Stimulating G Protein–Coupled Receptors

Cure or Cause for Heart Failure?

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Historically there has been intense interest in restoring the failing heart the ability to improve contractility to normal levels. This concept, which has been pursued with almost religious zeal for the last half century, is based on the intuitive assumption that the defect in heart failure resides at the end point, which is defective myocyte contraction.

This concept was given additional impetus by the observation by Chidsey et al1 that failing human hearts exhibit norepinephrine depletion. Over the last half century, the pharmaceutical industry has responded to this concept with a variety of β-adrenergic agonists designed to improve the contractility of the failing heart. For several years, isoproterenol was administered, which provided some short-term relief but was found to exert deleterious effects in most patients. Most likely, the isoproterenol-induced increases in cardiac rate, contractility, and oxygen consumption are maladaptive in patients with limited coronary reserve. This was followed by a series of β1-predominant or β1-selective agonists that induce enhanced contractility with little or no effect on heart rate or arterial pressure. Some of these agents were used for many years in clinical setting as well as under experimental conditions. It was not until carefully controlled long-term studies were carried out that it was found that mortality was increased in patients with heart failure on these drugs.2–4 The results of these studies suggest that agents that increase oxygen consumption over an extended period of time may not be salutary in patients with limited coronary reserve.

During the last 20 years, heart failure research has uncovered another major problem governing the efficacy of catecholamine stimulation of contractility, ie, the desensitization that occurs in patients and experimental animals with chronic heart failure.5,6 This presents another challenge to developing a therapy that is based on stimulating β-adrenergic receptors or increasing cAMP, ie, that downregulation of β-adrenergic receptors or even the catalytic unit of adenylyl cyclase may rapidly limit the usefulness of long-term therapy.

The study by Laugwitz et al7 in this issue of the Circulation Research proposes a potentially novel approach to the issue of replacement inotropic therapy in heart failure. These authors tested the hypothesis that heterotrimeric GTP-binding protein (G protein)–coupled receptors other than the β-adrenergic receptor might be resistant to desensitization and potentially useful in the treatment of heart failure. They examined the effects of transfected V2 vasopressin receptors (rV2 receptors) and P1 parathyroid hormone (PTH) and PTH-related peptide (rPTH1) receptors, which are not normally expressed in ventricular myocytes, on isolated ventricular myocytes from rabbits with and without rapid ventricular pacing–induced heart failure. Isolated adult myocytes were treated using recombinant adenoviral gene transfer of three different genes (rV2 receptors, rPTH1 receptors, and β2-adrenergic receptors). Basal contractility in myocytes with transfected rPTH1 receptors and β-adrenergic receptors was found to be constitutively activated and could not be additionally stimulated with specific agonists. In myocytes transfected with rV2 receptors, basal contractility was similar to control levels in untransfected myocytes, and contractility increased with V2 receptor agonist exposure and was additionally stimulated with isoproterenol via cAMP production.

The hypothesis proposed in the study by Laugwitz et al7 is that overexpressing a non–β-adrenergic G protein–coupled receptor in failing ventricular myocytes will ultimately improve myocardial function. The conclusion that transfection of rV2 receptors in cardiac myocytes may provide a useful long-term treatment for the failing heart is intriguing but remains clouded by several concerns. It is obvious that expression of rV2 receptors in these studies provides some improvement in contractility in failing myocytes when an rV2 receptor agonist is combined with isoproterenol stimulation. However, if rV2 receptors work through cAMP, then desensitization in the failing heart...
should still be an eventual outcome that will limit the utility of this therapy. Indeed, the catalytic unit of adenylyl cyclase was reported to be impaired in the failing heart, and proximal stimulation by rV2 receptors will not overcome a defect at a more distal site.

Thus, the most important questions remain unanswered in this study; ie, what are the long-term consequences of stimulating contraction through transfected V2 vasopressin receptors in heart failure? In view of the well-established concerns related to the problems of increasing oxygen consumption in the face of limited coronary reserve and the problems of desensitization, this critical question needs to be examined.

A first step in identifying potential long-term consequences of transfected V2 receptors could be accomplished in vitro. By applying appropriate agonists, it could be determined if the transfected V2 receptors predisposed myocytes to hypertrophy or apoptosis. An additional approach to addressing these concerns is to develop a transgenic animal model. This would provide long-term stimulation of V2 receptors, and it would be apparent if desensitization occurred. Several transgenic animals have been developed to examine overexpression of β-adrenergic signaling. Both β1-adrenergic receptors9 and β2-adrenergic receptors10 have been overexpressed as well as the G protein Gsα.11,12 Of these models, only mice with β1-adrenergic overexpression develop cardiomyopathy rapidly.9 Overexpression of Gsα requires more than 1 year for cardiomyopathy to develop.11,12 Overexpression of β2-adrenergic receptors also causes cardiomyopathy, given enough time.13 Despite these studies with pathological results, work is still progressing on chronically enhancing inotropy as a treatment for heart failure in genetically engineered animals. There is still hope that expressing β1-adrenergic receptors at a very low level or inhibiting β-adrenergic receptor kinase14,15 may prove useful. The present study using overexpression of V2 receptors may also ultimately prove to be useful. However, without more in vitro work and long-term studies in normal animals or, better yet, in models of heart failure, it is too premature to tell.

One final caveat requires mentioning. It may not be the long-term elevation of contractility and oxygen demand that is responsible for the deleterious action of G protein–coupled receptor activation under chronic conditions. It may be that distal signaling pathways are equally responsible for the hypertrophy, apoptosis, necrosis, and development of fibrosis that occurs in the long-term setting of overexpression of these receptors. For example, different signaling pathways stimulating extracellular signal–regulated kinase, mitogen-activated protein kinase, phospholipase C, or calcineurin pathways may be responsible for these negative effects independent of their action to increase contractility in vivo. In this connection, using a chimeric model where islands of overexpressed Gsα cells were mixed in a sea of nontransgenic myocytes, there was progression to hypertrophy and fibrosis, even in hearts with limited alterations in global left ventricular function.16

In conclusion, the study by Laugwitz et al7 has provided a potentially novel approach to heart failure treatment. However, it is important to understand what this treatment will do to myocardial oxygen consumption when V2 receptors are chronically stimulated and to desensitization of their action at the level of the receptor cAMP or on more distal mechanisms. Although the data in the present study demonstrate an acute efficacy,7 the critical question is whether the addition of V2 vasopressin receptors in the cardiac myocyte will alleviate or exacerbate the progression of heart failure.

References


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