β-Adrenergic Receptor Signaling in Congestive Heart Failure

by

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9 March 2012
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The sympathetic autonomic nervous system plays an important role in regulating the cardiovascular system. In order to modulate cardiac function, postganglionic sympathetic nerves release the catecholamine norepinephrine, which is recognized by β-adrenergic receptor (β-ARs) on the target cardiomyocytes (Windmaier 182). The catecholamine epinephrine can also stimulate β-ARs after it is released from the adrenal medulla in response to stress (Griffin and Ojeda 342). Sympathetic stimulation of β-ARs by circulating catecholamines causes increases in heart rate (chronotropism), contractility (inotropism), rate of muscle relaxation (lusitropism), and cardiac conduction velocity (Post, Hammond, and Insel 343-344).

Sympathetic stimulation of the heart is also implicated in various diseased states, notably congestive heart failure (CHF). Patients with CHF have significantly elevated levels of plasma catecholamines; yet, the cardiomyocyte β-ARs are less responsive to this sympathetic stimulation (Post, Hammond, and Insel 344). This results in both diminished β-AR signalling and a blunted cardiac response (Post, Hammond, and Insel 343).

**Characteristics of Congestive Heart Failure**

Congestive heart failure occurs when cardiac muscle looses the ability to pump blood in order to adequately perfuse tissues (Post, Hammond, and Insel 344). As a result, the heart cannot meet the requirements of the body’s metabolizing tissues without generating abnormally high blood pressures (Kumar et al. 380). Five million Americans are affected by CHF, causing over one million hospitalizations and three hundred thousand deaths a year (Kumar et al. 380). Most cases
are due to systolic dysfunction caused by cardiac ischemia or hypertension. This results in progressive deterioration of myocardial contractility and a decreased stroke volume (Windmaier 420). In contrast, CHF develops in some patients due to diastolic dysfunction, caused by diabetes mellitus or hypertension. This leads to decreased stroke volume, while ventricular contractility remains normal (Windmaier 420).

Chronically reduced cardiac output in CHF stimulates the arterial baroreceptor reflexes, which elicits abnormal increases in sympathetic innervation to the heart and activates the renin-angiotensin system. Persistent sympathetic signalling can be toxic to cardiomyocytes, which exacerbates the cardiac injury (Dorn 458). The damaged myocardial tissue responds to this signaling by increasing both the heart rate and the resistance of the peripheral vasculature, in an effort to compensate for the decreased contractility and stroke volume (Windmaier 421). This leads to elevated blood pressure, which increases the cardiomyocyte workload to produce further damage. Furthermore, high blood pressure in the capillaries promotes filtration of fluid out of the vasculature, resulting in edema (Windmaier 421). The role of sympathetic signaling in heart failure is illustrated below in figure 1.

![Image of a diagram illustrating the role of sympathetic signaling in heart failure]

Figure 1: Chronic sympathetic signaling in CHF promotes further myocardial damage (Dorn 458).
β-Adrenergic Receptor Signalling Following Catecholamine Stimulation Under Conditions of Health

β-adrenergic receptors are stimulated by the catecholamines epinephrine and norepinephrine. Epinephrine is released from the adrenal medulla in response to stress, and circulates throughout the body eliciting the ‘fight-or-flight’ response (Griffin and Ojeda 342). Norepinephrine is released in small amounts by the adrenal medulla. In addition, it acts as a local neurotransmitter in peripheral nerves, and only reaches the blood following persistent activation of the sympathetic nervous system (Griffin and Ojeda 342).

There are three subtypes of β-adrenergic receptors, β1, β2, and β3, each encoded by a distinct gene (Griffin and Ojeda 343). The mammalian heart predominantly expresses the β1 isoform, and smaller amounts of the β2 isoform (in about a 70:30 ratio). β2-ARs are mostly found in endothelial cells and fibroblasts (Post, Hammond, and Insel 344). Furthermore, several studies suggest that β3-ARs are expressed in cardiac tissue where they exert a negative inotropic effect only upon intense stimulation; however, the role of these receptors remains poorly understood (Gorre and Vandekerckhove 565).

