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Pharmacogenetic Profiling in the Treatment of Heart Disease

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Abstract

Pharmacogenetics is the study of gene-drug interactions. In the post-Human Genome era, and with the realization that personal genotypes differ by millions of bases (gene polymorphisms), the application of genetics to explain inter-individual differences in clinical drug response seems to offer great promise. Here, recent basic and translational developments in pharmacogenetic profiling of β -blocker response in heart failure are reviewed in the context of the possible consequences of such advances on drug development and clinical therapeutics.

Introduction

Six years after completing the draft Human Genome, routine clinical genetic testing for cardiovascular disease is focused mainly upon diagnosing rare familial hypertrophic and dilated cardiomyopathies. Inter-individual genetic variability of ~3–4 million single nucleotide polymorphisms (SNPs) per genome suggests that personal gene variation can impact cardiovascular disease, but identifying specific genetic risk factors and disease modifiers using genome wide association techniques has proven quite challenging(1). On the other hand, delineating specific genetic interactions that affect drug efficacy has born more fruit because polymorphism discovery and evaluation can be based upon a thorough understanding of the biology of drug availability and action. Not with standing well-known limitations of candidate gene approaches, cardiovascular pharmacogenomics research has successfully catalogued a number of relevant gene variants, demonstrated their functional consequences in experimental systems, and reproducibly shown their impact on drug availability or therapeutic effects in clinical studies. Altered β -blocker pharmacodynamics have been described with common genetic polymorphisms of β -adrenergic receptors (β AR) and the G-protein coupled receptor kinase that regulates β AR signaling that modify the effectiveness of β -blockers at their primary drug target. Likewise, altered β -blocker pharmacokinetics have been elucidated for loss-of-function polymorphisms in the major hepatic cytochrome P450 enzyme that inactivates lipophilic β -blockers such as metoprolol. Based on these results, it is reasonable to expect that cardiovascular practice in the coming years will include selection of optimal pharmacotherapeutics directed in some instances by individual genotype. This article provides an overview of our current understanding of the pharmacogenetics of β -adrenergic blocking agents. For another class of cardiovascular drugs for which pharmacogenetic interactions are likely to important, the interested reader is referred to a recent editorial summarizing the current

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state of the art in cytochrome P450 2C19 polymorphisms that impact anti-platelet therapy with clopidogrel versus prasugrel(2).

What are the genetic influences on response to β -blockers?

β -blockers are prescribed to millions of Americans for heart failure, angina, after myocardial infarction, and for hypertension. Except in heart failure, the therapeutic value of β -blockers resides in their ability to decrease cardiac work by lowering heart rate (negative chronotropism) and the force of cardiac contraction (negative inotropism). Depressing myocardial work favorably affects the mismatch between oxygen supply and demand that leads to angina, infarction, and some arrhythmias. Likewise, β -blockers blunt the hyper-adrenergic component of hypertension. In contrast, it would seem that negative inotropism caused by β -blockers would be counter-productive in heart failure, since cardiac output is already insufficient to meet normal physiological demands. Nevertheless, β -blockers are one of only two classes of drugs (the other being angiotensin converting enzyme inhibitors) that prolong life in heart failure (3,4). The clear mortality benefit and associated improvements in ventricular performance(5) that are thought to result from antagonism of β_1 -adrenergic receptor (β_1 AR) mediated cardiotoxicity in the context of pathologically increased systemic and myocardial catecholamines. Since β_2 AR effects in the heart are widely considered to be potentially beneficial, β -blocker treatment of clinical heart failure tends to focus on β_1 AR inhibition, and preserving the actions of vasodilatory and bronchodilatory β_2 ARs. Other differences in β -blocker pharmacological profile, i.e. whether they act like neutral antagonists or inverse agonists, whether or not they exhibit intrinsic sympathomimetic (partial agonist) activity, and whether they are water or lipid soluble, also have the potential to modify β -blocker efficacy in heart failure, and therefore to determine their susceptibility to specific pharmacogenomic interactions. To date, functionally significant polymorphisms in three different genes have reproducibly impacted β -blocker treatment effects in human studies, the β_1 AR Arg389Gly polymorphism (6), the G-protein Receptor Kinase 5 (GRK5) Gln41Leu polymorphism(7), and multiple loss-of-function polymorphisms of the cytochrome P450 enzyme, CYP2D6 (8). Each are described in detail below.

