_3-adrenoceptors mediate vasorelaxation of human coronary microarteries through nitric oxide and endothelium-dependent hyperpolarization. Circulation 110:948–954.

Dhalla, N.S., Ziegelhoffer, A., and Harrow, J.A. 1977. Regulatory role of membrane systems in heart function. Can. J. Physiol. Pharmacol. 55:1211–1234.

Dhalla, N.S., Dixon, I.M., Suzuki, S., Kaneko, M., Kobayashi, A., and Beamish, R.E. 1992. Changes in adrenergic receptors during the development of heart failure. Mol. Cell. Biochem. 114:91–95.

Dhalla, N.S., Wang, X., Sethi, R., Das, P.K., and Beamish, R.E. 1997. β-adrenergic linked signal transduction mechanisms in failing hearts. Heart Fail. Rev. 2:55–65.

Di Fusco, F., Hashim, S., and Anand-Srivastava, M.B. 2000. Volume overload cardiac hypertrophy exhibits decreased expression of $G_{s\alpha}$ and not of $G_{i\alpha}$ in heart. Am. J. Physiol. Cell. Physiol. 279:C990–C998.

Dixon, I.M., Lee, S.L., and Dhalla, N.S. 1990. Nitrendipine binding in congestive heart failure due to myocardial infarction. Circ. Res. 66:782–788.

Dixon, I.M., Hata, T., and Dhalla, N.S. 1992. Sarcolemmal calcium transport in congestive heart failure due to myocardial infarction in rats. Am. J. Physiol. Heart Circ. Physiol. 262:H1387–H1394.

Domanski, M.J., Krause-Steinrauf, H., Massie, B.M., Deedwania, P., Follmann, D., Kovar, D., Murray, D., Oren, R., Rosenberg, Y., Young, J., Zile, M., and Eichhorn, E.; BEST Investigators. 2003. A comparative analysis of the results from 4 trials of β-blocker therapy for heart failure: BEST, CIBIS-II, MERIT-HF, and COPERNICUS. J. Card. Fail. 9: 354–363.

Dorn, G.W., 2nd, and Brown, J.H. 1999. G_q signaling in cardiac adaptation and maladaptation. Trends Cardiovasc. Med. 9:26–34.

Eschenhagen, T., Mende, U., Nose, M., Schmitz, W., Scholz, H., Haverich, A., Hirt, S., Doring, V., Kalmar, P., Hoppner, W., et al. 1992. Increased messenger RNA level of the inhibitory G protein α subunit $G_{i\alpha}$-2 in human end-stage heart failure. Circ. Res. 70:688–696.

Forster, C., Naik, G.O., and Larosa, G. 1994. Myocardial β-adrenoceptors in pacing-induced heart failure: regulation by enalapril? Can. J. Physiol. Pharmacol. 72:667–672.

Frace, A.M., Mery, P.F., Fischmeister, R., and Hartzell, H.C. 1993. Rate-limiting steps in the β-adrenergic stimulation of cardiac calcium current. J. Gen. Physiol. 101:337–353.

Freeman, K., Lerman, I., Kranias, E.G., Bohlmeyer, T., Bristow, M.R., Lefkowitz, R.J., Iaccarino, G., Koch, W.J., and Leinwand, L.A. 2001. Alterations in cardiac adrenergic signaling and calcium cycling differentially affect the progression of cardiomyopathy. J. Clin. Invest. 107:967–974.

Freissmuth, M., Schutz, W., Weindlmayer-Gottel, M., Zimpfer, M., and Spiss, C.K. 1987. Effects of ischemia on the canine myocardial β-adrenoceptor-linked adenylate cyclase system. J. Cardiovasc. Pharmacol. 10:568–574.

Frigerio, M., and Roubina, E. 2005. Drugs for left ventricular remodeling in heart failure. Am. J. Cardiol. 96:10L–18L.