All three subtypes of β-ARs signal through seven-pass transmembrane G-protein coupled receptors (GPCRs). When stimulated by a catecholamine, the third intracellular loop and the carboxy-terminus of the receptor associate with the heterotrimeric G protein, forming the ternary complex (Post, Hammond, and Insel 345). The type of G-protein with which the receptor interacts depends on the receptor subtype (Marian 11). The formation of the ternary complex prompts the Gα subunit to exchange GDP for GTP, making the G-protein active (Post, Hammond, and Insel 345). Once active, the Gα subunit dissociates slightly from the Gβγ subunits, and the subunits can now exert downstream biological effects.
The β1 isoform of adrenergic receptors, which comprises 70-80% of β-ARs in the human heart, is coupled to the Gαs trimeric protein. When bound to GTP, the Gαs subunit activates the membrane-bound enzyme adenyl cyclase, which in turn will catalyze the formation of cyclic AMP (cAMP) (Griffin and Ojeda 58). Increased intracellular cAMP allows activation of protein kinase A (PKA), which phosphorylates numerous downstream targets, such as phospholamban, cardiac troponin, and L-type calcium channels (Marian 11). These phosphorylated molecules mediate the functional consequences of β1 signaling, including increased cardiac contractility, heart rate, rate of relaxation, and cardiomyocyte apoptosis. In addition, PKA can phosphorylate and inactive the receptor, causing a negative feedback effect on β-AR signaling (Post, Hammond, and Insel 346). The extent of PKA activity is limited by A kinase anchoring proteins (AKAP) and phosphodiesterases (Balck and Fitzgerald 4154).

β2-Adrenergic receptors, which comprise approximately 20-30% of the total β-AR population in the human heart, can be coupled to either Gαs or Gαi trimeric proteins (Black and Fitzgerald 4154). When β2-ARs are coupled to Gs proteins, catecholamine stimulation induces PKA activation, which has a positive inotropic effect on cardiomyocytes (Saucerman and McCulloch 353). Conversely, when coupled to Gi proteins, the GTP-bound Gαi subunit inhibits adenyl cyclase and PKA activity, and thereby causes a negative inotropic response (Post, Hammond, and Insel 345). Gi-protein signaling via β2-ARs has also been linked to activation of the MAP-kinase cascade, which functions to prevent apoptosis of cardiomyocytes (Black and Fitzgerald 4154). Two negative feedback loops exist to maintain homeostasis. First, upon catecholamine signaling, active PKA phosphorylates β2-ARs which promotes a coupling transition from Gαs to Gαi proteins (Black and Fitzgerald 4154). This increased Gαi activity then works to decrease cAMP production and PKA activation. Second, active β2-ARs recruit
phosphodiesterases, which oppose PKA action and the subsequent β2-AR coupling transition from Gs to Gi that is associated with MAP-kinase activation (Saucerman and McCulloch 356).

G-protein receptor kinases (GRKs) are essential for desensitization and downregulation of GPCRs, as seen in figure 2. Types 2 and 5 are the predominant isoforms of GRKS present in cardiomyocytes (Post, Hammond, and Insel 346). GRK2 is localized to the plasma membrane where it is specific for agonist-occupied β-ARs because it uses a pleckstrin homology domain to bind the Gβγ subunits, which are only available upon receptor activation (Dorn 456). GRK5 includes a PIP2-binding domain, which ensures its persistent localization to the plasma membrane (Dorn 456). GRKs phosphorylate agonist-bound β-ARs, which is necessary to recruit cytosolic β-arrestin to the GPCR (Dorn 455). Upon binding of β-arrestin to a Gαs-coupled β-AR, the Gαs-protein is displaced and can no longer be activated by the receptor. This effectively desensitizes the receptor by uncoupling it from its cAMP-dependent downstream signaling targets (Dorn 455). Conversely, if β-arrestin instead binds to a Gαi-coupled β-AR, β-arrestin functions as a scaffold protein to facilitate MAP-kinase signaling, which prevents apoptosis (Saucerman and McCulloch 355). Furthermore, β-arrestins have a role in endosome-mediated receptor internalization, by targeting the bound receptor to clathrin-coated pits. This process leads to receptor downregulation (Dorn 455).
Figure 2: G-protein receptor kinases function to terminate GPCR signaling through receptor desensitization and downregulation (Post, Hammond, and Insel 347).

