Turning Basic Research into Clinical Success

Beta-Adrenergic Receptors, from Their Discovery and Characterization through Their Manipulation to Beneficial Clinical Application

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Abstract

β-Adrenergic receptors (β-AR) are central to the overall regulation of cardiac function. From the first proposed receptor/transmitter concept to the latest clinical β-blocker trials β-AR have been shown to play an important role in cardiac disease and heart failure in particular. This study provides a historical perspective, reviews the latest discoveries and beliefs, and discusses the current clinical practices of β-AR and their modulation with their associated guanine-nucleotide regulatory protein/adenylylcyclasesignal transduction pathways.

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Introduction

β-Adrenergic receptors (β-AR) and their associated guanine nucleotide regulatory protein (G protein)/adenylyl cyclase (AC) signal transduction pathways are central to the overall regulation of cardiac function. In particular, β-AR stimulation is a primary control point for modulation of heart rate and myocardial contractility. However, β-AR signaling pathways undergo a number of adaptive and potentially maladaptive regulatory changes as a consequence of heart failure [1, 2]. This should not be surprising given that one of the best correlative makers for the degree and prognosis of chronic heart failure is plasma norepinephrine [3], an endogenous ligand for adrenergic receptors.

The human heart expresses two broad classes of adrenergic receptors, the α-adrenergic and the β-adrenergic families. Each of these families can be further subdivided into subclasses, the α_1- and the α_2-AR family and the β-AR family, with three well-defined subtypes. In this review, we will focus on the β-AR family, its signaling components in the context of cardiac function, and the therapeutic potential role of β-AR blockade in affecting the natural history of heart failure.

Historical Perspective

John Newport Langley (1852–1925), a physiologist at Cambridge in the early 1900s, first proposed the challenging concept of specific receptors that bind drugs or transmitter substances onto the cell, thereby either initiating biological effects or inhibiting cellular functions within the cell itself [4, 5]. Around the same time it was

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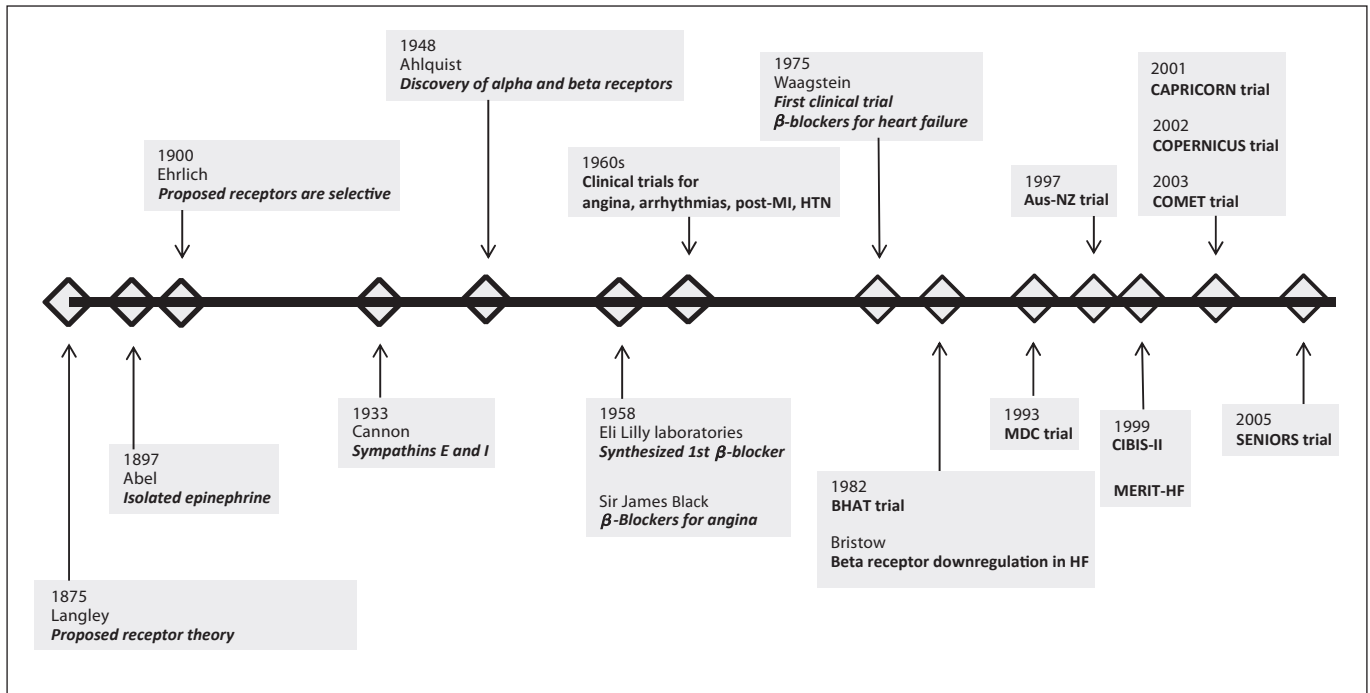Tel. +1 801 581 7715, E-Mail Edward.Gilbert@hsc.utah.edu

Fig. 1. Historical timeline of the discovery and characteristics to clinical applications of β-ARs. Please see text for further descriptions of listed trials.