β_1 adrenergic receptor Arg389Gly polymorphism— β_1 ARs mediate the positive cardiac inotropic (contractility), lusitropic (relaxation), and chronotropic (heart rate) effects of sympathetic catecholamines. They are the primary myocardial targets for β -blockers, which competitively inhibit agonist binding and thereby prevent catecholamine-stimulated receptor signaling (Figure). β_1 ARs are highly polymorphic, with multiple non-synonymous polymorphisms (i.e. polymorphisms that encode a change in amino acid sequence). The Arg to Gly substitution at amino acid 389 is generally common in multiple ethnic groups(9–11), and the functional consequences of this polymorphism have been characterized using recombinant expression of the Arg and Gly receptors in cultured cells. In comparison with β_1 AR Arg389, the Gly389 receptor couples less efficiently to the $G_{\alpha s}$ signaling protein that transmits activated membrane receptor responses to intracellular effectors and targets(6,12). Since agonist-stimulated signaling is diminished, homologous desensitization is also impaired, relative to β_1 AR Arg389 (13). In aggregate, cell-based studies showed that Gly389 receptors have similar signaling activity to desensitized Arg389 receptors.

Transgenic mice were created expressing either the Arg389 or Gly389 variant of human β_1 AR in the heart to examine the consequence of the different receptor signaling activities on the intact heart, and to explore whether pharmacological β -blockers would have different inhibitory effects on cardiac inotropy and chronotropy stimulated by the two receptors(14). For these studies, the non-selective (i.e. inhibits both β_1 AR and β_2 AR) β -blocker, propranolol, was used. When propranolol was acutely infused to isolated perfused working hearts or when chronically administered orally to live mice, mouse hearts expressing β_1 AR Arg389 exhibited

typical negative inotropy or chronotropy, whereas these responses were blunted or absent in mice expressing the Gly389 variant. Together, the experimental work in cells and mice expressing recombinant human β_1 AR indicate that the Gly389 receptor is intrinsically less active, and is less susceptible to inhibition by β -blockers, than the Arg389 receptor.

The pharmacological effects of polymorphic β_1 AR have been examined in several small human studies. Infusion of the β_1 AR-selective agonist, dobutamine, in *normal subjects* showed diminished inotropic and chronotropic responses in individuals who were homozygous for Gly389, compared to homozygous Arg389 subjects(15). Importantly, inhibition of these effects by the β -blocker bisoprolol was less effective in Gly389 than Arg389 subjects. Three small studies of *systolic heart failure* have directly examined at the effect of β_1 AR 389 genotype on cardiac functional improvement with β -blocker treatment. The change in left ventricular ejection fraction as a result of at least 6 months of treatment with the same dose of the combined α -blocker and β -blocker, carvedilol, was assessed by β_1 AR 389 genotype in a small heart failure study cohort(14). Gly389 homozygotes showed no significant change in ejection fraction, whereas Arg389 homozygotes exhibited a substantial functional improvement ($0.93 \pm 1.7\%$ vs $8.7 \pm 1.1\%$, respectively). These general findings were independently replicated in another small study (16). In both of these reports, heterozygous individuals (i.e. β_1 ARArg/Gly389) either had intermediate responses to carvedilol or acted more like Arg389 homozygotes. Similar results have also been described with the β_1 AR-selective blocker, metoprolol(17). Taken together, these findings in small human cohorts are remarkably similar to those from propranolol-treated transgenic mice(14). From a purely phenomenological basis, the data indicate that the Arg389 receptor appears hypersensitive to agonist stimulation, and is therefore exquisitely sensitive to pharmacological β -blockade. Looked at from the opposite perspective, the Gly389 receptor functions almost as if it were already “ β -blocked”.