The complex interplay of β1 and β2 AR signalling in the healthy human heart is illustrated in figure 3.

Figure 3: Effects of β-AR signaling in the human heart (Saucerman and McCulloch 6).

Changes in β-Adrenergic Receptor Signalling in CHF

In the early stages of CHF, decreased cardiac output induces increased sympathetic stimulation of the heart, which initially has beneficial positive inotropic effects (Gorre and Vandekerckhove 568). However, as the disease progresses and cardiac output remains chronically
insufficient, the resulting persistent adrenergic activation of the heart leads to myocardial cell apoptosis and harmful ventricular remodelling (Gorre and Vandekerckhove 568). The magnitude of sympathetic overstimulation can be quantified by measuring the levels of circulating catecholamines in CHF patient serum (Post, Hammond, and Insel 344). As seen in figure 4, there is a correlation between clinical severity of the disease, represented by declining intrinsic function of the heart, and the level of increase in adrenergic support and circulating catecholamines (Post, Hammond, and Insel 344).

![Figure 4: The relationship between declining left ventricular function and increasing sympathetic activation (Black and Fitzgerald 2010).](image)

Furthermore, CHF is characterized by changes in the activation and deactivation of β-AR signaling pathways, which despite elevated catecholamine levels, ultimately lead to reduced cardiac response to β-AR stimulation. This is the result of modifications in the expression or function of the following molecules: β-ARs, G-proteins, adenylyl cyclases and G-protein receptor kinases (also called β-adrenergic receptor kinases). The changes in β-AR signaling under conditions of constitutive adrenergic activation are summarized in table 1 (Santwani, Dec, and Narula 247).

<table>
<thead>
<tr>
<th>Component</th>
<th>Observed Effect</th>
</tr>
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<tbody>
<tr>
<td>β-AR</td>
<td>down-regulated, uncoupled</td>
</tr>
<tr>
<td>β-AR</td>
<td>Uncoupled</td>
</tr>
<tr>
<td>β-ARK</td>
<td>↑ mRNA, ↑ activity</td>
</tr>
<tr>
<td>Gi</td>
<td>↑ activity</td>
</tr>
<tr>
<td>AC</td>
<td>↓ activity</td>
</tr>
</tbody>
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AR = adrenergic receptor; β-ARK = β-adrenergic receptor kinase; Gi = inhibitory G protein; AC = adenyly cyclase.
At the onset of CHF, the sympathetic nervous system is induced as an adaptive mechanism to counteract the low cardiac output (CO) (Black and Fitzgerald 4148). The resulting catecholamine release leads to high levels of adenylyl cyclase activation, due to a β1-AR dominated response. This causes increased intracellular cAMP and PKA activation, which in turn leads to elevated PKA-mediated phosphorylation and desensitization of both β1 and β2 ARs (Post, Hammond, and Insel 345). Furthermore, when β2-AR is phosphorylated by PKA, it has been shown to couple preferentially to the Goi trimeric protein (Black and Fitzgerald 4154). Subsequently, upon further catecholamine stimulation, the now Gi-coupled β2-ARs will activate the MAP-kinase cascade and inhibit adenylyl cyclase, thereby lowering previously elevated intracellular cAMP. This contributes to the negative inotropic response seen in CHF, creating a vicious cycle where cardiac deterioration leads to excessive catecholamine release which further exacerbates the cardiac insufficiency (Post, Hammond, and Insel 345). The sympathetic innervation-mediated pathogenesis of CHF is illustrated in Figure 5.