postulated by Paul Ehrlich (1854–1915) that these receptors were selective. Ehrlich determined the preferential distribution of lead and dyes in different body tissues and then modified his theory to correspond with the body's immune response which later inspired his famous 'side-chain theory'. Ehrlich received the Nobel Prize for Medicine in 1908 [6]. In 1897, John Jacob Abel (1857–1938), who founded and chaired the first department of pharmacology in the USA at the University of Michigan and then went on to chair the pharmacology department at Johns Hopkins University, successfully isolated epinephrine. In 1933, W. B. Cannon, while studying the sympathetic nervous system in his 'fight-or-flight theory', concluded that there were two chemical transmitters that he called sympathins; sympathin E for excitatory responses and sympathin I for inhibitory pathways [7]. However, it was not until 1948, in his historical manuscript published in the *American Journal of Physiology*, where Raymond Ahlquist described the actions of adrenaline on two distinct receptors called alpha and beta and established the idea of a single sympathetic mediator producing both excitatory and inhibitory responses that the receptor theory was finally

embraced fully by the scientific community [8]. Naturally, following the discovery of the beta receptors, the first β-blocker, dichloroisoproterenol, was synthesized by Eli Lilly Laboratories in 1958 [9, 10]. Shortly thereafter, Sir James W. Black found the first clinical use of β-blockers for the management of angina pectoris with propranolol [11]. His contribution was considered to be one of the most important to clinical medicine and as such he received the Nobel Prize for his work. β-Blockers quickly gained popularity for their cardiac clinical uses with clinical trials studying the use of β-blockers for angina pectoris, hypertension, arrhythmias and post myocardial infarct. For example, the Beta-Blocker Heart Attack Trial (BHAT) was a randomized trial showing the benefit of propranolol in patients with acute myocardial infarcts [12]. The first clinical trial proposing the use of β-blockers for the treatment of heart failure was documented in 1975 in the *British Heart Journal* by F. Waagstein [13]. Afterwards, randomized controlled trials for the use of β-blockers in the treatment of heart failure began in the 1980's and gained clinical relevance in the 1990's (fig. 1).

β-AR Biology

To date, three subtypes of β-ARs have been identified at a molecular level, the β_1-, β_2- and β_3-AR [14–16]. The β_3-AR subtype has been associated primarily with metabolic regulation; however, there is some indication that unlike the β_1- and β_2-AR subtypes, it may inhibit myocardial contractility [17]. A fourth β-AR subtype has been proposed but will not be discussed within the context of this review.

The nonfailing human heart expresses a mixed population of β-ARs, with approximately 80% of the expressed receptors being of the β_1-AR subtype and approximately 20% of the β_2-AR subtype [1, 18]. However, in the failing human heart, the β_1-AR undergoes subtype selective downregulation at both the levels of mRNA and protein such that the β_1-:β_2-AR subtype proportions become approximately equal [19]. Although there are some differences in the gene expression patterns examined to date based on the etiology of heart failure (table 1), overall, the extent of β_1-AR downregulation correlates well with the severity of heart disease. The expression of myocardial β_1-ARs also correlates well with systemic or coronary sinus plasma norepinephrine concentrations. Many of the changes to the β-AR pathways associated with heart failure are also produced by the normal process of aging. There is also a good correlation between β_1-AR density and age; the older the individual, the lower the β_1-AR density [20]. Aging, like heart failure, does not appear to have a significant effect on β_2-AR density.

As stated above, the β_2-AR may be uncoupled from its signaling pathway but it is not downregulated in the failing human heart. There are a number of potential explanations for this. First, the endogenous catecholamine, norepinephrine, is approximately 10–30-fold more selective for the β_1- than the β_2-AR. Second, the β_1-AR appears to be localized to the synaptic cleft, thus it is more than likely exposed to higher concentrations of norepinephrine. Because of the relative preservation of β_2-AR expression in the failing human heart, it has been the focus of therapeutic interest both from the development of β_2-AR-selective pharmacological agents, both agonist and antagonist, and from a gene-therapy approach [21] of increased cardiac contractility. However, there is now substantial evidence to support the use of the β_1-AR-selective antagonists such as metoprolol, as well as some nonselective β-AR antagonists, in the treatment of chronic congestive heart failure. These issues are discussed in detail below.

Table 1. Changes in the β-AR/G protein/adenylyl cyclase signal transduction pathways associated with myocardial failure

Abnormality	Extent of effect (0–3+)	Type of heart disease
β_1-AR downregulation	++	IDC
	+	ISCH
β_1-AR uncoupling	–	IDC
	+	ISCH
β_2-AR uncoupling	+	IDC
	++	ISCH
Decrease in Gαs activity	+/–	IDC, ISCH
Increase in Gαi activity	++	IDC, ISCH
Increased βARK activity	++	
Decrease in AC activity	+	IDC (RV only)
	–	ISCH

IDC = Idiopathic dilated cardiomyopathy; ISCH = ischemic heart disease; RV = right ventricle; βARK = β-AR kinase. Modified from Bristow et al. [18].

