Mechanisms for Myocardial β-Adrenergic Receptor Desensitization in Heart Failure

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Congestive heart failure is associated with pronounced alterations in adrenergic nervous system function. Levels of myocardial norepinephrine are decreased, as first reported in 1963,1 a phenomenon later found to be associated with increased sympathetic nervous system activation and high levels of circulating plasma catecholamines2 in combination with abnormalities in neural reuptake of norepinephrine in the heart.3 In animal models of heart failure, the heart was found to be poorly responsive to nerve stimulation.4 In 1982, a plausible explanation for decreased adrenergic responsiveness of the heart was uncovered. In end-stage dilated heart failure in humans, myocardial β-adrenergic receptors (βAR) were found to be decreased in number, and hormonal activation of adenylate cyclase in myocardial homogenates from explanted hearts was decreased.5 βAR downregulation in heart failure appears to be relatively selective for the β1-receptor subtype, but even though the number of β2-adrenergic receptors in the heart is generally unchanged, functional coupling of β2-adrenergic receptors to adenylate cyclase is impaired.6 Although no definitive studies have been performed, the genesis of subtype-selective downregulation of βAR may be that myocardial β2-adrenergic receptors (more than myocardial β1-adrenergic receptors) are in close proximity to adrenergic nerve terminals7 and that the neurotransmitter norepinephrine has a greater affinity for β2 than for β1-receptors. Thus, both on an anatomic and pharmacological basis, there may be a greater agonist-induced stimulus for downregulation of β2 than β1-receptors.

These observations provide a general understanding of why there might be subtype-selective βAR downregulation but do little to offer a molecular mechanism by which such phenomena may occur.

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The article by Ungerer et al8 in this issue of Circulation describes additional mechanisms potentially important in the pathogenesis of altered adrenergic function in heart failure. Specifically, in hearts removed from patients with end-stage dilated heart failure, steady-state levels of messenger RNA (mRNA) for the β1-receptor are decreased compared with left ventricular samples obtained from control patients. These data suggest that transcriptional regulation or decreased mRNA stability may be important elements in determining β1-adrenergic receptor protein levels in vivo in heart failure. Why steady-state levels of mRNA are decreased selectively for only one receptor subtype is not addressed. Furthermore, the work of Ungerer et al8 does not address what has occurred to transcription rates or turnover rates of mRNA for the β1-receptor. Other studies in isolated cells have determined that sustained βAR stimulation results in decreased steady-state mRNA levels for β2-receptors but that transcription rate for β2-receptor mRNA is unaltered and that decreased mRNA levels result from decreased message stability.9,10 Since receptor degradation is a process that may be enhanced by agonist stimulation, it is not unreasonable to presume that decreased cell-surface receptor number may also reflect posttranslational events, such as agonist-promoted downregulation secondary to receptor internalization and intracellular degradation.11 Protein turnover rates are difficult to measure in vivo, especially in human disease. Until methods become available to quantify receptor turnover rates and measure mRNA transcription rates and stability in the setting of heart failure, the precise molecular mechanisms responsible for decreased myocardial βAR number in vivo will remain unknown. Nevertheless, an important observation suggested by Ungerer et al8 is that there may be a linkage between βAR stimulation and receptor mRNA levels in vivo. Such a connection has been made before in isolated cells9,10 but this study shows that similar mechanisms may be operative in human heart failure.

Their data concerning βAR kinase (βARK), an enzyme involved in hormone-specific phosphorylation of the βAR,12 are of potentially more interest in elucidating the molecular mechanisms for βAR desensitization in the setting of sustained sympathetic activation. Receptor phosphorylation and dephosphorylation play key roles in modulating signal transduction.13 Protein kinase A (PKA) is activated by agonists that increase cyclic AMP (cAMP), including βAR agonists. PKA interacts with two specific serine residues near the cytoplasmic carboxyl terminus of the βAR, phosphorylates the receptor at these residues, and thereby diminishes the ability of the receptor to activate Gs, the stimulatory guanine nucleotide (GTP) binding protein that links receptor activation with stimulation of adenylate cyclase. PKA functions whether the βAR is occupied or not and may be activated through any pathway that results in the production of

