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Carvedilol Promotes Cardiac Inotropic Response by Biased Agonism of the Nitric Oxide Pathway

Wang Q, Wang Y, West TM, Liu Y, Reddy GR, Barbagallo F, Xu B,Shi Q, Deng B, Wei W, Xiang YK. Carvedilol induces biased d1 adrenergic receptor-nitric oxide synthase 3-cyclic guanylyl monophosphate signalling to promote cardiac contractility. **Cardiovasc Res. 2021. 29;117(10):2237-2251. https://doi.org 10.1093/cvr/cvaa266.**

One of the most important effects of cardiac sympathetic stimulation is the increase in myocardial contractility, mainly through catecholaminergic activation of β1 adrenergic receptors. The production of cyclic adenosine monophosphate (cAMP) induced by β1-activation of the intracellular Gs protein promotes, via protein kinase A (PKA), phosphorylation of the proteins involved in myocyte excitation-contraction coupling. In pathological conditions, such as heart failure, pharmacological blockade of β1-adrenergic receptors is used to counteract the cardiotoxicity of cAMP signaling in the heart. Moreover, several additional physiological and pathophysiological β-blocker effects have been described both experimentally and clinically. In particular, one type of β-blockers, including carvedilol and nebivolol, evoke pleiotropic effects mediated by nitric oxide (NO) and cyclic guanosine monophosphate (cGMP), but their pharmacological activation mechanism is still unknown.

Wang et al. began to study the molecular signaling pathways underlying the inotropic and cardioprotective action induced by some β-blockers. A mice model overfed for 14 weeks with a high- or low-fat diet to simulate diabetes and isolated rat cardiomyocytes were used. Firstly, the acute administration of carvedilol showed a positive effect on the contractile shortening of isolated cardiomyocytes, independently of significant modifications on the calcium transient. This was not observed with acute administration of metoprolol. Mice on a high-calorie diet showed increased blood glucose levels and oral glucose intolerance, accompanied by impaired ejection fraction and ventricular remodeling. The 4-week treatment with carvedilol or metoprolol improved both ventricular remodeling and function. Isolated cardiomyocytes from these hearts were used to study contractility and its relationship with intracellular calcium management. Myocytes from carvedilol-treated mice showed improved contractile shortening, without major changes in calcium transients, which was not observed in the metoprolol-treated group. This suggests that both drugs promote different mechanisms of action on cardiac remodeling and function in this experimental model. Molecular studies showed that carvedilol, but not metoprolol, induces endothelial nitric oxide synthase (eNOS), Akt protein, phospholamban, and ryanodine 2 receptor phosphorylation, the last two closely linked to the excitation-contraction coupling mechanism. Biochemical and molecular studies demonstrated a selective increase of cellular cGMP levels induced by β1 stimulation in the group treated with carvedilol. The use of transgenic mice not expressing cardiac eNOS did not show the benefits of carvedilol treatment previously described. Finally, carvedilol treatment reduced cell apoptosis in hearts with diabetic disease.

Biased agonism is the mechanism whereby a ligand preferentially activates one signal pathway over another, acting on the same receptor. The β1-adrenergic receptor is a type of receptor coupled to an intracellular G protein. G proteins are a family of proteins that translate signals from the receptor to which they are coupled to the downstream effector protein in the intracellular signaling cascade. Depending on the G-protein subtype, different effects, often opposite, can be achieved through changes in the levels of the second messengers, cAMP or cGMP, among others.

Wang et al. results are in agreement with recent studies suggesting that β1-receptor stimulation is capable of translating various intracellular effects, and not only the increase in cAMP through the intracellular Gs protein. In fact, the transgenic modification of the β1-receptor structure achieved the opposite effect of reducing the levels of intracellular cAMP after the experimental administration of isoproterenol. Furthermore, studies in dogs and humans have shown that acute administration of carvedilol can promote cardiac contractility. A study using fibroblasts clearly demonstrated that carvedilol can promote β1-receptor coupling to the Gi protein and translate the activation of the MAPK cell survival pathway. Thus, in recent years, basic and clinical evidence has been collected validating that the cardioprotective effect of carvedilol is mediated by its action as a biased β1-adrenergic receptor agonist. Wang et al. show that carvedilol acts as a biased ligand to promote a robust and longer-range stimulus on the β1-cGMP receptor pathway compared with a minimal and restricted signal on the β1-cAMP receptor pathway. This biased β1-cGMP signaling is dependent on eNOS activation via the Gi-PI3K-Akt pathway. Through PKG, this new pathway assumes a dual beneficial effect, by activating cell protection signals and increasing contractility by an independent mechanism of direct calcium mobilization. Interestingly, these benefits were observed in both healthy hearts and the hearts of diabetic-compromised mice. These new results not only expand our understanding on the biased agonism of carvedilol in ventricular physiology, but also open new pathways for the study of these mechanisms as potential therapeutic targets for the management of heart failure with reduced ejection fraction and myocardial protection in cardiovascular diseases.