Fu, L.X., Bergh, C.H., Hoebeke, J., Liang, Q.M., Sjogren, K.G., Waagstein, F., and Hjalmarson, A. 1991. Effect of metoprolol on activity of β-adrenoceptor coupled to guanine nucleotide binding regulatory proteins in adriamycin-induced cardiotoxicity. Basic Res. Cardiol. 86:117–126.

Fukumoto, K., Kobayashi, T., Komamura, K., Kamakura, S., Kitakaze, M., and Ueno, K. 2005. Stereoselective effect of amiodarone on the pharmacokinetics of racemic carvedilol. Drug Metab. Pharmacokinet. 20:423–427.

Galinier, M., Senard, J.M., Valet, P., Arias, A., Daviaud, D., Glock, Y., Bounhoure, J.P., and Montastruc, J.L. 1994. Cardiac β-adrenoceptors and adenylyl cyclase activity in human left ventricular hypertrophy due to pressure overload. Fundam. Clin. Pharmacol. 8:90–99.

Ganguly, P.K., Dhalla, K.S., Shao, Q., Beamish, R.E., and Dhalla, N.S. 1997. Differential changes in sympathetic activity in left and right ventricles in congestive heart failure after myocardial infarction. Am. Heart J. 133:340–345.

Geng, Y.J., Ishikawa, Y., Vatner, D.E., Wagner, T.E., Bishop, S.P., Vatner, S.F., and Homcy, C.J. 1999. Apoptosis of cardiac myocytes in $G_{s\alpha}$ transgenic mice. Circ. Res. 84:34–42.

Hammond, H.K., Roth, D.A., McKirnan, M.D., Ping, P. 1993. Regional myocardial downregulation of the inhibitory guanosine triphosphate-binding protein (Gi alpha 2) and beta-adrenergic receptors in a poreine model of chronic episodic myocardial ischemia. J. Clin. Invest. 92: 2644–2652.

Hodsman, G.P., Kohzuki, M., Howes, L.G., Sumithran, E., Tsunoda, K., Johnston, C.I. 1998. Neurohormonal responses to chronic myocardial infarction in rats. Circulation 78: 376–381.

Homcy, C.J., Vatner, S.F., and Vatner, D.E. 1991. β-adrenergic receptor regulation in the heart in pathophysiologic states: abnormal adrenergic responsiveness in cardiac disease. Annu. Rev. Physiol. 53:137–159.

Horackova, M., Beresewicz, A., Rowden, G., and Wilkinson, M. 1991. Neurohumoral regulation of excitation-contraction coupling in ventricular myocytes from cardiomyopathic hamsters. Cardiovasc. Res. 25:1023–1034.

Horwich, T.B., Fonarow, G.C., Hamilton, M.A., MacLellan, W.R., Woo, M.A., and Tillisch, J.H. 2001. The relationship between obesity and mortality in patients with heart failure. J. Am. Coll. Cardiol. 38:789–795.

Iaccarino, G., Tomhave, E.D., Lefkowitz, R.J., and Koch, W.J. 1998. Reciprocal *in vivo* regulation of myocardial G protein-coupled receptor kinase expression by β-adrenergic receptor stimulation and blockade. Circulation 98:1783–1789.

Iaccarino, G., Dolber, P.C., Lefkowitz, R.J., and Koch, W.J. 1999. β-adrenergic receptor kinase-1 levels in catecholamine-induced myocardial hypertrophy: regulation by β- but not α_1-adrenergic stimulation. Hypertension 33:396–401.

Iaccarino, G., Keys, J.R., Rapacciuolo, A., Shotwell, K.F., Lefkowitz, R.J., Rockman, H.A., and Koch, W.J. 2001. Regulation of myocardial βARK1 expression in catecholamine-induced cardiac hypertrophy in transgenic mice overexpressing α_{1B}-adrenergic receptors. J. Am. Coll. Cardiol. 38:534–540.

Ikegaya, T., Kobayashi, A., Hong, R.B., Masuda, H., Kaneko, M., and Noboru, Y. 1992. Stimulatory guanine nucleotide-binding protein and adenylate cyclase activities in Bio 14.6 cardiomyopathic hamsters at the hypertrophic stage. Mol. Cell. Biochem. 110:83–90.