In the human heart, the β_1- and β_2-ARs are coupled to the stimulatory G protein, Gs (fig. 2). The presence of β-AR agonist causes a conformational change in the receptor protein affecting the dissociation of the heterotrimeric G protein into its subunit components, Gαs and βγ, both of which can act as signaling entities. A primary effect of the β-AR is stimulation of adenylyl cyclases, multiple subtypes of which are expressed in human cardiac tissues. Adenylyl cyclases catalyze the conversion of ATP to the second messenger, cAMP, which in turn binds to the regulatory subunits of protein kinase A (PK-A) causing the release of active catalytic PK-A subunits. PK-A phosphorylates serine and threonine residues on a number of proteins thereby affecting a spectrum of cellular processes ranging from contractility to global gene expression patterns. Important PK-A targets that acutely modulate myocardial contractility are protein β-ARs themselves, L-type Ca^{++} channels, the sarcoplasmic reticular Ca^{++}/ATPase inhibitory protein, phospholamban and troponin I.

In addition to activating PK-A, β-AR stimulation activates members of the G protein receptor kinase family, including βARK1 and βARK2. βARKs phosphorylate β-ARs in an agonist-occupancy dependent manner. When β-ARs are stimulated by agonist, the dissociated G protein βγ subunits interact with βARKs via their pleckstrin-homology domains, bringing the kinases within close proximity of the transmembrane β-ARs (fig. 2). Phosphorylation of β-ARs by βARKs reduces the affinity of

Fig. 2. In cardiomyocytes, β-ARs (β1-, β2-ARs) are coupled to the stimulatory G protein, Gs, which in turn activates AC causing the production of cAMP from ATP. The second messenger, cAMP, activates PK-A which phosphorylates a number of protein targets including β-ARs, transcription factors, L-type calcium channels, phospholamban (PLB) and elements of the contractile apparatus. (Other abbreviations: SR = sarcoplasmic reticulum; PK-C = protein kinase C; MAP-K = mitogen-activated protein kinases, PIP_2 = phosphoinositide triphosphate; DAG = diacylglycerol).
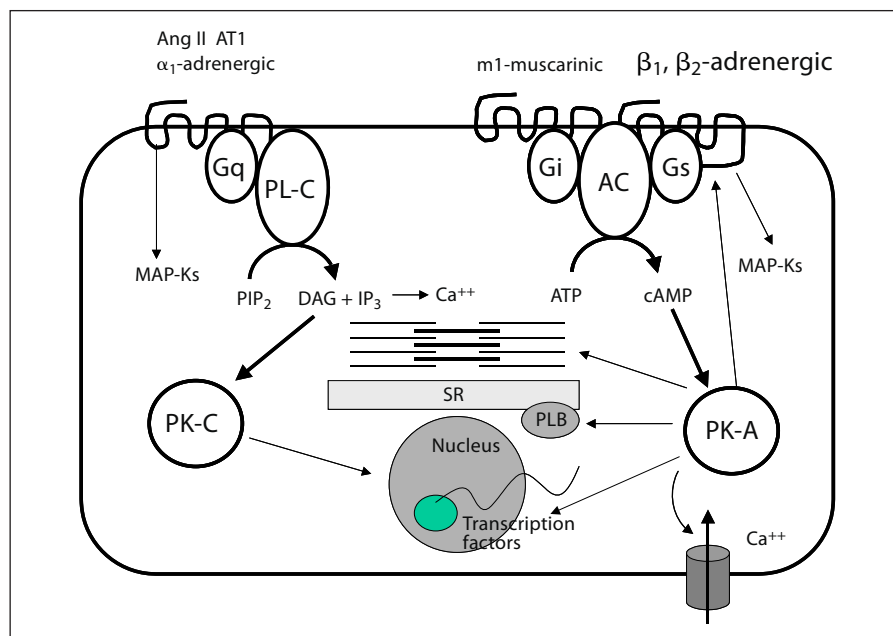
interaction of the receptor for the stimulatory G protein, Gs, and apparently increases the affinity of interaction for the inhibitory G protein, Gi [22]. Furthermore, phosphorylation leads to the interaction of β-ARs with β-arrestin adaptor proteins which facilitate the internalization of receptors into clathrin-coated pits and endosomic vesicles. These processes are involved in receptor resensitization/reexpression and in receptor downregulation. βARKs are upregulated in heart failure and thus contribute to the decrease in β-AR signal transduction [23].

As stated above, the $β_1$- and $β_2$-AR signaling pathways are both coupled to stimulation adenylyl cyclases. However, the coupling efficiency of the two receptor subtypes is markedly different. In homogenates of human ventricular myocardium, stimulation of the $β_2$-AR is several-fold more efficiently coupled to the production of cAMP than is the $β_1$-AR [2, 24]. Regardless, there appears to be a more direct relationship between total β-AR density and myocardial contractility; that is to say, $β_2$-ARs do not appear to stimulate contractility more efficiently than $β_1$-ARs. This finding argues strongly in favor of compartmentalization of intracellular cAMP pools. In this context, in addition to apparent regional differences the localization of $β_1$- and $β_2$-AR subtypes, it is now well established that the intracellular localization of PK-A is highly specific based on its interaction with PK-A anchoring proteins, or AKAPs [25]. Thus, β-AR subtypes and distal components of their signaling pathways appear to be discretely organized [26].