![Figure 5: Increased sympathetic signaling leads to decreased β-AR responsiveness in CHF.](image)

Additionally, the activity of G-protein receptor kinases increases two- to threefold in patients with CHF (Dorn 457). This is an adaptive mechanism intended to protect cardiomyocytes against the cytotoxic effects of excessive catecholamine stimulation; however, constitutive GRK
action can have deleterious effects (Dorn 457). These enzymes phosphorylate agonist-occupied β-ARs on serine residues at the carboxy-terminus, which functions to desensitize and downregulate the receptors (Dorn 455). Constitutive sympathetic innervation to the heart in CHF causes increased GRK-mediated phosphorylation, desensitization, and downregulation of β-ARs. This decreases the ability of cardiomyocytes to respond to catecholamine signaling, thereby preventing the chronotropic, inotropic and lusitropic responses necessary to counteract the chronically decreased cardiac output (Dorn 457). In this way, excessive GRK-mediated uncoupling of β-AR signaling contributes to the progression of CHF (Dorn 459). In CHF, both GRK protein and mRNA levels increase, suggesting transcriptional upregulation of the enzyme in response to persistent stress-induced sympathetic stimulation. Figure 6 demonstrates the decrease in phosphorylated phospholamban (a PKA phosphorylation target) associated with CHF. This is due to upregulation of GRK2, which blunts β-AR signaling, decreases adenylyl cyclase activation, and inhibits PKA activity (Briston et al. 10).

Figure 6: A and B show decreased phosphorylation of phospholamban (a PKA target) at two phosphorylation sites in cardiomyocytes experiencing heart failure (HF). This indicates decreased activity of PKA. Graph C indicated the increased expression of GRK2 protein in cardiomyocytes undergoing HF (Briston et al. 10).
Through the compensatory mechanisms described above, cytotoxic levels of catecholamine stimulation in the heart leads to a marked reduction in the number and sensitivity of β-ARs, which serves to protect cardiomyocytes from necrosis due to overstimulation (Post, Hammond, and Insel 348). Interestingly, the number of β1-ARs decreases dramatically in the hearts of patients with CHF, on average causing a 60% selective decrease in the β1-AR population (Lamba and Abraham 10). In fact, the level of decrease is proportional to the clinical severity of the disease (Lamba and Abraham 10). Conversely, the number of β2-ARs in cardiomyocytes remains relatively unchanged (Black and Fitzgerald 4155). The β1 receptor downregulation is achieved through protein degradation and mRNA destabilization by agonist-induced transcript binding proteins, such as AUF-1 (Marian 11). Furthermore, both β1 and β2 adrenergic receptors are uncoupled from the adenylyl cyclase-dependent signal transduction pathways. This is due to PKA and GRK-mediated inhibitory phosphorylation of Gs-coupled β-ARs, which functions to recruit β-arrestin and desensitize the receptor (Lamba and Abraham 10).

The mechanism for selective β1-AR degradation in CHF is explained by the ability of β2-ARs to couple to Gi trimeric proteins, which is suggested to protect cardiomyocytes from catecholamine cytotoxicity (Ahles and Engelhardt 189). The initially increased levels of PKA activity lead to β2-AR phosphorylation, which prompts a transition in the coupling of β2-ARs from Gs to Gi trimeric proteins. This is supported by data showing increased levels of Gi in the failing myocardium, potentially due to a cAMP response element in the Gi promoter region (Lamba and Abraham 10)(Post, Hammond, and Insel 352). Instead of its usual role in Gs-coupled β-AR desensitization and downregulation, when β-arrestin bind to β2-ARs coupled to Gi, the β-arrestin promotes β2-AR signalling by acting as a scaffold protein to facilitate MAP-kinase activation. This spares the β2 isoform from degradation in CHF. Upon further stimulation
by catecholamines, high levels of active G\(\alpha_i\) oppose \(\beta_1\)-AR action and leads to both inhibition of adenyl cyclase (causing a negative inotropic response) and greater stimulation of the MAP-kinase pathway (causing an anti-apoptotic response) (Black and Fitzgerald 4155). Therefore, elevated G\(\alpha_i\) levels in failing myocardium serves as an adaptive response that protects the heart from \(\beta_1\)-AR overstimulation and subsequent cytotoxicity (Saucerman and McCulloch 355). However, when this \(\beta_2\)-AR adaptive response is prolonged, it may exacerbate the heart failure phenotype by contributing to a diminished cardiac output (Post, Hammond, and Insel 352). In addition, norepinephrine is released at a constitutively high concentration in sympathetic neural synapses during CHF, where it has a greater affinity for \(\beta_1\)-ARs compared to \(\beta_2\)-ARs. This could lead to greater stimulation-induced receptor downregulation of \(\beta_1\)-ARs due to elevated levels of GRKs (Post, Hammond, and Insel 349).