Itoh, H., Toyama, R., Kozasa, T., Tsukamoto, T., Matsuoka, M., and Kaziro, Y. 1988. Presence of three distinct molecular species of G_i protein α subunit. Structure of rat cDNAs and human genomic DNAs. J. Biol. Chem. 263:6656–6664.

Iwai-Kanai, E., and Hasegawa, K. 2004. Intracellular signaling pathways for norepinephrine- and endothelin-1-mediated regulation of myocardial cell apoptosis. Mol. Cell. Biochem. 259:163–168.

Iwata, A., Miura, S., Nishikawa, H., Kawamura, A., Matsuo, Y., Sako, H., Kumagai, K., Matsuo, K., and Saku, K. 2006. Significance of combined angiotensin II receptor blocker and carvedilol therapy in patients with congestive heart failure and arginine variant. J. Cardiol. 47:1–7.

Janssen, P.M., Schillinger, W., Donahue, J.K., Zeitz, O., Emami, S., Lehnart, S.E., Weil, J., Eschenhagen, T., Hasenfuss, G., and Prestle, J. 2002. Intracellular β-blockade: overexpression of $G_{\alpha i2}$ depresses the β-adrenergic response in intact myocardium. Cardiovasc. Res. 55:300–308.

Juneau, C., Calderone, A., and Rouleau, J.L. 1992. Myocardial β-adrenergic and mechanical properties in pacing-induced heart failure in dogs. Am. J. Physiol. 262:H1458–H1467.

Karliner, J.S., Barnes, P., Brown, M., and Dollery, C. 1980. Chronic heart failure in the guinea pig increases cardiac α_1- and β-adrenoceptors. Eur. J. Pharmacol. 67:115–118.

Karliner, J.S., Stevens, M.B., Honbo, N., and Hoffman, J.I. 1989. Effects of acute ischemia in the dog on myocardial blood flow, β receptors, and adenylate cyclase activity with and without chronic β blockade. J. Clin. Invest. 83:474–481.

Kawamoto, H., Ohyanagi, M., Nakamura, K., Yamamoto, J., and Iwasaki, T. 1994. Increased levels of inhibitory G protein in myocardium with heart failure. Jpn. Circ. J. 58:913–924.

Kessler, P.D., Cates, A.E., Van Dop, C., and Feldman, A.M. 1989. Decreased bioactivity of the guanine nucleotide-binding protein that stimulates adenylate cyclase in hearts from cardiomyopathic Syrian hamsters. J. Clin. Invest. 84:244–252.

Khattar, R.S., Senior, R., Soman, P., van der Does, R., and Lahiri, A. 2001. Regression of left ventricular remodeling in chronic heart failure: Comparative and combined effects of captopril and carvedilol. Am. Heart J. 142:704–713.

K.-Laflamme, A., Oster, L., Cardinal, R., and de Champlain, J. 1997. Effects of renin-angiotensin blockade on sympathetic reactivity and β-adrenergic pathway in the spontaneously hypertensive rat. Hypertension 30:278–287.

Kohout, T.A., Takaoka, H., McDonald, P.H., Perry, S.J., Mao, L., Lefkowitz, R.J., and Rockman, H.A. 2001. Augmentation of cardiac contractility mediated by the human β_3-adrenergic receptor overexpressed in the hearts of transgenic mice. Circulation 104:2485–2491.

Kozasa, T., Itoh, H., Tsukamoto, T., and Kaziro, Y. 1988. Isolation and characterization of the human G_s α gene. Proc. Natl. Acad. Sci. USA 85:2081–2085.

Lainscak, M., Keber, I., and Anker, S.D. 2006. Body composition changes in patients with systolic heart failure treated with β blockers: a pilot study. Int. J. Cardiol. 106:319–322.