The β-AR stimulation can also lead to the downstream activation of members of the MAP kinase [27, 28], jun kinase and p38 kinase families [29], no doubt in a subtype-selective manner. These findings have significant implications for modulation of mitogenic and proapoptotic actions of β-AR pathways. In particular, it is becoming increasingly clear that the $β_1$-AR and $β_2$-AR signaling pathways can be quite distinct [30]. For example, the $β_1$-AR appears to be coupled primarily to the Gs/adenylyl cyclase/PK-A pathway and to modulation of L-type Ca^{++} channels and phospholamban. In marked contrast, the $β_2$-AR is not only coupled to Gs/adenylyl cyclase/PK-A, but, importantly, also to the Gi pathway, and to 'G protein-independent' functions such as regulation of the Na^+/H^+ exchanger.

One of the more important ramifications of differential coupling of β-AR subtypes to distinct signaling pathways, and in particular lack of $β_1$-AR coupling to the Gi, is the observation in cardiomyocytes that stimulation of the $β_1$-AR appears to be proapoptotic whereas stimulation of the $β_2$-AR is not [31], an observation that has been extended to transgenic mouse models. Milano et al. [32] demonstrated previously that cardiac-directed overexpression of the human $β_2$-AR in a transgenic mouse produced a significant increase in cardiac performance with limited, if any, histopathological consequences. Similarly, overexpression of a mini-peptide inhibitor of βARK produced a hyperdynamic mouse with no apparent histopathology [33]. In contrast, authors have described a trans-

genic mouse overexpressing the human β_1-AR in ventricular myocardium [34, 35]. The β_1-AR mouse, unlike the β_2-AR overexpressing mouse, demonstrates a time-dependent reduction in myocardial contractility as well as marked myocyte hypertrophy, myofibrillar disarray and replacement fibrosis. Interestingly, the β_1-AR mouse demonstrates upregulation of proapoptotic proteins as well as direct evidence of apoptosis. In this regard, the β_1-AR mouse is more similar to transgenic mice overexpressing the stimulatory G protein, Gαs [36], than it is to the β_2-AR mouse. Although the effect of β-AR blockade has yet to be examined in β_1-AR overexpressing mice, it is clear that β-blockade (propranolol) can prevent the myocardial damage produced by overexpression of Gαs [37]. Therefore, attenuation of Gαs signaling, and presumably β_1-AR signaling, by β-blockade, recapitulates the positive clinical experience of the use of β-blockade to treat chronic congestive heart failure.

Consequences of Adrenergic Activation in Heart Failure

In heart failure, sympathetic drive is selectively activated in several organ systems including the kidney, skeletal muscle and the heart. Increases in cardiac adrenergic activity result in marked increases in interstitial concentrations of norepinephrine within the failing human heart [38]. As discussed above, one consequence of the exposure of cardiomyocytes to high concentrations of norepinephrine is an alteration in cardiac adrenergic receptor pharmacology [39]. These changes decrease the sensitivity of cardiomyocytes to both endogenous and exogenous catecholamines. For example, there is a downward and rightward shift in dobutamine dose response curves in patients with heart failure compared to subjects with normal left ventricular function [40]. Maximal exercise workload as measured by peak VO$_2$ also falls in proportion to the loss of cardiac β-receptors [41].

Cardiomyocyte growth is modulated in part by β_1-, β_2- and α_1-adrenergic receptors. Increases in signal transduction through these receptor pathways in the failing heart thus can contribute to pathological remodeling. Activation of these three receptors also results in increases in inotropic and chronotropic response. Myocardial energetics are adversely affected by these changes. Additionally, cardiac adrenergic receptor activation may promote dysrhythmias.

Another consequence of increased exposure of cardiomyocytes to increased concentrations of norepinephrine is myocyte toxicity. In tissue culture systems there is both a time- and concentration-dependent relationship between norepinephrine exposure and cardiomyocyte death [42]. The toxic effects of norepinephrine incubation can be partially blocked with the addition of a β-adrenergic receptor antagonist and completely prevented with the addition of both a β- and α-blocker to the culture media. Apoptosis of cardiomyocytes can be induced in tissue culture by norepinephrine. This effect appears to be mediated primarily through the β_1-AR. Clinical examples of toxic effects of increased cardiac adrenergic drive include the observation of significant left ventricular dysfunction after catastrophic brain injury. However, the most compelling clinical support for the cardiotoxic role of cardiac norepinephrine are the beneficial effects that occur with the use of β-adrenergic receptor agonists in patients with heart failure.

Pharmacology of β-AR Antagonists

β-AR antagonists (or β-blockers) are a heterogeneous group of pharmacologic agents. Some of the pharmacologic actions that β-blockers may possess include β_1- and β_2-AR antagonism, intrinsic sympathomimetic activity (ISA), inverse agonism and guanine nucleotide-modulatable binding. β-Blockers may also possess additional properties such as vasodilatation via α_1-AR antagonism. In addition, these agents have substantially different pharmacokinetics. The potential clinical importance of these differences will be discussed below. A summary of the pharmacologic profile of β-blockers that have been evaluated in controlled clinical trials of heart failure is given in table 2.