A novel experimental platform supports the findings of functional differences between Arg389 and Gly389 β_1 AR, and has provided additional insight on both the mechanisms involved, and on different pharmacogenetic interactions for β -blockers used in heart failure. In the first description of intra-molecular Fluorescence Resonance Energy Transfer (FRET) to explore differences in drug effect on polymorphic β_1 ARs, Rochais et al examined the molecular configuration of Arg389 and Gly389 receptors in response to agonist (norepinephrine) and the three β -blockers currently used to treat heart failure (metoprolol, bucindolol, and carvedilol) (18). Utilizing the different conformations of agonist and β -blocker occupied receptor as a readout for inverse agonist activity (which generates a receptor conformation that turns off all signaling), they observed that the effects of metoprolol and bisoprolol did not differ between Arg389 and Gly389 receptor. In contrast, the Arg389 receptor was much more sensitive to inverse agonism by carvedilol than was the Gly389 receptor. These studies demonstrate that the β_1 AR 389 polymorphism can determine specific responses to individual β -blockers.

The potential for the β_1 AR 389 polymorphism to determine β -blocker response in human heart failure was revealed by Liggett and Bristow (19). They integrated laboratory studies of myofiber contractile responses from Arg389 or Gly389 hearts with a mortality analysis of heart failure in patients stratified both by β_1 AR389 genotype and by treatment with the non-selective and highly sympatholytic β -blocker, bucindolol. When the contractile properties of non-failing right ventricular trabeculae were studied in organ baths, those from individuals carrying one or two Gly389 alleles (termed “carriers”) showed depressed contractility compared to homozygous Arg389 hearts. Similar, but smaller, differences were seen in trabeculae from failing hearts. Of most interest, forskolin-contracted trabeculae from failing Arg389 or Gly389 hearts showed equivalent negative inotropic responses to carvedilol, whereas the experimental β -blocker bucindolol decreased contractile force only in Arg389 hearts (i.e. it acted as an inverse agonist in this group only). Although the experimental design used forskolin to pre-contract the muscle fibers, which completely bypassed β AR signaling to directly stimulate

downstream adenylyl cyclase, the results support the idea that intrinsic pharmacological properties of β -blockers are an important factor in pharmacogenomic interactions.

The clinical arm of this study consisted of an analysis of mortality/hospitalization benefit from bucindolol in the genetic substudy of the BEST trial(20), examining outcomes in placebo- and bucindolol-treated subjects stratified by β 1AR Arg/Gly389 genotype. Kaplan-Meier survival analysis identified a single treatment group with improved survival compared to the other groups, Arg389 homozygotes receiving bucindolol. In contrast, subjects with one or two Gly389 alleles had identical survival with placebo or bucindolol. In summary, Arg389 homozygotes act as bucindolol responders, whereas Gly 3889 carriers did not. The upshot of these findings is that genetic testing can be used to personalize therapy with agents, within a broad class of indicated therapeutics, that have the optimal pharmacological profile for a given individual's genotype/phenotype.

G-protein Receptor Kinase 5 Gln41Leu polymorphism—GRKs desensitize β ARs, thereby modulating adrenergic responses under conditions such as heart failure wherein β AR signaling pathways are chronically activated by persistently elevated catecholamines (21). GRK-mediated desensitization therefore represents an endogenous protective response that is analogous to that provided by β -blocker treatment (Figure). Given the critical regulatory function of GRKs on the primary target of β -blockers, it is not surprising that the same conceptual approach described for β 1ARs (identification of polymorphic variants by human screening, functional analysis of recombinant variants in cultured cells and genetically manipulated mice, and genotype-phenotype association studies in human heart failure) has likewise revealed significant pharmacogenomic interactions.

Two GRKs are expressed at high levels in myocardium, GRK2 (originally designated the “ β -adrenergic receptor kinase” or “ β -ARK”) and GRK5(22,23). Comprehensive GRK2 and GRK5 exomic resequencing of several dozen ethnically diverse human genomic DNAs did not detect any common non-synonymous polymorphisms of GRK2, but did identify four amino acid changing variants in GRK5. Three were extremely rare, but a Gln to Leu substitution at amino acid 41 was uniquely common in African Americans(7). Cell-based studies have shown that the Leu41 variant exhibited enhanced activity for β 1AR and β 2AR, although the intrinsic kinase activity was not altered, consistent with a modification in one of the kinase's regulatory domains(7,24). Thus, the GRK5 Leu41 variant more efficiently desensitizes β AR signaling, and acts (as do β -blockers) to suppress β AR signaling.