Lamba, S., and Abraham, W.T. 2000. Alterations in adrenergic receptor signaling in heart failure. Heart Fail Rev 5:7–16.

Leineweber, K., Brandt, K., Wludyka, B., Beilfuss, A., Ponicke, K., Heinroth-Hoffmann, I., and Brodde, O.E. 2002. Ventricular hypertrophy plus neurohumoral activation is necessary to alter the cardiac β-adrenoceptor system in experimental heart failure. Circ. Res. 91:1056–1062.

Leineweber, K., Seyfarth, T., Abraham, G., Gerbershagen, H.P., Heinroth-Hoffmann, I., Ponicke, K., and Brodde, O.E. 2003. Cardiac β-adrenoceptor changes in monocrotaline-treated rats: differences between membrane preparations from whole ventricles and isolated ventricular cardiomyocytes. J. Cardiovasc. Pharmacol. 41:333–342.

Lemoine, H., Schonell, H., and Kaumann, A.J. 1988. Contribution of β_1- and β_2-adrenoceptors of human atrium and ventricle to the effects of noradrenaline and adrenaline as assessed with (-)-atenolol. Br. J. Pharmacol. 95:55–66.

Liu, X., Callaerts-Vegh, Z., Evans, K.L., and Bond, R.A. 2002. Chronic infusion of β-adrenoceptor antagonist and inverse agonists decreases elevated protein kinase A activity in transgenic mice with cardiac-specific overexpression of human β_2-adrenoceptor. J. Cardiovasc. Pharmacol. 40:448–455.

Lowes, B.D., Gill, E.A., Abraham, W.T., Larrain, J.R., Robertson, A.D., Bristow, M.R., and Gilbert, E.M. 1999. Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. Am. J. Cardiol. 83:1201–1205.

Maisel, A.S., Motulsky, H.J., and Insel, P.A. 1985. Externalization of β-adrenergic receptors promoted by myocardial ischemia. Science 230:183–186.

Maisel, A.S., Motulsky, H.J., Ziegler, M.G., and Insel, P.A. 1987. Ischemia- and agonist-induced changes in α- and β-adrenergic receptor traffic in guinea pig hearts. Am. J. Physiol. Heart Circ. Physiol. 253:H1159–H1166.

Makino, T., Hattori, Y., Matsuda, N., Onozuka, H., Sakuma, I., and Kitabatake, A. 2003. Effects of angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor blockade on β-adrenoceptor signaling in heart failure produced by myocardial Infarction in rabbits: reversal of altered expression of β-adrenoceptor kinase and $G_{i\alpha}$. J. Pharmacol. Exp. Ther. 304:370–379.

Manolopoulos, V.G., Liu, J., Unsworth, B.R., and Lelkes, P.I. 1995. Adenylyl cyclase isoforms are differentially expressed in primary cultures of endothelial cells and whole tissue homogenates from various rat tissues. Biochem. Biophys. Res. Commun. 208:323–331.

Marzo, K.P., Frey, M.J., Wilson, J.R., Liang, B.T., Manning, D.R., Lanoce, V., and Molinoff, P.B. 1991. β-adrenergic receptor-G protein-adenylate cyclase complex in experimental canine congestive heart failure produced by rapid ventricular pacing. Circ. Res. 69:1546–1556.

Matsuda, N., Hattori, Y., Akaishi, Y., Suzuki, Y., Kemmotsu, O., and Gando, S. 2000. Impairment of cardiac β-adrenoceptor cellular signaling by decreased expression of $G_{s\alpha}$ in septic rabbits. Anesthesiology 93:1465–1473.

Meggs, L.G., Huang, H., Li, P., Capasso, J.M., and Anversa, P. 1991. Chronic nonocclusive coronary artery constriction in rats. β-adrenoceptor signal transduction and ventricular failure. J. Clin. Invest. 88:1940–1946.

MERIT-HF Study Group. 1999. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 353:2001–2007.