Nonselective versus Selective β-Blockers
The first group of β-blockers to be developed possesses equal affinities for the β_1- and β_2-AR and no other pharmacologic properties. Examples of these 'first generation' β-blockers include propranolol and timolol. Selective β-blockers generally possess a greater affinity for the β_1-AR. Examples of these 'second generation' agents include metoprolol and bisoprolol. While these agents were developed in the hope that they would be 'cardioselective', such specific target organ actions have not been definitively demonstrated.

Intrinsic Sympathomimetic Activity
β-Blockers with ISA possess partial agonist activity. Administration of these agents results in a mild positive

Table 2. Pharmacological effects of β-blockers studied in heart failure

Agent	Selectivity	ISA	Inverse agonism	GNMB	α_1-AR blockade	Comments
Propranolol	non	no	yes	no	no	not tolerated, no long-term data
Metoprolol	β_1-AR[1]	no	yes	no	no	improved LV function, mortality benefit
Bisoprolol	β_1-AR	no	yes	no	no	mortality benefit
Nebivolol	β_1-AR	no	yes	no	no	improved LV function
Xamoterol	non	yes	yes	no	no	improved exercise, increased mortality
Celiprolol	β_1-AR	yes[2]	yes	no	no	no effect on LV function or mortality
Carvedilol	non[3]	no	yes	yes	yes	improved LV function, mortality benefit
Bucindolol	non	no	no	yes	yes[4]	improved LV function, morbidity benefit

GNMB = Guanine nucleotide-modulatable binding.
[1] At high doses metoprolol may lose its β_1-selectivity.
[2] Celiprolol is a β_2-agonist.
[3] Carvedilol is partially β_1-selective, but is nonselective at doses ≥6.25 mg.
[4] Bucindolol is a much less potent α_1-antagonist than carvedilol.

agonist response; however, they also antagonize the agonist effects of full agonists such as norepinephrine. Examples of these agents include xamoterol and celiprolol. When these agents were developed it was hoped that ISA would improve the tolerability of β-blockers. However, these agents appear to have a neutral or even harmful effect on the natural history of heart failure and are currently not recommended.

Inverse Agonism

Inverse agonism is the ability of an antagonist to inactivate active-state receptors. This occurs even in the absence of occupancy of the receptor by an agonist (fig. 3). Compared with other β-blockers, bucindolol appears to possess the least amount of inverse agonism. This has measureable clinical consequences. Data from 24-hour ambulatory electrocardiograms in subjects with heart failure demonstrate that bucindolol reduces mean and peak heart rate but does not reduce minimum heart rate. In contrast, β-blockers that possess inverse agonism such as metoprolol and carvedilol reduce minimum, mean and peak heart rate.

Guanine Nucleotide-Modulatable Binding

Carvedilol and bucindolol possess the property of guanine nucleotide-modulatable binding. These agents result in a rightward shift of GppNHp competitive-binding curves in heart membrane preparations without possessing detectable agonist-like activity as detected by more conventional means [43].
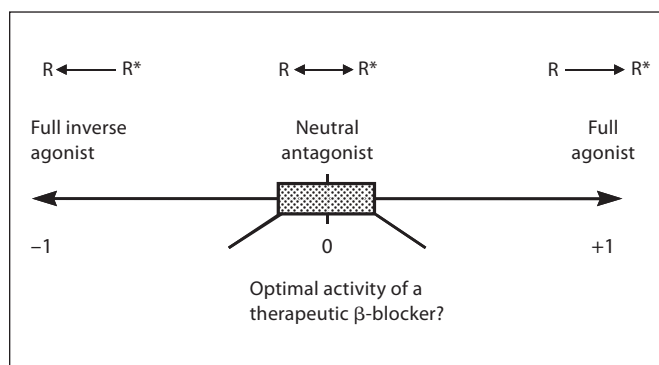

Fig. 3. Agents that bind to β-ARs can range in activity from full agonists, e.g. (–)isoproterenol, to full antagonists or 'inverse-agonists'. Full agonists drive receptors to their active (R*) G protein-coupled state. Neutral antagonists have no effect on the normal distribution of R and R* receptors. Inverse agonists actively drive receptors into the (R) uncoupled state.

Vasodilator Activity

Several β-blockers possess vasodilator activity via α_1-AR antagonism. Examples of these 'third generation' β-blockers include labetalol, carvedilol, bucindolol and nebivolol. Initially, vasodilator properties were incorporated with β-blockade to increase the antihypertensive actions of these compounds. Theoretically, the addition of vasodilator activity may increase the 'tolerability' of nonselective β-blockers in heart failure.

β-blockers may also possess pharmacologic properties that are independent of their adrenergic effects. For example, high concentrations of many β-blockers produce quinidine-like (or 'membrane stabilizing') effects in model systems. It is doubtful that this action is significant at the usual clinical doses of these agents. Carvedilol and one of its metabolites have significant antioxidant properties. These properties have been demonstrated in model systems and in one study of normal human subjects [44]. It is unknown if these antioxidant effects contribute to the clinical benefits that occur with carvedilol administration.