Isolated perfused hearts from transgenic mice expressing human GRK5 Gln41 or Leu41 in the heart exhibited similar decreases in inotropic response to the non-selective β AR agonist, isoproterenol, compared to non-transgenic mice(7). This is the expected result from simply increasing overall myocardial GRK levels in both mouse lines. However, Leu41 transgenic hearts demonstrated accelerated desensitization of isoproterenol-stimulated cardiac inotropism, compared to Gln41 overexpressing hearts. This result mimicked both the cell culture results with recombinant polymorphic GRK5 and the functional consequences of β -blockade. For this reason, the effects of GRK5 Leu41, GRK5 Gln41, and pharmacological β -blockade with propranolol were compared in an experimental model of heart failure created by chronic catecholamine excess, continuous infusion of isoproterenol administered via subcutaneously implanted osmotic mini-pump. Left ventricular remodeling (increased echocardiographic end-systolic and end-diastolic dimensions) is rapid and pronounced in this model, and β -blocker therapy largely prevents the cardiomyopathy. Similar to propranolol, GRK5 Leu41-expressing mice were protected from chronic β AR stimulation, whereas GRK5 Gln41 mice developed the characteristic cardiomyopathic dilation and depressed ejection performance(7).

Since the data in experimental systems indicated that GRK5 Leu41 and β -blockers both decreased β AR signaling and were cardioprotective under conditions of chronic agonist stimulation, the effects of GRK5 genotype were examined on mortality in a small pilot study of human heart failure, stratified by β -blocker treatment status. Since the GRK5 Leu41 polymorphism is prevalent only in African Americans (~40% carry one or two alleles, whereas fewer than 2% of Caucasians do), this study was limited to 375 African Americans with ischemic or non-ischemic heart failure. As with the β 1AR 389 polymorphism, a case-control analysis showed similar Leu41 allele frequencies in non-affected and heart failure populations. Thus, GRK5 Leu41 is not an independent risk factor for developing heart failure. However, among patients not treated with β -blockers, study subjects carrying one or two GRK5 Leu41 alleles had strikingly longer transplant-free survival times than subjects homozygous for Gln41. Hazards modeling after adjusting for age and sex showed that the protective effect of GRK5 Leu41 was comparable to that of β -blockers.

Examining the combined effects of β 1AR 389 and GRK5 41 polymorphisms on the β -blocker mortality benefit in heart failure—The concordance of β 1AR Gly389 and GRK5 Leu41 effects in cell culture, transgenic mice, and early studies of human heart failure suggested that gene-drug interactions can significantly impact inter-individual variability of β -blocker treatment response. Given their different frequencies in populations with different genetic ancestry, we were specifically interested in whether these two genetic polymorphisms might contribute to reported differences in β -blocker mortality effect between Caucasians and African Americans with heart failure. While an overall mortality benefit for β -blocker therapy has been repeatedly demonstrated, the results of sub-group analyses of African Americans have been inconsistent. In part this relates to study design and power, but we considered that population differences in the prevalence of the β 1AR Gly389 and GRK5 Leu41 polymorphisms that alter heart failure outcome could also be playing a role. To test this hypothesis, we examined mortality as a function of β 1AR and GRK5 genotype in a large bicenter heart failure cohort of 2,460 subjects that included 711 African Americans(11). Within this cohort, 82% of subjects were being treated with β -blockers (largely carvedilol and metoprolol), permitting us to assess outcome as a function of genotype and (non-randomized) β -blocker treatment status.

When the combined results of all subjects were analyzed without regard to geographic ancestry, β -blocker treatment significantly improved mean survival time ($P=0.0008$) and protected against heart failure mortality (age- and sex-adjusted hazard ratio = 0.78, $P=0.003$). Sub-group analysis confirmed the β -blocker survival benefit in Caucasians ($P=0.0004$), but it was not significant in African Americans ($P=0.327$). We examined reasons for the apparent difference in β -blocker effect by comparing outcomes between Caucasians and African Americans within the untreated or β -blocker-treated groups. In subjects not treated with β -blockers, survival times were similar between African Americans and Caucasians, whereas in subjects taking β -blockers, African Americans had shorter survival times than Caucasians ($P=0.0005$). Thus, the absence of a significant β -blocker treatment effect in this African American heart failure study cohort was attributable to a greater mortality benefit from β -blocker therapy in Caucasians.