Meszaros, J., and Levai, G. 1992. Catecholamine-induced cardiac hypertrophy uncouples β-adrenoceptors from slow calcium channels. Eur. J. Pharmacol. 210:333–338.

Milano, C.A., Allen, L.F., Rockman, H.A., Dolber, P.C., McMinn, T.R., Chien, K.R., Johnson, T.D., Bond, R.A., and Lefkowitz, R.J. 1994. Enhanced myocardial function in transgenic mice overexpressing the β_2-adrenergic receptor. Science 264:582–586.

Morisco, C., Zebrowski, D.C., Vatner, D.E., Vatner, S.F., and Sadoshima, J. 2001. β-adrenergic cardiac hypertrophy is mediated primarily by the β_1-subtype in the rat heart. J. Mol. Cell. Cardiol. 33:561–573.

Mukherjee, A., Bush, L.R., McCoy, K.E., Duke, R.J., Hagler, H., Buja, L.M., and Willerson, J.T. 1982. Relationship between β-adrenergic receptor numbers and physiological responses during experimental canine myocardial ischemia. Circ. Res. 50:735–741.

Muller, F.U., Boheler, K.R., Eschenhagen, T., Schmitz, W., and Scholz, H. 1993. Isoprenaline stimulates gene transcription of the inhibitory G protein alpha-subunit $G_{i\alpha}$-2 in rat heart. Circ. Res. 72:696–700.

Ohyanagi, M., Yamamoto, J., Nakamura, K., Shibuya, J., Morita, M., Masutani, M., Arii, T., and Iwasaki, T. 1995. Messenger RNA for the guanine nucleotide-binding regulatory protein (G protein) is reduced in the acute ischemic myocardium. J. Mol. Cell. Cardiol. 27:1131–1139.

Panagia, V., Singh, J.N., Anand-Srivastava, M.B., Pierce, G.N., Jasmin, G., and Dhalla, N.S. 1984. Sarcolemmal alterations during the development of genetically determined cardiomyopathy. Cardiovasc. Res. 18:567–572.

Patrianakos, A.P., Parthenakis, F.I., Mavrakis, H.E., Diakakis, G.F., Chlouverakis, G.I., and Vardas, P.E. 2005. Comparative efficacy of nebivolol versus carvedilol on left ventricular function and exercise capacity in patients with nonischemic dilated cardiomyopathy. A 12-month study. Am. Heart J. 150:985.

Pela, G., Missale, C., Raddino, R., Condorelli, E., Spano, P.F., and Visioli, O. 1990. β_1- and β_2-receptors are differentially desensitized in an experimental model of heart failure. J. Cardiovasc. Pharmacol. 16:839–846.

Persad, S., Takeda, S., Panagia, V., and Dhalla, N.S. 1997. β-adrenoceptor-linked signal transduction in ischemic-reperfused heart and scavenging of oxyradicals. J. Mol. Cell. Cardiol. 29:545–558.

Persad, S., Panagia, V., and Dhalla, N.S. 1998. Role of H_2O_2 in changing β-adrenoceptor and adenylyl cyclase in ischemia-reperfused hearts. Mol. Cell. Biochem. 186:99–106.

Remme, W., Boccanelli, A., Cline, C., Cohen-Solal, A., Dietz, R., Hobbs, R., Keukelaar, K., Sendon, J.L., Macarie, C., McMurray, J., Rauch, B., Ruzyllo, W., and Zannad, F; SHAPE Study. 2004. Increasing awareness and perception of heart failure in Europe and improving care—rationale and design of the SHAPE Study. Cardiovasc. Drug Ther. 18:153–159.

Rocha-Singh, K.J., Honbo, N.Y., and Karliner, J.S. 1991. Hypoxia and glucose independently regulate the β-adrenergic receptor-adenylate cyclase system in cardiac myocytes. J. Clin. Invest. 88:204–213.