Pharmacokinetic Properties

There are significant differences in the pharmacological half-lives between β-blockers. Metoprolol, bucindolol and carvedilol must be administered twice daily for the treatment of heart failure. Bisoprolol and metoprolol succinate CR can be given once daily. Metoprolol, bucindolol, carvedilol and nebivolol are all highly lipophilic compounds that are extensively metabolized and cleared by the liver. Because of first-pass hepatic metabolism, these agents have a low bioavailability. Liver dysfunction, as observed with right heart failure, will increase the relative potency of these agents; therefore, their doses must be decreased. Bisoprolol is less lipophilic and is cleared by both hepatic and renal routes. Either renal or hepatic dysfunction necessitates a reduction in dose with bisoprolol.

Effects of β-Blocker Therapy in Heart Failure

Tolerability of β-Blockers

Therapy of chronic heart failure with β-blockers has distinct acute (pharmacologic) and chronic (biologic) effects. The pharmacologic effects are the consequence of the acute changes in function that occur with withdrawal of sympathetic agonism and include a decrease in heart rate and contractile state. These detrimental effects can be tolerated only by initiating therapy with very low doses of β-blocker and slow up-titration of the dose over several weeks. There is significant variation in the severity of myocardial depression with different generations of β-blockers. Nonselective β-blockers such as propranolol reduce the contractile state and increase systemic resistance which profoundly decreases cardiac output [45]. As a consequence, the intolerance to initiation of propranolol is high (<20%) and these agents have not been successfully used in long-term placebo-controlled trials. The ini-

tiation of β_1-AR-selective β-blockers such as metoprolol and bisoprolol is much better tolerated by heart failure patients. This appears to occur because unblocked β_2-ARs can support cardiac function either directly or indirectly (by β_2-AR-mediated facilitation of sympathetic norepinephrine release). In addition, peripheral β_2-ARs can mediate vasodilatation. Thus, the overall detrimental effect upon organ perfusion is less severe than that observed with first generation compounds. β_1-AR-selective β-blockers have been utilized successfully in prospective trials in heart failure with a tolerability >80%. The third generation β-blockers possess vasodilator properties which counteract the negative properties of adrenergic withdrawal. This permits a more comprehensive blockade of cardiac adrenergic pathways with high tolerability ($\geq$90% in clinical trials of carvedilol and bucindolol).

Effects of Long-Term Treatment

Phase II trials of β-blockers, typically lasting 3–6 months, demonstrated that β-blocker treatment in heart failure results in improvements in right heart hemodynamics, reversal of ventricular remodeling (as evidenced by reductions in left ventricular volumes, increases in right and left ventricular ejection fraction, decreases in left ventricular mass and favorable effects upon left ventricular geometry), and improvements in heart failure symptoms [46]. Prospective, randomized, placebo-controlled outcome trials of carvedilol, bisoprolol and metoprolol succinate in heart failure have shown significant reductions in mortality and hospitalizations, as well as an improvement in patient well-being [47–50]. Premature termination of these trials because of the superior efficacy of these agents compared to placebo limited the duration of post-trial follow-up to less than 18 months [US Carvedilol Trial 6 months (12 months in the mild heart failure group); CIBIS II 1.3 years; MERIT-HF 12 months; COPERNICUS 10.4 months]. However, a 12-year follow-up of evaluating the long-term use of carvedilol demonstrated sustained improvements in left ventricular remodeling and symptoms. Long-term survival was good, particularly in patients with a nonischemic etiology for their dilated cardiomyopathy [51]. The clinical evidence for the long-term benefit of β-blocker therapy is so strong that it is now recommended therapy in all patients with Class II or III heart failure symptoms who do not have specific contraindications.

To date, three specific β-blockers have been shown to be effective in the treatment of heart failure: bisoprolol, sustained release metoprolol succinate and carvedilol. The first placebo-controlled multicentered trial, Meto-

prolol in Dilated Cardiomyopathy trial, studied metoprolol tartrate (100–150 mg daily) which showed a trend toward a reduction in morbidity of patients with idiopathic dilated cardiomyopathy [52]. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) used a more effective formula with metoprolol succinate and showed a significant relative risk reduction in mortality in patients with New York Heart Association (NYHA) functional class II–IV [49, 53]. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) demonstrated bisoprolol improved all-cause mortality by 32%, sudden cardiac death by 45% and reduced heart failure hospitalization by 30% [48]. The Australian New Zealand Heart Failure Research Collaborative Group (ANZ-HeFT) demonstrated significant improvement in left ventricular function and a significant reduction of left ventricular end diastolic volume index in a carvedilol group at 12 months in patients with NYHA class II or III [54]. Similarly, the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial showed benefit in patients with NYHA class IV and an ejection fraction of <25% with 38% mortality risk reduction at 12 months [55]. The CAPRICORN trial focused on patients postinfarct with LV dysfunction of <40% and incorporated current recommended therapy with the treatment of ACE inhibitors. The authors demonstrated a 23% further reduction of mortality with patients also receiving carvedilol 25 mg twice daily [56]. A head-to-head study of the Carvedilol or Metoprolol European Trial (COMET) compared a carvedilol 25 mg twice daily dosing to a metoprolol tartrate 50 mg twice daily dosing. The results showed a 33% reduction in all-cause mortality in patients using carvedilol [57]. The SENIORS trial focused on elderly patients (>70 years old) with heart failure (ejection fractions <35%) and demonstrated that nebivolol is an effective and well-tolerated treatment in this selected patient group [58].