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cAMP. In contrast, βARK also phosphorylates the carboxy terminus of the βAR but at 11 potential residues and only when the βAR is occupied with agonist. Furthermore, uncoupling of the βARK and Gs, in the case of βARK-mediated phosphorylation, requires the presence of an additional protein, β-arrestin.14 Whereas phosphorylation through PKA has been shown to occur with both β1- and β2-adrenergic receptor subtypes, phosphorylation through βARK, thus far, has been shown to occur only with β2-adrenergic receptors.15

Ungerer et al18 show that the activity of βARK, as suggested from an in vitro bioassay, is increased in left ventricular homogenates of explanted hearts from patients with end-stage dilated heart failure. Furthermore, increased βARK activity is associated with increased steady-state levels of mRNA for βARK, a finding that underscores the idea that protein expression is increased. Although these data fall short of conclusively demonstrating that the mechanism for desensitization is dependent on the action of βARK, there are sufficient data to suggest that this may be the case, at least for the β2-receptor. It is provocative that continued agonist stimulation in vivo may be linked to increased synthesis and activity of an enzyme that regulates the responsiveness of the receptor. One may speculate that such an association might result from a cAMP-mediated increase in transcription of βARK mRNA. Whether this actually occurs will require measurement of transcription rates. It will also be of interest to determine whether the gene for βARK contains structural and functional cAMP-responsive elements, thereby providing a mechanism by which CAMP production may be linked with increased transcription of a gene whose expression may lead to inactivation of hormone stimulation. However, speculations regarding the importance of the present findings with respect to β1-receptor desensitization must be restrained. To date, there has been no demonstration that βARK is important for phosphorylating the β1-receptor. Furthermore, in previous studies, β1-receptors on human SK-N-MC neurotumor cells have been shown to be resistant to βARK-mediated desensitization15 but susceptible to PKA-dependent desensitization, a mechanism for desensitization not addressed in the current study.

Despite these limitations with respect to precise molecular mechanisms for desensitization, the data of Ungerer et al have potentially important implications regarding future strategies to combat myocardial βAR desensitization. If, in fact, increased βARK activity is an important element in desensitization, a potential pharmacological strategy might be to prevent transcription of βARK or to construct βARK inhibitors, thereby increasing the ability of the heart to respond to adrenergic stimulation. Enthusiasm for such an approach must be tempered, however, since increasing sympathetically activating the failing heart can have deleterious effects, making an individual more susceptible to ventricular arrhythmias, sudden death, and angina pectoris.16 Indeed, increased βARK activity may be an adaptive mechanism by which sustained agonist stimulation is turned off by uncoupling receptors from Gs, thereby decreasing myocardial metabolic demands.

Whether changes in βAR number and βARK activity are specific for heart failure or are general phenomena associated with sustained sympathetic nervous system activation is an important and unanswered question. For example, myocardial βARK downregulation and depressed adenylate cyclase activation occur in the setting of circulatory congestion associated with aortocaval fistulas,17 a model characterized by elevated plasma catecholamines in which myocardial contractile function is normal.18 Data from the aortocaval fistula model of circulatory congestion suggest that marked abnormalities in myocardial adrenergic receptor expression can occur in the absence of primary defects in myocyte function. Could it be that βARK is not upregulated in response to heart failure but instead in response to sustained adrenergic activation from any cause? This would imply that the data of Ungerer et al pertain to heart failure only as a special case of adrenergic activation and that the findings may not be of pathogenetic importance in heart failure per se.

In summary, the present article furthers our understanding of the desensitization of the myocardial βARK. Specifically, selective myocardial β1-downregulation is associated with selective decrease in the steady-state level for mRNA for the β2-receptor. Neither β2-receptors nor steady-state levels of β2-receptor mRNA are decreased. Furthermore, both the in vitro biological activity of βARK and the steady-state level of βARK mRNA are increased, suggesting that desensitization may result, in part, from increased activation of a phosphorylating enzyme that, in vitro, serves to uncouple β2-adrenergic receptors from Gs. These studies provide important new descriptive information and offer strategies for more mechanistic studies aimed at determining the molecular pathogenesis of decreased adrenergic responsiveness of the heart in the setting of heart failure or sustained βARK stimulation.

References

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