Rockman, H.A., Chien, K.R., Choi, D.J., Iaccarino, G., Hunter, J.J., Ross, J., Jr., Lefkowitz, R.J., and Koch, W.J. 1998. Expression of a β-adrenergic receptor kinase 1 inhibitor prevents the development of myocardial failure in gene-targeted mice. Proc. Natl. Acad. Sci. USA 95:7000–7005.

Sabri, A., Wilson, B.A., and Steinberg, S.F. 2002. Dual actions of the $G_{\alpha q}$ agonist Pasteurella multocida toxin to promote cardiomyocyte hypertrophy and enhance apoptosis susceptibility. Circ. Res. 90:850–857.

Saffitz, J.E., and Liggett, S.B. 1992. Subcellular distribution of β_2-adrenergic receptors delineated with quantitative ultrastructural autoradiography of radioligand binding sites. Circ. Res. 70:1320–1325.

Saito, S., Hiroi, Y., Zou, Y., Aikawa, R., Toko, H., Shibasaki, F., Yazaki, Y., Nagai, R., and Komuro, I. 2000. β-adrenergic pathway induces apoptosis through calcineurin activation in cardiac myocytes. J. Biol. Chem. 275:34528–34533.

Sayar, K., Ugur, M., Gurdal, H., Onaran, O., Hotomaroglu, O., and Turan, B. 2000. Dietary selenium and vitamin E intakes alter β-adrenergic response of L-type Ca-current and β-adrenoceptor-adenylate cyclase coupling in rat heart. J. Nutr. 130:733–740.

Schotten, U., Filzmaier, K., Borghardt, B., Kulka, S., Schoendube, F., Schumacher, C., and Hanrath, P. 2000. Changes of β-adrenergic signaling in compensated human cardiac hypertrophy depend on the underlying disease. Am. J. Physiol. Heart Circ. Physiol. 278:H2076–H2083.

Searles, R.P., Midson, C.N., Nipper, V.J., and Machida, C.A. 1995. Transcription of the rat β_1-adrenergic receptor gene. Characterization of the transcript and identification of important sequences. J. Biol. Chem. 270:157–162.

Sethi, R., and Dhalla, N.S. 1995. Inotropic responses to isoproterenol in congestive heart failure subsequent to myocardial infarction in rats. J. Card. Fail. 1:391–399.

Sethi, R., Bector, N., Takeda, N., Nagano, M., Jasmin, G., and Dhalla, N.S. 1994. Alterations in G-proteins in congestive heart failure in cardiomyopathic (UM-X7.1) hamsters. Mol. Cell. Biochem. 140:163–170.

Sethi, R., Dhalla, K.S., Beamish, R.E., and Dhalla, N.S. 1997. Differential changes in left and right ventricular adenylyl cyclase activities in congestive heart failure. Am. J. Physiol. Heart Circ. Physiol. 272:H884–H893.

Sethi, R., Elimban, V., Chapman, D., Dixon, I.M., and Dhalla, N.S. 1998. Differential alterations in left and right ventricular G-proteins in congestive heart failure due to myocardial infarction. J. Mol. Cell. Cardiol. 30:2153–2163.

Sethi, R., Shao, Q., Takeda, N., and Dhalla, N.S. 2003. Attenuation of changes in G_i-proteins and adenylyl cyclase in heart failure by an ACE inhibitor, imidapril. J. Cell. Mol. Med. 7:277–286.

Sethi, R., Wang, X., Ferrari, R., and Dhalla, N.S. 2004. Improvement of cardiac function and β-adrenergic signal transduction by propionyl L-carnitine in congestive heart failure due to myocardial infarction. Coron. Artery Dis. 15:65–71.

Sethi, R., Saini, H.K., Wang, X., Elimban, V., Babick, A., and Dhalla, N.S. 2006. Differential changes in β-adrenoceptor signal transduction in left and right ventricles of infarcted rats. Can. J. Physiol. Pharmacol. 84:747–754.

Shite, J., Qin, F., Mao, W., Kawai, H., Stevens, S.Y., and Liang, C. 2001. Antioxidant vitamins attenuate oxidative stress and cardiac dysfunction in tachycardia-induced cardiomyopathy. J. Am. Coll. Cardiol. 38:1734–1740.