Conclusions

From the discovery and characterization to their manipulation in clinical practices, β-ARs have been shown to play an important role in cardiac disease, and heart failure in particular. Their alterations result in pathway desensitization and (perhaps of greater importance) result in harmful effects upon the myocardium that lead to pathologic ventricular remodeling and heart failure progression. Over the last decade, the consensus of many large multicenter trials have shown that therapy with β_1-selective and third-generation β-blockers results in significant improvements in cardiac function and clinical outcomes. To date, current guidelines recommend the use of bisoprolol, carvedilol and metoprolol succinate for the treatment of heart failure unless proven to be intolerant.

References

1 Bristow MR, Ginsburg R, Umans V, et al: Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. Circ Res 1986;59:297–309.

2 Bristow MR, Hershberger RE, Port JD, Minobe W, Rasmussen R: Beta 1- and beta 2-adrenergic receptor-mediated adenylate cyclase stimulation in nonfailing and failing human ventricular myocardium. Mol Pharmacol 1989;35:295–303.

3 Cohn JN, Levine TB, Olivari MT, et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. New Engl J Med 1984;311:819–823.

4 Langley JN: Preliminary notice of experiments on the physiological action of jaborandi. Br Med J 1875;1:241–242.

5 Maehle AH: 'Receptive substances': John Newport Langley (1852–1925) and his path to a receptor theory of drug action. Med Hist 2004;48:153–174.

6 Limbird LE: The receptor concept: a continuing evolution. Mol Interv 2004;4:326–336.

7 von Euler US: Hormones of the sympathetic nervous system and the adrenal medulla. Br Med J 1951;1:105–108.

8 Ahlquist RP: A study of the adrenotropic receptors. Am J Physiol 1948;153:586–600.

9 Frishman WH: Fifty years of beta-adrenergic blockade: a golden era in clinical medicine and molecular pharmacology. Am J Med 2008;121:933–934.

10 Bylund DB: Alpha- and beta-adrenergic receptors: Ahlquist's landmark hypothesis of a single mediator with two receptors. Am J Physiol Endocrinol Metab 2007;293:E1479–1481.

11 Stapleton MP: Sir James Black and propranolol: the role of the basic sciences in the history of cardiovascular pharmacology. Tex Heart Inst J 1997;24:336–342.

12 Goldstein S: The beta blocker heart attack trial: at last, an effective medical therapy to prevent death from coronary heart disease. Henry Ford Hosp Med J 1982;30:173–174.

13 Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I: Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 1975;37:1022–1036.

14 Frielle T, Collins S, Daniel KW, Caron MG, Lefkowitz RJ, Kobilka BK: Cloning of the cDNA for the human beta 1-adrenergic receptor. Proc Natl Acad Sci USA 1987;84: 7920–7924.

15 Kobilka BK, Dixon RA, Frielle T, et al: cDNA for the human beta 2-adrenergic receptor: a protein with multiple membrane-spanning domains and encoded by a gene whose chromosomal location is shared with that of the receptor for platelet-derived growth factor. Proc Natl Acad Sci USA 1987;84:46–50.

16 Emorine LJ, Marullo S, Briend-Sutren MM, et al: Molecular characterization of the human beta 3-adrenergic receptor. Science 1989;245:1118–1121.

17 Gauthier C, Tavernier G, Charpentier F, Langin D, Le Marec H: Functional beta3-adrenoceptor in the human heart. J Clin Invest 1996;98:556–562.

18 Bristow MR, Anderson FL, Port JD, et al: Differences in beta-adrenergic neuroeffector mechanisms in ischemic versus idiopathic dilated cardiomyopathy. Circulation 1991; 84:1024–1039.

19 Bristow MR, Hershberger RE, Port JD, et al: Beta-adrenergic pathways in nonfailing and failing human ventricular myocardium. Circulation 1990;82:I12–25.

20 White M, Roden R, Minobe W, et al: Age-related changes in beta-adrenergic neuroeffector systems in the human heart. Circulation 1994;90:1225–1238.

21 Drazner MH, Peppel KC, Dyer S, Grant AO, Koch WJ, Lefkowitz RJ: Potentiation of beta-adrenergic signaling by adenoviral-mediated gene transfer in adult rabbit ventricular myocytes. J Clin Invest 1997;99:288–296.

22 Daaka Y, Luttrell LM, Lefkowitz RJ: Switching of the coupling of the beta2-adrenergic receptor to different G proteins by protein kinase A. Nature 1997;390:88–91.

23 Ungerer M, Bohm M, Elce JS, Erdmann E, Lohse MJ: Altered expression of beta-adrenergic receptor kinase and beta 1-adrenergic receptors in the failing human heart. Circulation 1993;87:454–463.

24 Levy FO, Zhu X, Kaumann AJ, Birnbaumer L: Efficacy of beta 1-adrenergic receptors is lower than that of beta 2-adrenergic receptors. Proc Natl Acad Sci USA 1993;90:10798–10802.

25 Colledge M, Scott JD: AKAPs: from structure to function. Trends Cell Biol 1999;9:216–221.

26 Zhou YY, Cheng H, Bogdanov KY, et al: Localized cAMP-dependent signaling mediates beta 2-adrenergic modulation of cardiac excitation-contraction coupling. Am J Physiol 1997;273:H1611–1618.