We then compared heart failure survival times as a function of β 1AR 389 or GRK5 41 genotype in addition to geographic ancestry and β -blocker treatment status. β 1AR Gly389 was associated with shorter survival in β -blocker untreated Caucasians only ($P=0.03$), consistent with a previously reported modest benefit for the Arg389 genotype (10). β 1AR 389 genotype did not affect the mortality benefit from carvedilol or metoprolol. For GRK5 Leu41, which is almost exclusively expressed in individuals of African ancestry, the numbers in Caucasians were too small to power a comparative analysis between races. However, within African Americans with heart failure, GRK5 Leu41 was associated with significantly longer survival times in subjects not being treated with β -blockers ($P=0.01$), which is consistent with the previous report (7). Thus, in this heart failure cohort the β 1AR 389 polymorphism was associated with altered

outcome only in Caucasians, and the GRK5 41 polymorphism that is observed almost exclusively in African Americans also altered outcome. Since the differences in β -blocker effect on outcome between populations with differing geographic ancestry originally seen in our study failed to incorporate these genetic factors, we re-examined our data comparing heart failure outcome between Caucasians and African Americans only in subjects with β 1AR Arg/Arg389 and GRK5 Gln/Gln genotype (i.e. lacking the functional polymorphic alleles). When survival was matched for genotype in this manner, the mortality benefit for β -blocker therapy was significant in both Caucasians, ($P=0.005$) and African Americans ($p=0.037$), and the previously observed differences between survival times in β -blocker treated subjects disappeared. These results demonstrate the importance of accounting for relevant genotypes when examining drug effect. Taken together, the totality of the data with the β 1AR 389 and GRK5 41 polymorphisms indicates that *enhanced β AR desensitization in the face of catecholamine excess, which is observed in the β 1AR Arg389 and GRK5 Leu41 variants, is the key functional characteristic protecting against early mortality in β -blocker untreated heart failure.*

Loss-of-function polymorphisms of CYP2D6—Lipophilic β -blockers, such as metoprolol, undergo extensive hepatic metabolism and are cleared from the body by cytochrome P450 enzymes, especially CYP2D6 (Figure)(25). These metoprolol metabolites are functionally inactive at the concentrations achieved in vivo(26). Therefore, the rate of metoprolol metabolism by CYP2D6 is a primary determinant of active drug levels. To date, over 80 allelic variants of CYP2D6 have been described (<http://www.cypalleles.ki.se/>), and functionally significant CYP2D6 polymorphisms interact to confer distinct human pharmacokinetic phenotypes. Scoring systems have been proposed that relate complex genotypes to metabolizer phenotype and account for the relative function of different allelic variants and their combinatorial interactions (27). For the purposes of this review, however, we will use the traditional system in which pharmacokinetic profiles are assigned by the ability to metabolize specific CYP2D probe drugs and are broadly related to genotype (8,28). In this system phenotypes are classified as ultrarapid metabolizers (~5% of Caucasians), extensive metabolizers (~70% of Caucasians), intermediate metabolizers (~15% of Caucasians), and poor metabolizers (~10% of Caucasians)(29). Ultrarapid and extensive metabolizers have two fully functional CYP2D6 alleles, intermediate metabolizers have the equivalent of one functional allele (in many instances representing two hypofunctional alleles), and poor metabolizers have no functional alleles(29,30). Altered drug clearance as a result of CYP2D6 polymorphisms has striking consequences on metoprolol pharmacokinetics(31), with the elimination half-life ranging from 2.8 hours in extensive metabolizers to 7.5 hours in poor metabolizers(25). Indeed, multiple studies in normal subjects, hypertensive patients, and individuals with heart failure have demonstrated the strong relationship between CYP2D6 genotype, metabolizer phenotype, and metoprolol concentrations, even after chronic treatment at standard doses (32,33). Accordingly, the possible consequences of altered metabolic clearance include altered drug efficacy (because of insufficient drug levels in extensive metabolizers, or increased drug levels in poor metabolizers) or increased toxicity (from high drug levels in poor metabolizers).