Shizukuda, Y., and Buttrick, P.M. 2002. Subtype specific roles of β-adrenergic receptors in apoptosis of adult rat ventricular myocytes. J. Mol. Cell. Cardiol. 34:823–831.

Steinfath, M., Danielsen, W., von der Leyen, H., Mende, U., Meyer, W., Neumann, J., Nose, M., Reich, T., Schmitz, W., Scholz, H., et al. 1992. Reduced β_1- and β_2-adrenoceptor-mediated positive inotropic effects in human end-stage heart failure. Br. J. Pharmacol. 105:463–469.

Stiles, G.L., Caron, M.G., and Lefkowitz, R.J. 1984. β-adrenergic receptors: biochemical mechanisms of physiological regulation. Physiol. Rev. 64:661–743.

Strasser, R.H., Krimmer, J., Braun-Dullaeus, R., Marquetant, R., and Kubler, W. 1990. Dual sensitization of the adrenergic system in early myocardial ischemia: independent regulation of the β-adrenergic receptors and the adenylyl cyclase. J. Mol. Cell. Cardiol. 22:1405–1423.

Sunahara, R.K., Dessauer, C.W., and Gilman, A.G. 1996. Complexity and diversity of mammalian adenylyl cyclases. Annu. Rev. Pharmacol. Toxicol. 36:461–480.

Tate, K.M., Briend-Sutren, M.M., Emorine, L.J., Delavier-Klutchko, C., Marullo, S., and Strosberg, A.D. 1991. Expression of three human β-adrenergic-receptor subtypes in transfected Chinese hamster ovary cells. Eur. J. Biochem. 196:357–361.

Tavernier, G., Toumaniantz, G., Erfanian, M., Heymann, M.F., Laurent, K., Langin, D., and Gauthier, C. 2003. β_3-adrenergic stimulation produces a decrease of cardiac contractility *ex vivo* in mice overexpressing the human β_3-adrenergic receptor. Cardiovasc. Res. 59:288–296.

The Xamoterol in Severe Heart Failure Study Group. 1990. Xamoterol in severe heart failure. Lancet. 336:1–6.

Urasawa, K., Sato, K., Igarashi, Y., Kawaguchi, H., Yasuda, H. 1992. A mechanism of catecholamine tolerance in congestive heart failure-alterations in the hormone sensitive adenylyl cyclase system of the heart. Jpn. Circ, J. 56: 456–461.

van den Ende, R., Batink, H.D., Michel, M.C., and van Zwieten, P.A. 1994. Influence of ischaemia and reperfusion on cardiac signal transduction. G protein content, adenylyl cyclase activity, cyclic AMP content, and forskolin and dibutyryl cyclic AMP-induced inotropy in the rat Langendorff heart. Fundam. Clin. Pharmacol. 8:408–416.

Vatner, D.E., Knight, D.R., Shen, Y.T., Thomas, J.X., Jr., Homcy, C.J., and Vatner, S.F. 1988. One hour of myocardial ischemia in conscious dogs increases β-adrenergic receptors, but decreases adenylate cyclase activity. J. Mol. Cell. Cardiol. 20:75–82.

Vatner, D.E., Young, M.A., Knight, D.R., and Vatner, S.F. 1990. β-receptors and adenylate cyclase: comparison of nonischemic, ischemic, and postmortem tissue. Am. J. Physiol. Heart Circ. Physiol. 258:H140–H144.

Waagstein, F., Caidahl, K., Wallentin, I., Bergh, C.H., and Hjalmarson, A. 1989. Long-term β-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 80:551–563.

Wallukat, G. 2002. The β-adrenergic receptors. Herz 27:683–690.

Wang, X., and Dhalla, N.S. 2000. Modification of β-adrenoceptor signal transduction pathway by genetic manipulation and heart failure. Mol. Cell. Biochem. 214:131–155.