27 Bogoyevitch MA, Andersson MB, Gillespie-Brown J, et al: Adrenergic receptor stimulation of the mitogen-activated protein kinase cascade and cardiac hypertrophy. Biochem J 1996;314:115–121.

28 Luttrell LM, Ferguson SS, Daaka Y, et al: Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. Science 1999;283:655–661.

29 Williams NG, Zhong H, Minneman KP: Differential coupling of alpha1-, alpha2-, and beta-adrenergic receptors to mitogen-activated protein kinase pathways and differentiation in transfected PC12 cells. J Biol Chem 1998;273:24624–24632.

30 Steinberg SF: The molecular basis for distinct beta-adrenergic receptor subtype actions in cardiomyocytes. Circ Res 1999;85:1101–1111.

31 Communal C, Singh K, Sawyer DB, Colucci WS: Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. Circulation 1999;100:2210–2212.

32 Milano CA, Allen LF, Rockman HA, et al: Enhanced myocardial function in transgenic mice overexpressing the beta 2-adrenergic receptor. Science 1994;264:582–586.

33 Koch WJ, Rockman HA, Samama P, et al: Cardiac function in mice overexpressing the beta-adrenergic receptor kinase or a beta ARK inhibitor. Science 1995;268:1350–1353.

34 Bisognano JD, Weinberger HD, Bohlmeyer TJ, et al: Myocardial-directed overexpression of the human beta(1)-adrenergic receptor in transgenic mice. J Mol Cell Cardiol 2000;32:817–830.

35 Engelhardt S, Hein L, Wiesmann F, Lohse MJ: Progressive hypertrophy and heart failure in beta1-adrenergic receptor transgenic mice. Proc Natl Acad Sci USA 1999;96:7059–7064.

36 Iwase M, Uechi M, Vatner DE, et al: Cardiomyopathy induced by cardiac Gs alpha overexpression. Am J Physiol 1997;272:H585–589.

37 Asai K, Yang GP, Geng YJ, et al: Beta-adrenergic receptor blockade arrests myocyte damage and preserves cardiac function in the transgenic G(salpha) mouse. J Clin Invest 1999;104:551–558.

38 Joseph J, Gilbert EM: The sympathetic nervous system in chronic heart failure. Prog Cardiovasc Dis 1998;41:9–16.

39 Bristow MR, Ginsburg R, Minobe W, et al: Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. New Engl J Med 1982;307:205–211.

40 Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR: Assessment of the beta-adrenergic receptor pathway in the intact failing human heart: progressive receptor down-regulation and subsensitivity to agonist response. Circulation 1986;74:1290–1302.

41 White M, Yanowitz F, Gilbert EM, et al: Role of beta-adrenergic receptor downregulation in the peak exercise response in patients with heart failure due to idiopathic dilated cardiomyopathy. Am J Cardiol 1995;76:1271–1276.

42 Mann DL, Kent RL, Parsons B, Cooper GT: Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992; 85:790–804.

43 Bristow MR, Larrabee P, Minobe W, et al: Receptor pharmacology of carvedilol in the human heart. J Cardiovasc Pharmacol 1992; 19(suppl 1):S68–80.

44 Dandona P, Karne R, Ghanim H, Hamouda W, Aljada A, Magsino CH Jr: Carvedilol inhibits reactive oxygen species generation by leukocytes and oxidative damage to amino acids. Circulation 2000;101:122–124.

45 Talwar KK, Bhargava B, Upasani PT, Verma S, Kamlakar T, Chopra P: Hemodynamic predictors of early intolerance and long-term effects of propranolol in dilated cardiomyopathy. J Card Fail 1996;2:273–277.

46 Lombardi WL, Gilbert EM: Carvedilol in the failing heart. Clin Cardiol 2001;24:757–766.

47 Packer M, Bristow MR, Cohn JN, et al: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. New Engl J Med 1996;334:1349–1355.

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

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

50 Packer M, Coats AJ, Fowler MB, et al: Effect of carvedilol on survival in severe chronic heart failure. New Engl J Med 2001;344:1651–1658.

51 MacGregor JF, Wachter SB, Munger M, Stoddard G, Bristow MR, Gilbert EM: Carvedilol produces sustained long-term benefits: follow-up at 12 years. Congest Heart Fail 2009;15:5–8.

52 Waagstein F, Bristow MR, Swedberg K, et al: Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet 1993;342:1441–1446.

53 Wikstrand J, Hjalmarson A, Waagstein F, et al: Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). J Am Coll Cardiol 2002;40:491–498.

54 Australia/New Zealand Heart Failure Research Collaborative Group: Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet 1997;349:375–380.

55 Wollert KC, Drexler H: Carvedilol prospective randomized cumulative survival (COPERNICUS) trial: carvedilol as the sun and center of the beta-blocker world? Circulation 2002;106:2164–2166.

56 Dargie HJ: Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;357:1385–1390.

57 Poole-Wilson PA, Swedberg K, Cleland JG, et al: Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.

58 Flather MD, Shibata MC, Coats AJ, et al: Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005; 26:215–225.