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$_3$-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 shown β-adrenoceptors as coupling quite faithfully to their respective, function and alterations in chronic heart 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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References