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COMMENTARY

Combined blockade of β- and α_1-adrenoceptors in left ventricular remodeling induced by hypertension: Beneficial or not?

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Adrenergic stimulation has a crucial role in the physiological regulation of cardiac function. In addition, chronic adrenergic stimulation is one of the main signaling pathways contributing to the progression of left ventricular (LV) remodeling in pathophysiological states.[1,2] Catecholamines released from the sympathetic nervous system act on adrenoceptors (ARs) in cardiac myocytes to regulate heart inotropy, chronotropy and growth.[1–6] ARs are part of the large family of seven transmembrane receptors that interact with heterotrimetric G proteins (G protein-coupled receptors). AR subtypes couple to different G proteins, activating distinct signaling pathways.

In the human heart, β_1-, β_2- and α_1-ARs are the main receptor subtypes expressed,[1,2,5] with β_1-AR being the most abundant. Acute stimulation of β-ARs regulates cardiac excitation–contraction coupling through phosphorylation of various Ca^{2+}-handling proteins, producing a strong positive inotropic effect.[3,4] Myocardial α_1-AR density in the human heart is considerably lower than that of β-ARs (about 20%), and, consequently, the contribution of α_1-ARs to AR-mediated cardiac inotropy is less prominent.[1,3]

Chronic AR stimulation promotes pathological remodeling, leading to hypertrophy and/or heart failure.[2,7,8] β_1-AR signaling shows strong down-regulation in pathophysiological conditions, whereas α_1-AR expression does not change.[5] Relative increases in α_1-AR expression levels raise this receptor subtype to a more important role in the regulation of cardiac function in pathophysiological conditions.[5]

In this conceptual framework, adrenergic blockade is one of the central targets for preventing the progression of LV remodeling and for reverse remodeling in human heart failure.[2,9] The beneficial role of blocking β-ARs has been widely investigated. However, the importance of α_1-AR blockade is still unclear and controversial, despite the fact that α_1-AR blockers are widely used for the treatment of hypertension and heart failure. Early clinical trials have shown that treatment with selective α_1-AR antagonists, such as doxazosin and prazosin results in an increase in cardiovascular events in hypertensive and heart failure patients.[5] In contrast, carvedilol, a combined β-AR/α_1-AR antagonist, was shown to reverse remodeling and survival in human heart failure.[9] Here, three important questions have been raised: (1) can combined blockade of β-ARs and α_1-ARs suppress the LV remodeling induced by hypertension compared with selective β-AR antagonists? (2) If so, what is the mechanism underlying the beneficial role of combining β-AR and α_1-AR blockade? (3) Finally, why is α_1-AR blockade alone harmful, whereas the combined blockade of β-ARs and α_1-ARs is beneficial?

In this issue of *Hypertension Research*, Chen and colleagues test the hypothesis that non-selective AR blockade is more efficient in suppressing LV remodeling when compared with AR subtype-selective antagonists in a spontaneously hypertensive rat model.[10] A previous study compared non-AR subtype-selective and AR subtype-selective inhibition on LV dysfunction and remodeling induced by chronic coronary stenosis and coronary occlusion,[11] showing benefit from a non-selective inhibitor; however, a detailed mechanism was not investigated in that study. Chen and colleagues compared the effect of the β_1-AR antagonist bisoprolol, the β_1- and β_2-AR antagonist propranolol and the α_1-, β_1- and β_2-AR antagonist carvedilol on LV remodeling by hypertension (see also Figure 1). The authors showed that AR blockers inhibited LV remodeling in hypertensive animals and affected receptor expression and post-receptor signaling using multiple experimental approaches (*in vivo* assessments of cardiac function, morphological studies and biochemical studies). It is surprising that, overall blockade of ARs (α_1-, β_1- and β_2-ARs) by carvedilol was not found to be superior to bisoprolol and propranolol in suppressing LV remodeling in their animal model. However, carvedilol was the most effective in attenuating cardiomyocyte apoptosis and normalizing downstream signaling by changing the expression level of ARs and G proteins compared with other AR antagonists.

In the healthy human heart, β_1-AR has been shown to be more abundant than β_2-AR, with a ratio of approximately 7:3.[2] β_1-ARs are known to couple with G_s proteins and stimulate intracellular cyclic AMP production, whereas β_2-AR couples with G_i proteins and inhibits cyclic AMP signaling (Figure 1).[1] In addition, β_2-ARs strongly activate a protective anti-apoptotic pathway (phosphoinositide 3-kinase-Akt), which counteracts pro-apoptotic G_s—cyclic AMP–PKA signaling.[2,6] Thus, selective activation of cardiac β_2-ARs may provide beneficial effects under pathophysiological conditions. In their study, Chen *et al.* found decreases in the expression levels of β-ARs (β_1- and β_2-AR) due to enhanced sympathetic stimulation,

