The yin and yang of increased β-adrenergic signaling: β1-adrenergic genetic polymorphism and protection against acute myocardial ischemic injury

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The yin and yang of increased β-adrenergic signaling: β_1-adrenergic genetic polymorphism and protection against acute myocardial ischemic injury

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SIGNIFICANT IMPROVEMENTS in the treatment and prevention of cardiac diseases have led to declining morbidity and mortality over the past three decades (2), and drugs targeting adrenergic signaling have played a key role in the beneficial effects recently afforded to these patients. However, genetic heterogeneity may translate into differences in clinical response and benefit. β-Adrenergic receptor (β-AR) polymorphisms might provide a rationale to better understand the pathophysiology of cardiovascular diseases, to better identify patients at risk, and to establish targeted therapies that begin to entertain the possibility for pharmacogenetically tailored (anti)adrenergic therapy or "personalized medicine."

In humans, the β_1-, β_2-, and β_3-AR genes all have one or more polymorphisms at sites that alter encoded amino acids (13), and single nucleotide polymorphism (SNP) mutations within the β_1-AR have been associated with aspects of congestive heart failure. Two major SNPs have been described in the human β_1-AR coding region. At position 49 in the amino terminus of the receptor, a serine is substituted by a glycine, and at position 389 in the proximal part of the carboxy terminus, a glycine is substituted by an arginine (11). Cell culture experiments in vitro exhibited an increased basal and agonist-stimulated adenylyl cyclase activity with the Gly49β_1-AR as well as enhanced agonist-induced downregulation compared with the Ser49β_1-AR variant (9). In functional studies using the carboxyl terminal β_1-AR variants, matched expression of the Arg389 form showed an increased basal and a three- to fourfold higher maximal isoproterenol-induced stimulation of adenylyl cyclase than did the Gly389 variant, which was due to more effective coupling of the Arg389 receptor to the heterotrimeric G protein G_s than the Gly389β_1-AR (10). These differences have clinical implications because therapeutic responses to β_1-AR antagonists are found to be greater in patients having the Arg389 variant than in patients carrying the Gly389 allele (8). Moreover, Wagoner et al. (15) observed an increased cardiac exercise capacity (and $\dot{V}O_2$) for homozygous Arg389 heart failure patients compared with homozygous Gly389β_1-AR-carrying subjects.

In this issue of *American Journal of Physiology-Heart and Circulatory Physiology*, the findings reported by Akhter and colleagues (1) underscore the significance of adrenergic polymorphisms in cardiovascular diseases such as myocardial ischemia and reperfusion (I/R) injury. By using transgenic mouse models with cardiac-targeted overexpression of either the Gly389 or Arg389 containing β_1-ARs, the authors demonstrate that these variants associate with varying degrees of protection of the heart to acute ischemic injury. Increased β_1-AR density due to cardiac specific overexpression of either the Gly389- or the Arg389-β_1-AR translated into differentially activated signaling pathways, which are known to be cardioprotective in I/R injury. Specifically, increased β_1-AR signaling in the mouse heart due to overexpression of the Arg389 variant led to increased G protein-coupled receptor kinase 2 (GRK2) activity, which desensitizes agonist-occupied β_1- and β_2-ARs, whereas increased Gly389β_1-AR signaling did not affect GRK2 activity. Furthermore, ERK phosphorylation was differentially affected by overexpression by either the Gly389- or the Arg389-β_1-AR with increased phosphorylated ERK2 in the Arg389 transgenic mice and not Gly389β_1-AR mice. Thus increased Arg389β_1-AR signaling translated into two mechanisms known to be potentially cardioprotective during ischemic injury (5, 6), resulting in reduced myocardial damage. Importantly, the activation of GRK2 could protect the heart in two ways: *1*) the desensitization of receptors (most notably β-ARs) that can induce apoptosis in myocytes and *2*) enhanced GRK2 could be the mechanism by which ERK activation is increased because GRK2 causes increased G protein-coupled receptor internalization that leads to β-arrestin-mediated kinase cascades including ERK (7).

What is also of interest from the current data of Akhter et al. (1) is that overexpression of both β_1-AR variants leads to significantly increased cardiac function in the transgenic mice. Thus this is a clear illustration of how there is a remarkable dissociation between the obvious expected "classical" phenotype of enhanced LV function and the resistance to acute ischemic injury, demonstrating that the increased contractile state of the heart "per se" is not detrimental and responsible for the heart failure but that "nonclassical" signaling of β-ARs (7) can contribute as well to pathology. This certainly adds to the recently appreciated complexity of cardiac β-AR signaling in cardiac disease, especially in heart failure (12).

Importantly for clinical application of these data, differential signaling due to β_1-AR SNPs in the general population might correlate with subgroup-specific differences of the therapeutic benefit to (anti)adrenergic therapy in cardiovascular disease. For example, it is recognized that African Americans tend to have poorer responses to β_1-AR blockers than Caucasians (8). Moreover, the β-Blocker Evaluation of Survival Trial (BEST) gave evidence for a lack of efficacy in specific subgroups like advanced heart failure (New York Heart Association class IV) and black patients that was due to a pronounced sympatholytic effect of the unique β-blocker/sympatholytic agent bucindolol (3, 4). The Arg389 allele occurs in ~71–78% of Caucasians and Chinese patients but only in 58% of African Americans, and the loss of function α_{2C}-AR deletion mutation is also enriched in blacks. Because it is shown that the population carrying the combination of the Arg389β_1-AR SNP and α_{2C}-AR mutation has a 10-fold risk for the development of heart failure (14), sympatholysis might well affect clinical outcome in subpopulations within the BEST trial. Finally, the current study by Akhter et al. (1) also shows that differential

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cardioprotective signaling due to β_1-AR polymorphisms is age related at least in mice (1). This finding indicates the potential significance of β_1-AR mutations during the progression of cardiovascular disease or during aging. Overall, the implications of β-AR polymorphisms related to age, the stage of the disease, and the interactions with the genetic background might contribute to achieve a tailored (anti)adrenergic therapy, thus further optimizing the outcome in cardiovascular disease, and begin to use "personalized medicine" to an individual's therapeutic benefit.

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