### \(\beta\)-Adrenergic Receptor Localization and CHF

\(\beta\)-adrenergic receptor localization plays an important role in receptor function and signalling. Cardiomyocytes have specialized invaginations of the cell membrane called T-tubules, which are bordered on either side by cell crests. Under conditions of health, \(\beta_1\)-ARs are found in both the cell crest and the cell tubule of the cardiomyocytes; whereas \(\beta_2\)-ARs are found only in the T-tubule membrane (Black and Fitzgerald 4154). This is demonstrated below by localized cAMP production in response to \(\beta\)-AR stimulation in healthy rat hearts (figure 7). If cAMP is produced upon agonist administration, this indicates presence of the receptor. In addition, the lack of \(\beta_2\)-mediated cAMP production in the tubules was shown to be independent of both cAMP degradation and \(\beta_2\)-G\(\alpha_i\) coupling (Nikolaev et al. 1654).
Figure 7: Receptor-type specific agonist stimulation of β1 and β2 adrenergic receptors in a healthy adult rat heart. A decrease in the fluorescence resonance energy transfer (FRET) ratio (also defined as YFP/CFP) represents an increase in cAMP levels, indicating the presence of the receptor. When IBMX was administered to inhibit phosphodiesterases (which degrade cAMP), the relative cAMP levels in the tubules and crests upon β2 stimulation remained unchanged, indicating that low cAMP levels at crests are due to lack of receptor and not accelerated cAMP degradation. When PTX (a Gi protein inhibitor) was administered, no significant changes were observed in relative cAMP levels, indicating that coupling of Gαi to β2-ARs does not affect receptor distribution and cAMP production in healthy rats. (Nikolaev et al. 1654)

In CHF, many studies have shown decreased responsiveness to β-AR activation and an extensive loss of T-tubules in the failing myocardial tissue. This loss of T-tubules causes re-localization of β2-ARs to the cell crest (Black and Fitzgerald 4154). When these re-localized β2-ARs are activated by chronic sympathetic signalling, it results in diffuse cAMP production throughout the entire cytosol. The redistribution of β2-ARs seen in CHF may contribute to the clinical progression of the disease because it uncouples β2-ARs from localised PKA populations responsible for inhibiting the receptor (Black and Fitzgerald 4154). Certain A Kinase Anchoring
Proteins (AKAP79) are responsible for binding to β2-ARs, thereby facilitating binding of localized PKA, phosphorylation of β2-ARs, and subsequent desensitization by β-arrestin. When β2 is redistributed in CHF, it can no longer be adequately inhibited by this localized PKA, which allows uncontrolled β2-mediated production of cAMP upon catecholamine stimulation (Black and Fitzgerald 4154). This increased β2-AR activity may contribute to the heart failure phenotype by causing cardiomyocyte overstimulation and cell death (Nikolaev et al. 1657). As a result, selective β2-AR blockade is currently being explored as a possible therapeutic target (Black and Fitzgerald 4155). Below in figure 8, cAMP levels are shown to increase in the cell tubule and cell crest upon stimulation of both β1-ARs and β2-ARs in CHF rat cardiomyocytes. This indicates that in the diseased state, β2-ARs are re-distributed to the cell crest (Nikolaev et al. 1655).