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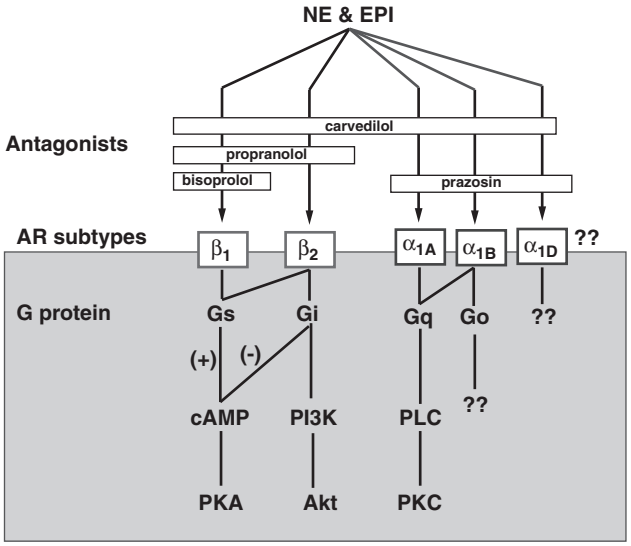

Figure 1 Cardiac adrenoceptor subtypes and their antagonists. EPI, epinephrine. NE, norepinephrine. PI3K, phosphoinositide 3-kinase. PLC, phospholipase C.

which recovered spontaneously in hypertensive rats treated with AR antagonists.[10] Moreover, the expression level of β_2-AR was increased in proportion to β_1-AR in the carvedilol-treated group compared with animals treated with propranolol (a β_1- and β_2-AR antagonist); however, carvedilol is known to be relatively selective to β_1-AR.[12] This specific recovery of β_2-AR signaling by carvedilol may, in part, contribute to the attenuation of cardiomyocyte apoptosis. However, further studies are needed to clarify the mechanism of carvedilol protection of β_2-AR signaling in the hypertensive heart.

In the human heart, three α_1-AR subtypes (α_{1A}-, α_{1B}- and α_{1D}-ARs) are expressed (Figure 1).[5] The α_{1A}- and α_{1B}-ARs couple mainly to G_q proteins, activating protein kinase C (PKC) signaling.[5,13] However, little evidence has been reported regarding the effect of stimulating α_{1D}-AR on the activation of functional downstream signaling pathways in cardiac myocytes. Transgenic mice overexpressing α_{1B}-AR showed a more severe hypertrophic heart phenotype and heart failure compared with that of α_{1A}-AR-overexpressing mice.[5] In contrast, α_{1A}-AR-overexpressing mice showed high contractility without hypertrophy.[5] At the cultured cell level, α_{1A}-AR signaling enhanced survival signaling in cardiomyocytes.[2] In their study, Chen *et al.* found that the expression level of α_{1B}-AR was significantly increased in spontaneously hypertensive rats, although α_{1A}-AR expression was not changed.[10] Moreover, the expression level of α_{1B}-AR and its downstream signaling pathways (PKCα and δ) were normalized only in the carvedilol-treated group. PKC represents a large gene family and has up to 12 isoforms, seven of which are expressed in the human heart.[14] PKC isoforms are involved in a variety of chronic cardiac diseases, including hypertrophy and heart failure, as well as in acute cardiac injuries and preconditioning. One of the Ca^{2+}-dependent PKC isoforms, PKCα, is the most abundant isoform in the human heart. Activation of this isoform has been linked to cardiomyocyte hypertrophy. PKCδ induces apoptosis in response to cardiac ischemia and reperfusion damage by mitochondrial translocation. The suppression of α_{1B}–AR–PKC signaling by carvedilol may also contribute to the attenuation of cardiomyocyte apoptosis.

Finally, why is the blockade of α_1-AR alone harmful but the combination of β- and α_1-AR blockade by carvedilol beneficial? This is possibly due to the specific pharmacological properties of carvedilol. Frishman showed that the α_1-AR antagonist activity of carvedilol was relatively weak compared with its blocking effect on β-ARs, which may have prevented harmful hemodynamic changes.[15] In addition, carvedilol had a relatively high affinity to α_{1B}-AR compared with α_{1A}-AR,[5] which contributed to the block of apoptotic and hypertrophic α_{1B}-AR signaling and maintained α_{1A}-AR-mediated increases in contractile function and survival. Finally, carvedilol is known to possess antioxidant properties unrelated to AR blocking.[15] Further investigation is necessary to clarify the contribution of each of these pathways to the beneficial effects of carvedilol.

In summary, the work by Chen *et al.* showed that the overall blockade of ARs (α_1-, β_1- and β_2-ARs) by carvedilol had stronger effects on promoting cardiomyocyte survival and normalization of downstream AR signaling compared with other AR antagonists. However, they found that the suppression of LV remodeling was similar to the other specific AR antagonists tested. Their results imply that long-term treatment with carvedilol may be beneficial for preventing the progression of LV remodeling induced by hypertension. Future studies should be directed toward elucidating the molecular mechanisms of AR subtype-specific LV remodeling, which may lead to the development of novel approaches for the treatment of LV remodeling.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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