Wang, X., Wang, J., Takeda, S., Elimban, V., and Dhalla, N.S. 2002. Alterations of cardiac β-adrenoceptor mechanisms due to calcium depletion and repletion. Mol. Cell. Biochem. 232:63–73.

Wang, X., Ren, B., Liu, S., Sentex, E., Tappia, P.S., and Dhalla, N.S. 2003. Characterization of cardiac hypertrophy and heart failure due to volume overload in the rat. J. Appl. Physiol. 94:752–763.

Wang, X., Sentex, E., Saini, H.K., Chapman, D., and Dhalla, N.S. 2005. Upregulation of β-adrenergic receptors in heart failure due to volume overload. Am. J. Physiol. Heart Circ. Physiol. 289:H151–H159.

Weber, M.A. 2005. The role of the new β-blockers in treating cardiovascular disease. Am. J. Hypertens. 18:169S–176S.

Weil, J., and Schunkert, H. 2006. Pathophysiology of chronic heart failure. Clin. Res. Cardiol. 95:1–17.

Will-Shahab, L., Rosenthal, W., Schulze, W., and Kuttner, I. 1991. G protein function in the ischaemic myocardium. Eur. Heart J. 12:135–138.

Witte, K., Olbrich, H.G., Langer, L., and Lemmer, B. 1993. Uncoupling of β_1-adrenoceptors from cardiac adenylyl cyclase in cardiomyopathic and control hamsters. Eur. J. Pharmacol. 247:215–218.

Wollert, K.C., Studer, R., von Bulow, B., and Drexler, H. 1994. Survival after myocardial infarction in the rat. Role of tissue angiotensin-converting enzyme inhibition. Circulation 90:2457–2467.

Xiao, R.P., Avdonin, P., Zhou, Y.Y., Cheng, H., Akhter, S.A., Eschenhagen, T., Lefkowitz, R.J., Koch, W.J., and Lakatta, E.G. 1999. Coupling of β_2-adrenoceptor to G_i proteins and its physiological relevance in murine cardiac myocytes. Circ. Res. 84:43–52.

Yoshida, H., Tanonaka, K., Miyamoto, Y., Abe, T., Takahashi, M., Anand-Srivastava, M.B., and Takeo, S. 2001a. Characterization of cardiac myocyte and tissue β-adrenergic signal transduction in rats with heart failure. Cardiovasc. Res. 50:34–45.

Yoshida, H., Takahashi, M., Tanonaka, K., Maki, T., Nasa, Y., and Takeo, S. 2001b. Effects of ACE inhibition and angiotensin II type 1 receptor blockade on cardiac function and G proteins in rats with chronic heart failure. Br. J. Pharmacol. 134:150–160.

Yoshie, H., Tobise, K., and Onodera, S. 1994. Intraventricular changes in the β-adrenoceptor-adenylate cyclase system of the rat heart with the progress of monocrotaline-induced right ventricular hypertrophy. Jpn. Circ. J. 58:855–865.

Yoshikawa, T., Handa, S., Suzuki, M., and Nagami, K. 1994. Abnormalities in sympathoneuronal regulation are localized to failing myocardium in rabbit heart. J. Am. Coll. Cardiol. 24:210–215.

Yu, H.J., Unnerstall, J.R., and Green, R.D. 1995. Determination and cellular localization of adenylyl cyclase isozymes expressed in embryonic chick heart. FEBS Lett. 374:89–94.

Zhou, Y., Friedman, E., Roberts, J., and Johnson, M.D. 1995. Modulation of aortic and cardiac G protein alpha subunits and their mRNAs during norepinephrine infusion in rats. J. Vasc. Res. 32:16–23.

Zhu, W.Z., Zheng, M., Koch, W.J., Lefkowitz, R.J., Kobilka, B.K., and Xiao, R.P. 2001. Dual modulation of cell survival and cell death by β_2-adrenergic signaling in adult mouse cardiac myocytes. Proc. Natl. Acad. Sci. USA 98:1607–1612.