Figure 8: Receptor-type specific agonist stimulation of β1 and β2 adrenergic receptors in CHF rat cardiomyocytes. A decrease in the FRET ratio (also defined as YFP/CFP) represents an increase in cAMP levels, indicating the presence of the receptor. When IBMX was administered to inhibit phosphodiesterases (which degrade cAMP), the relative cAMP levels in the tubules and crests upon β2 stimulation remained relatively unchanged. When PTX (a Gi protein inhibitor) was
administered, no significant changes were observed in relative cAMP levels, indicating that coupling of $G_\text{ox}$ to $\beta_2$-ARs does not affect cAMP distribution CHF. (Nikolaev et al. 1655)

**β-Antagonists in Clinical Treatment of CHF**

β-blockers are structurally similar to catecholamines and act as competitive antagonists for β-ARs; they are a common therapeutic treatment for CHF (Shin and Johnson 187). As seen below in figure 9, excessive sympathetic drive in a human heart can be directly toxic to myocardial cells. In fact, the degree of myocardial damage and severity of the disease is proportional to the concentration of norepinephrine administered (Lamba and Abraham 9). Consequently, β-antagonists improve ventricular function and cardiac output by blocking the cytotoxic effects of chronic sympathetic stimulation, thereby protecting the myocardium from further damage. More specifically, β-blockers prevent the overstimulation-induced desensitization of β-ARs; thereby thwarting the subsequent decreases in β-AR number, β-AR uncoupling, and increases in $G_\text{ox}$ activity (Lamba and Abraham 11). This works to restore both myocardial catecholamine responsiveness, and the associated positive inotropic effects. As a result, CHF patients treated with β-blockers have prolonged survival (Dorn 458).

![Figure 9: The directly cytotoxic effects of norepinephrine can be observed when administered to cultures of human heart cells. A decreased percent of rod-shaped cells indicates increased myocardial cell death, which is directly proportional to the concentration of norepinephrine administered (Lamba and Abraham 9).](image)
β-antagonists were historically contraindicated in CHF patients, due to their initially negative inotropic effects; although they have now been proven to be beneficial to many patients. Many studies over the past 15 years have demonstrated that β-blockers such as metoprolol, bisoprolol, and carvedilol are effective in reducing morbidity and mortality in many CHF patients, as compared to a placebo treatment (Shin and Johnson 187). However, it is important to note that patients experience variable responses to the drugs, and not all β-blockers are beneficial. In fact, approximately 25% of patients must stop β-blocker therapy as a result of drug intolerance. This is likely in part due to several genetic polymorphisms in the β1 and β2 receptors (Shin and Johnson 187). Another significant shortcoming of β-blocker therapy is that it requires careful dose titration, and during this lengthy process patient health may significantly worsen (Black and Fitzgerald 4151).

There are three classes of β-blockers in clinical use. First generation blockers, such as propanolol, are non-selective and block β1 and β2 receptors with equal affinity. Second generation antagonists, such as metoprolol and bisoprolol, are β1-selective and thus have very little antagonistic effect on β2-ARs. Third generation blockers, such as carvedilol, block β1 and β2 ARs with equal affinity and have other ancillary properties such as α-AR blocking and vasodilation (Santwani, Dec, and Narula 246-247). Second and third generation blockers are most commonly used in clinical treatment of CHF.

Second-generation β-antagonists function by reducing chronic β1-AR activation and the subsequent increases in cAMP production and PKA activation (Post, Hammond, and Insel 352). This helps to restore β-AR responsiveness in two ways. First, since GRK can only act on agonist-occupied receptors, antagonist binding diminishes GRK-mediated downregulation of β1-ARs (Satwani, Dec, and Narula 247). Furthermore, these antagonists reverse the associated Gαs to Gαi
coupling transition that occurs in PKA phosphorylated β2-ARs, by decreasing PKA activation. This was demonstrated by a study conducted in pigs with CHF, which indicated that when treated with bisoprolol, significant reduction in the mRNA levels and expression of Gαi trimeric proteins could be observed. Years later, this reduction in Gαi expression upon β-antagonist treatment was also demonstrated in human patients with CHF (Post, Hammond, and Insel 352). This effect is beneficial to patients because the enhanced β-AR-Gαi coupling associated with CHF has a negative inotropic response, which essentially aggravates the disease. Therefore, β1-selective blockers are therapeutic because they increase β1-AR numbers by preventing GRK activity and promote a positive inotropic response by re-coupling β2 receptors with Gαs (Post, Hammond, and Insel 352). This allows both cardiac output and patient health to increase.