The preponderance of evidence supporting an effect of CYP2D6 genotype on metoprolol treatment effect derive from three recent studies, two in hypertension and one after myocardial infarction(34–36). Clinical efficacy of metoprolol was assessed as the change in heart rate and diastolic or mean arterial blood pressure after treatment. In each of these studies, patients with no fully functional CYP2D6 alleles (i.e. poor metabolizers) exhibited enhanced negative chronotropism, and in the case of the hypertensive cohorts a greater hypotensive effect, from metoprolol. However, poor metabolizers represent only a small fraction of the general population (7–10% of the Caucasian population), and so it is understandable that these findings have not been reproduced in smaller studies that lacked sufficient power to independently

examine this subgroup. When these types of analyses have compared metoprolol effect in subjects with two functional CYP2D6 alleles (i.e. extensive metabolizers [70% of population]) versus combined intermediate and poor metabolizers (15 and 10% of the population, respectively), differences have not been significant(33). Thus, while there is little doubt that CYP2D6 genotype can determine metabolizer status and affect metoprolol levels, increased drug effect is clearly significant only in poor metabolizers who represent a small fraction of the population. Since evaluating metoprolol efficacy can be as simple as recording pulse and blood pressure during dose titration, there appears to be little indication for antecedent genotyping to gauge optimal drug dosing in this instance.

The other potential application for CYP2D6 genotyping is to identify poor metabolizers who, due to impaired drug clearance, may develop metoprolol side effects at standard doses. Support for this approach was provided in a retrospective study describing increased prevalence of poor metabolizers (38%) among patients who discontinued metoprolol because of adverse effects (37). Subsequent reports have failed to establish an unambiguous relationship between CYP2D6 genotype/phenotype and adverse events from metoprolol treatment, despite showing strong associations with plasma levels (17,31,38). Again however, the poor metabolizer group tended to be under-represented in these studies, and this is the group that has displayed a higher incidence of side effects from other drugs cleared in a CYP2D6-dependent manner (39–41). Given the wide therapeutic window and safety profile for metoprolol and other lipophilic β -blockers, any conclusion regarding the utility of genetic testing in the functionally brittle heart failure population to identify poor metabolizers who might receive alternate drug dosing or increased surveillance requires properly powered prospective studies in this disease.

Summary—The goal of this review was to examine potential opportunities for genotype-directed drug treatment in heart failure, so-called preprescription genotyping. A critical need is to define the necessary steps to begin implementation of genotype-directed therapy. Specifically regarding β -blockers, their use in heart failure and after myocardial infarction is a class I indication based on rigorous evidence for a group mean effect(42). A highly regarded colleague and expert in the area has suggested that pharmacogenetics may never be applied to β -blocker therapy, not with standing the scientific evidence for pharmacodynamic and pharmacokinetic interactions, because of the undeniable group benefit. It is his belief that necessary proof of concept studies cannot be performed because it would be unethical to modify established life-prolonging treatment regimens in order to explore possible benefits of targeted therapeutics based on individual genotype. Indeed, in the case of heart failure, there are really only three β -blockers that are accepted as reducing mortality and morbidity (43), and it is not clear under what conditions it would be permissible, even under carefully controlled experimental conditions, to substitute a different β -blocker for one of these old standards, or even to exchange the same β -blocker in a different formulation. One approach would be to perform initial prospective pharmacogenetic evaluations in a different patient population, such as hypertensives, where there is greater latitude to prescribe a variety of β -blockers, and in whom typical endpoints of drug effectiveness (change in heart rate and blood pressure) can be evaluated in the near and long-term. Another possibility is to evaluate individual treatment responses in heart failure patients using these same surrogate endpoints of drug effectiveness in short-term trials. By way of example, clinically stable and well-compensated heart failure study subjects selected by genotype for specific analyses could be withdrawn from their standard β -blockers (typically carvedilol or metoprolol XL) for a few weeks under careful supervision in order to assess chronotropic and inotropic responses or plasma levels after administration of one of the newer generation of β -blockers. Normal treatments could then be resumed after this relatively brief interruption. If the results from such studies demonstrated specific gene-drug interactions, they could support trials comparing β -blocker effectiveness in subject randomized either to being guided, or not guided, by genotype, and using intermediate term endpoints such as change in left ventricular ejection fraction after 6 months(5). These

issues represent some formidable challenges that will need to be addressed through the coordinated efforts of practicing clinicians, geneticists, pharmacologists, and an understanding of the complexities involved on the parts of institutional review boards and data safety monitoring committees.

