Adrenergic Receptor Polymorphisms and Cardiac Function (and Dysfunction)
A Failure to Communicate?
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For a number of cardiovascular diseases, it has been proposed that both the susceptibility to disease and the interindividual variability in response to treatment relates in part to genetic polymorphisms, particularly those polymorphisms for neurotransmitter and drug receptors. Perhaps the most intensively studied family of receptors are the G-protein–coupled receptors, of which the β-adrenergic receptor is the prototype.

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The β-adrenergic receptor family members (β₁, β₂, and β₃) are highly polymorphic. Further, specific single-nucleotide polymorphisms have been associated with a range of cardiovascular diseases and cardiovascular risk factors, including obesity, hypertension, diabetes, and congestive heart failure.1 However, although a number of genetic polymorphisms of the β₂-adrenergic receptor have been linked to an increased risk of cardiovascular and respiratory diseases, ultimately the proof of the importance of these polymorphisms beyond that of a risk marker is dependent on the characterization of an intermediate phenotype that could be linked to the presentation of the disease or a response to therapy. This is the importance of the current findings from Brodde and colleagues2 in this issue of Circulation.

In patients with congestive heart failure, polymorphisms of both β₁- and β₂-adrenergic receptors have been linked with disease expression. N-terminal polymorphisms of the β₁-adrenoceptor have been associated with an increased risk of developing idiopathic dilated cardiomyopathy.3 However, most attention has been focused on single-nucleotide polymorphisms of the β₂-adrenergic receptor. Specifically, a relatively rare polymorphism at amino acid 164 of the β₂-adrenergic receptor (Ile164, occurring in <5% of the general population) has been associated with worse outcomes in patients with congestive heart failure⁴ and greater impairment in exercise capacity in these patients.⁵ However, the pathological mechanism linking this genetic risk factor to adverse outcomes was unknown. Specifically, it is unclear whether the expression of this polymorphism only represented a prognostic index (presumably reflecting linkage disequilibrium of this polymorphism with another gene accounting for the increased risk) or whether the expression of the polymorphism causally contributed to the accelerated course of heart failure in these patients.

The Ile164 polymorphism of the β₂-adrenergic receptor has a reduced ability to activate the downstream effector pathway of the β₂-adrenergic receptor (ie, adenylyl cyclase activation via interaction with a G-protein of stimulation).⁶ In the parlance of the field, the expression of this polymorphism results in a functional “uncoupling” of the receptor from the G-protein (at least relative to the more common Thr164 receptor). Further, when this polymorphism was expressed in transgenic mice in a targeted manner in the heart, there was both an impairment in receptor activation at a cellular level (as represented by reduced β₂-adrenergic–stimulated adenylyl cyclase activity) and impaired isoproterenol-mediated cardiac inotropic and chronotropic responses.⁷ However, the relevance of these findings to human cardiac function remained unknown.

Brodde et al² screened 220 German volunteers and identified 7 who were heterozygous for the 164Ile polymorphism. By assessing terbutaline-mediated increases in heart rate and systolic time interval, they demonstrated impaired maximal heart rate increases and QSₐc shortening in the Ile164 volunteers compared with control volunteers expressing the wild-type receptor.

These findings are significant in several respects. First, they represent the first demonstration that the Ile164 polymorphism of the β₂-adrenergic receptor exhibits a functionally significant depression of adrenergic-mediated cardiac responses. These data provide support for the hypothesis that this impairment in response may be causally related to the adverse impact of the expression of the Ile164 polymorphism in both cardiac performance and as a predictor of survival in patients with congestive heart failure. Despite the significance of their findings, the authors have recognized several limitations. Because of the low incidence of the polymorphism (<5% of the population), no homozygotes were identified for analysis. Whether this reflects the rarity of this polymorphism or the lethality of expression of a homozygous 164Ile β₂-adrenergic receptor is yet to be resolved. Also, whether these findings could be confounded by differences in sex distribution is unlikely but could not absolutely be ruled out given the small sample size. In addition, whether the reduction in chronotropic responses was solely accounted for by the Ile164 polymorphism or was influenced by other β₂-adrenergic receptor polymorphisms could also not be definitively resolved because of the small sample size. It is notable that the depressed exercise performance in heart failure is reportedly best predicted by a specific haplotype of the 3 most common β₂-adrenergic receptor polymorphisms, rather than the simple expression of the single Ile164 poly-
Further, among the total of 13 single-nucleotide polymorphisms identified for the β2-adrenergic receptor (including 8 in the 5'-untranslated region), only 12 distinct haplotypes were identified, and only 4 had a frequency >5%. Thus, this story will not really be complete until comparisons such as that by Brodde et al2 are based not on single-nucleotide polymorphisms, but on haplotypes.

Notwithstanding the importance of these findings, significant questions still remain regarding the role of these β-adrenergic receptor polymorphisms and, more generally, the importance of preserved β-adrenergic function in heart failure. Although these findings in aggregate suggest the deleterious effects of impaired β-adrenergic response in heart failure (and the inference that preserved β-adrenergic response is protective), this hypothesis is not easily reconcilable with the findings that (1) β-adrenergic receptor blockade predicts improved outcome9 and (2) overexpression of β-adrenergic receptors in the heart are associated with cardiomyopathy.10

Are these divergent observations reconcilable? One suggestion has been that the deleterious effects of the unfavorable β2-adrenergic receptor Ile164 polymorphism in heart failure reflect the selective roles of the β-adrenergic receptor subtypes in cardiac function and the differential regulation of these subtypes in congestive heart failure. Thus, preserved β2-adrenergic receptor function in the setting of impaired β1-adrenergic receptor function might be seen as protective. However, this does not explain why even nonselective β-adrenergic receptor antagonists have been associated with improved survival in patients with congestive heart failure.9 Many in the field might think that the impairment of β-adrenergic response, whether via an unfavorable polymorphism or β-adrenergic blockade, might lead to the same results (ie, reduced adrenergic function and thereby improved outcomes in patients with heart failure). However, it is important to appreciate that there may be important differences between “uncoupled receptors” and “blocked receptors,” which might explain this apparent paradox.

The conventional definition of receptor coupling relates to the assessment of the functional interaction of the receptor with a single downstream effector pathway. In the context of the β2-adrenergic receptor, this has been assessed as an impairment in receptor/G-protein simulator interaction and, ultimately, adenylyl cyclase activation. However, alternate mechanisms by which β2-adrenergic receptors might mediate physiological effects have now been identified. These include interaction with the inhibitory G-protein (Gi) and, more recently, pathways that intersect with tyrosine kinase activation through the nonreceptor tyrosine kinase Src (generally in association with the β-arrestin complex; β-arrestin is a receptor-interacting protein with a higher affinity for phosphorylated, uncoupled receptors).11,12 These alternate pathways may modulate a range of downstream mechanisms, including the regulation of several mitogen-activated protein kinases (including the extracellular receptor kinase and p38).13 These pathways, although perhaps less important in the short-term regulation of cardiac performance, may be very important in the modulation of cardiac myocyte growth and death. Thus, whether “uncoupled but unblocked receptors” might show impaired chronotropic response but poten-

References

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_Circulation_. 2001;103:1042-1043
doi: 10.1161/01.CIR.103.8.1042

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/8/1042

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