Third generation β-blockers function by inhibiting GRKs and recoupling desensitized β-ARs in order to improve sympathetic signalling efficiency. Unlike second-generation compounds, these antagonists do not increase the numbers of β1-ARs in cardiomyocytes (Santwani, Dec, and Narula 246-247). Furthermore, these compounds have ancillary vasodilatory actions, which protect the damaged ventricles by decreasing the blood pressure and thus the workload. In patients with CHF, administration of carvedilol is associated with increased left-ventricular ejection fraction, and decreased mortality and hospitalization rates (figure 10) (Bristow 35).
Recently, there has been increased interest in the therapeutic value of ß2-selective blockers. It has been determined that ß2-overexpression in transgenic mice leads to myocardial damage under hypertensive conditions (Black and Fitzgerald 4155). In addition, it is well established that adrenergic overstimulation leads to increased activation of Gαi proteins, which has a negative inotropic effect thereby accelerating the progression of the disease. Therefore, selective blockade of the increased ß2-mediated Gαi action may be beneficial to patients with CHF (Black and Fitzgerald 4156). However, ß2-antagonists remain uncommon in clinical practice.

**G-Protein Receptor Kinase Inhibition Therapy in CHF**

Current research is focusing on inhibiting GRK activity as a possible therapeutic measure for patients with CHF. GRK2 inhibition would prevent ß-AR desensitization and downregulation. This would help to restore the positive inotropic response to adrenergic signalling, thereby attenuating the body’s perceived need for excessive catecholamine release (Dorn 458). GRK2 inhibition through transgenic expression of a peptide inhibitor improved ventricular function in both in vivo models of rat and rabbit myocardial infarction and in vitro models of human and rat failing cardiomyocytes. Moreover, the therapeutic value of GRK inhibition was further investigated in mouse cardiomyocyte GRK2 knockout models. When the GRK2 gene was ablated before experimentally-induced myocardial infarction, this allowed increased ß-AR signalling responsiveness and protected against ventricular remodelling, as compared to GRK2 wild-type mice with induced myocardial infarction (Dorn 458). When the GRK2 gene was deleted 10 days after experimentally-induced myocardial infarction, ventricular performance increased, survival increased and ventricular remodelling decreased, as compared to GRK2 wild-type mice with heart failure (Dorn 458).
The results from the study detailed above appear to conflict with an experiment where isoprotenol (β-agonist) was chronically administered to GRK knockouts in order to induce heart failure. Compared to GRK wild-type mice, the GRK2 knockouts experienced increased ventricular remodelling and more rapid progression of the disease upon chronic isoprotenol stimulation (Dorn 458). The clinical findings of these two studies appear inconsistent; however, this may be explained by an important difference between these experimental systems. In the induced myocardial infarction model, as ventricular function increases due to improved β-AR responsiveness there is a negative feedback effect on catecholamine release, leading to normalization of catecholamine signalling levels (Dorn 458). In the isoprotenol model, adrenergic stimulation remains constitutively high, regardless of ventricular function. This overstimulation leads to ventricular cell death and deterioration of health. These two studies illuminate the therapeutic potential for GRK-inhibitors to restore β-AR responsiveness and the key role of GRKs in protecting cardiomyocytes from damage by unrelenting overstimulation (Dorn 458).

**Future Directions**

Despite extensive research over past decades, cardiovascular disease remains the number one cause of death in the developed world (Kumar et al. 380). Future research is focusing on the effect of individual variation in treatment efficacy. Genetic polymorphisms have been shown to impact the therapeutic success of many drugs, most notably β-blocker treatment. As a result, more studies are needed to predict how these polymorphisms will affect patient responses to treatment (Ahles and Engelhardt 188). A more personalized approach to CHF management and individualized drug selection will hopefully reduce patient mortality.