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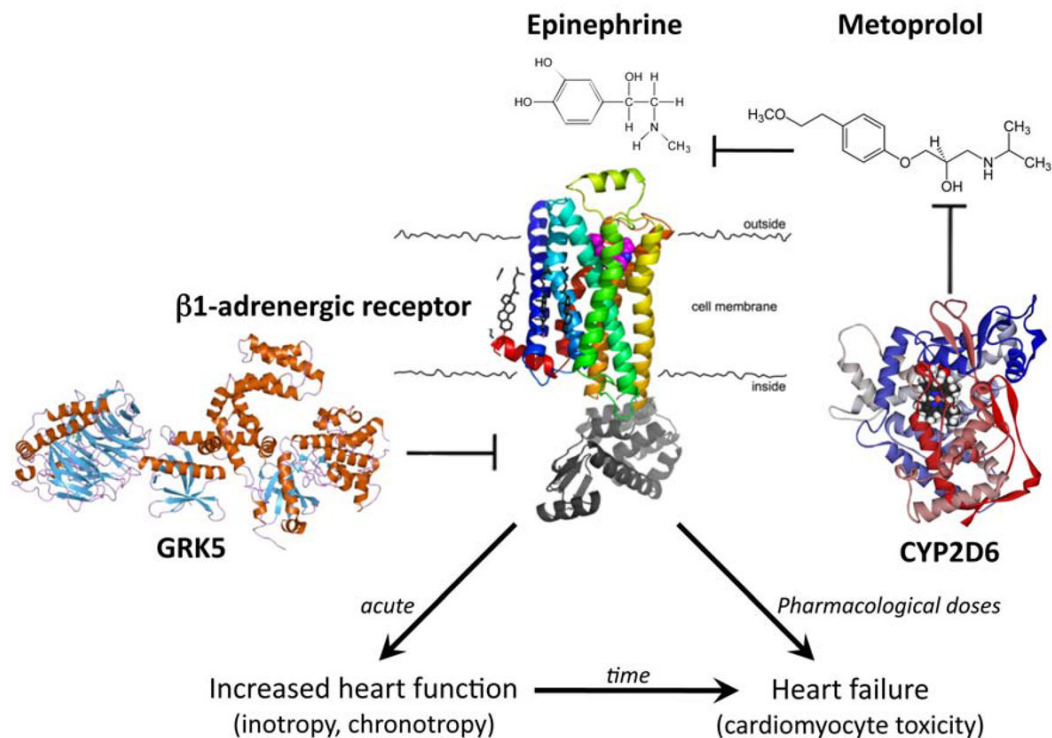


Figure. Modulating factors on β_1 -adrenergic receptor signaling

The endogenous catecholamines epinephrine and norepinephrine (not shown) bind to and stimulate β_1 -adrenergic receptors (β_1 AR), thereby increasing heart rate (positive chronotropy) and myocardial contraction (positive inotropy). At high doses or over prolonged periods, catecholamine stimulation contributes to heart failure by injuring cardiomyocytes. β -blockers, such as metoprolol, competitively inhibit epinephrine/norepinephrine binding to β_1 AR, which interrupts cardiotoxic catecholamine signaling and prolongs life in heart failure. The Arg389 polymorphism of β_1 AR makes it hyper-responsive to agonist stimulation and inhibition by β -blockers, compared to Gly389. Lipophilic β -blockers like metoprolol, but not hydrophilic β -blockers, are metabolized and cleared from the circulation by hepatic cytochrome P450 enzyme, CYP2D6. Multiple loss of function CYP2D6 polymorphisms create “poor metabolizers” that exhibit increased metoprolol levels and clinical effects. G-protein receptor kinase 5 (GRK5) desensitizes agonist-bound β_1 AR by disrupting intracellular signal transduction. The Leu41 polymorphism of GRK5 is more efficient at receptor desensitization, which mimics the effects of pharmacological β -blockade.