Editorial

In this issue of *The Journal*, Gauthier and colleagues provide evidence for the presence of a third β-adrenoceptor subtype, the β_3-adrenoceptor, in human heart. However, unlike β_1- or β_2-adrenoceptors, the β_3-adrenoceptor functions to inhibit cardiac contractility (1). The authors state that "this unexpected finding could interfere with the pathogenesis of cardiac failure, during which modification of β_1- and β_2-adrenoceptor occurs" (1).

In heart failure, there is an increase in circulating and released epinephrine and norepinephrine in an attempt to stimulate contractility through β_1- and β_2-adrenoceptor activation. While this presence of excess stimulation may initially improve cardiac function, the long-term consequences are diminished contractility of the myocardium through desensitization and a subsequent loss of β-adrenoceptors (primarily of the β_1-subtype) (2). Thus, activation of the inhibitory β_3-adrenoceptors described by Gauthier et al. could produce further decreases in contractility and possible exacerbation of the clinical symptoms associated with heart failure. There are three factors which make this a plausible conclusion. First, the β_3-adrenoceptor has been demonstrated to be relatively resistant to chronic, agonist-induced desensitization processes since it lacks the relevant sites for phosphorylation by G protein–coupled receptor kinases (3). Therefore, it may play an important role in the presence of diminished numbers of β_1-adrenoceptors. Second, norepinephrine, the primary neurotransmitter released by the sympathetic innervation to the heart, has relatively high affinity for the β_3-adrenoceptor, unlike the β_2-subtype. Also, studies of the β_3-adrenoceptor in certain tissues have shown responses to sympathetic nerve stimulation suggesting a postjunctional localization in at least some tissues. Third, there is evidence to suggest that G_i, the G protein implicated in the β_3-adrenoceptor signaling in human ventricle, may be upregulated in certain types of heart failure (4). An increase in the amount of available G protein may produce increases in cellular responses, even at the same level of receptor activation. That an increase in G_i protein levels is responsible for the "promiscuous coupling" of the β_3-adrenoceptor in this report is unlikely because the studies were performed on tissue samples from the donor hearts, not the hearts removed due to failure.

At a basic research level, the report by Gauthier et al. is intriguing because, to our knowledge, it is the first report implicating a β-adrenoceptor whose primary biochemical function appears to be inhibitory. Most reports in native systems have described β-adrenoceptors as coupling quite faithfully to their preferred second messenger G protein, G_s, resulting in activation of adenylate cyclase. Indeed, there is pharmacological evidence for the existence of a stimulatory β_3-adrenoceptor in human atrium (5). Inhibitory pertussis toxin–sensitive responses to β_2- and β_3-adrenoceptor stimulation have been reported, but these responses were attenuation of the primary response of increasing adenylate cyclase (6, 7). Thus, the net response of receptor activation was still an increase in adenylate cyclase activity. The results obtained by Gauthier et al. show that whether as a result of coupling to a single inhibitory G protein, or to multiple signaling pathways, the net effect of β_3-adrenoceptor activation is inhibition of ventricular myocardial contractility (1). The results also stress the dangers of screening for a receptor based on presumed second messenger function. For example, it is likely that assaying for increases in adenylate cyclase activity would not have revealed a functional β_3-adrenoceptor in human heart.

To summarize, the existence of functional β_3-adrenoceptors in human myocardium which inhibit contractility adds another dimension to the current framework of how disordered adrenergic regulation of the heart may contribute to the pathogenesis of cardiac failure. At a time when marked increases in sympathetic tone and cardiac norepinephrine release have rendered the inotropic β_1-adrenoceptor system relatively unresponsive, the desensitization-resistant β_3-adrenoceptors would presumably continue to mediate a negative inotropic effect via an interaction with an upregulated pool of G_i proteins. If these mechanisms do in fact operate as the heart fails, then one might speculate that drugs which block β_3-adrenoceptors might be of therapeutic benefit in such circumstances. This conjecture is even more provocative in the light of recent findings that certain β-adrenoceptor antagonists are of therapeutic value in the treatment of chronic congestive heart failure (8).

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