Editorial

Heart failure is a symptom complex that is primarily attributable to inadequate tissue perfusion and pulmonary and systemic venous congestion. Compensatory adaptations include activation of a variety of neurohormonal pathways, including the renin-angiotensin system and the sympathetic nervous system. Activation of the renin-angiotensin system has a number of consequences, including vasoconstriction and sodium and water retention secondary to aldosterone action on the kidney. Similarly, sympathetic nervous system activation promotes β-adrenergic receptor–mediated positive inotropy and chronotropy, as well as increased α-adrenergic receptor–promoted vasomotor tone. In recent years, concerns have been raised about the negative consequences associated with activation of such neurohormonal systems and the clinical benefit that may occur from blockade of these systems. Indeed, the use of angiotensin converting enzyme inhibitors has become a clinically important addition to the management of patients with heart failure (1). Whether adrenergic receptor blocking agents might also prove beneficial in this setting is a controversial subject of current clinical interest (2).

Activation of the sympathoadreneral system in heart failure is associated with alterations in receptors and receptor-mediated signaling. Bristow et al. (3) have published a series of studies that have extended their original observation of a decrease (i.e., downregulation) of cardiac β-adrenergic receptors. The heart contains both β_1- and β_2-adrenergic receptors. In the setting of heart failure β_1-adrenergic receptors are downregulated, while β_2-adrenergic receptors are uncoupled from postreceptor events (4). Recent data have suggested that increased expression of the β-adrenergic receptor kinase is associated with β-adrenergic receptor uncoupling (5).

Why do β_1-adrenergic receptors decrease in number? A possible answer is that increases in norepinephrine enhance receptor turnover and degradation (6). However, as shown in the paper by Bristow et al. (7) in this issue of the *Journal*, this explanation may not be the sole mechanism for the decrease in β_1-adrenergic receptor binding. Bristow et al. (7) have used quantitative polymerase chain reaction (QPCR) to quantitate receptor mRNA, and these authors show that β_1-adrenergic receptor, but not β_2-adrenergic receptor, mRNA is substantially ($\sim$ 50%) decreased in the failing left ventricle. Two issues that complicate this work are the low abundance of β-adrenergic receptor mRNA in the heart (a problem that is well suited to the use of QPCR) and the fact that β-adrenergic receptors have intronless genes (thereby increasing the possibility of amplification of receptor genes in contaminating DNA). Use of an internal standard and poly(A)$^+$-enriched RNA provided essential solutions to these problems in the QPCR assay described by Bristow et al. (7). Results with QPCR were confirmed using RNase protection assays. Furthermore, the decrease in β_1-adrenergic receptor mRNA was correlated with a decrease in radioligand binding to receptors.

These data, which confirm and extend those reported earlier this year by another group (5), raise a number of intriguing questions. What is the mechanism by which β_1 mRNA is decreased? Why is this decrease in mRNA expression selective for β_1-adrenergic receptors? Are there *cis*-active elements in the β_1-adrenergic receptor promoter (8) that are inhibited or not activated in the setting of heart failure by *trans*-acting factors or is mRNA stability for the β_1-adrenergic receptor selectively decreased (relative to β_2-adrenergic receptor mRNA) in heart failure? Is the decrease in β_1-adrenergic receptor mRNA and protein expression a favorable or unfavorable adaptation for the failing heart? The work by Bristow et al. (7) sets the stage for future work directed at such questions. The answers to these questions and the related issues of changes in postreceptor components are likely to require work in animal models of heart failure (9–12) as well as in human subjects. We believe that such studies are likely to provide new insights regarding the pathophysiology of heart failure and may provide new approaches to the treatment of the failing heart.

Paul A. Insel
H. Kirk Hammond
Departments of Pharmacology and Medicine
University of California, San Diego

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