Beta-3 Adrenoreceptor: Boon or Bane in Heart Failure?

Giuliani Renz G. Paas, Jeremy Owen G. Go*, Ezekiel Morena S. Rivera, Margarita Ysabel S. Mangahas, Eunice Marie Perez-Trajano and Raul D. Jara

*Correspondence:
Jeremy G. Go, MD, University of the Philippines Manila, UER-MMCI, Philippines.

Received: 30 July 2020; Accepted: 19 August 2020

Citation: Giuliani Renz G Paas, Jeremy Owen G Go, Ezekiel Morena S. Rivera, et al. Beta-3 Adrenoreceptor: Boon or Bane in Heart Failure?. Cardiol Vasc Res. 2020; 4(3): 1-5.

ABSTRACT

Background: In a recent publication, four beta blockers—Metoprolol, Carvedilol, Bisoprolol, and Nebivolol have shown good effects in heart failure. Published studies on the role of beta-3 receptor (B3AR) agonism over the past 3 decades had conflicting results. Recent experimental studies described its role in coupling mechanisms with nitric oxide, offering protection in damaged cardiac myocytes.

Objectives: The general objective is to study the role of B3AR in heart failure and to identify the effects of four known beta blockers used in guideline-directed medical therapy on B3AR. Specifically, we want to know which beta blocker will upregulate or downregulate B3AR.

Methods: A systematic review was carried out through literature search on PubMed, MEDLINE, Herdin, and Cochrane for human studies describing the effects of B3AR upregulation in heart failure. Specifically, we searched for published studies regarding proposed mechanisms by which beta blockers utilized in guideline-directed medical therapy can provide cardioprotective effects through B3AR upregulation or downregulation.

Conclusion: The beneficial effects of the four identified beta-blockers on heart failure patients are well-established, but their effects on B3AR are varied with different mechanistic beneficial effect.

Keywords
Beta-3 adrenergic receptor, B3AR, Metoprolol, Bisoprolol, Carvedilol, Nebivolol, Heart failure.

Introduction

A. Research Question
Will the stimulation of B3AR have better hemodynamic effect in patients with heart failure?

B. Significance of The Study
Only experimental data are available regarding the role of B3AR in heart failure. The researchers would like to review the current evidence regarding B3AR and its utility in heart failure. Up to the time of writing, there are no published studies in the Philippines regarding B3AR.

Objectives
The general objective is to study the role of B3AR upregulation and/or downregulation in heart failure.

Materials and Methods

Study Selection
We searched for publications on human studies, review articles, and experimental studies on PubMed, MEDLINE, Herdin, and Cochrane using the following keywords: beta-3 adrenergic receptor, beta-3 adrenoceptors, B3AR, beta blockers, and heart failure in the past 30 years.

Inclusion criteria
We included published studies on humans, review articles, and experimental studies in human tissues published in PubMed, MEDLINE, Herdin, and Cochrane which discussed the effects...
of B3AR agonism and antagonism, its pharmacodynamics, and expression of these receptors in heart failure in the last 30 years. The following keywords are used: beta-3 adrenergic receptor, B3AR, metoprolol, bisoprolol, carvedilol, nebivolol, and heart failure.

Exclusion criteria
We excluded animal studies about B3AR that were published in PubMed, MEDLINE, Herdin, and Cochrane.

Results and Discussion
The Beta-3 Adrenergic Receptor

The Beta-3 Adrenoreceptor: A walk down memory lane

The human gene that encodes the beta-3 adrenoreceptor was first isolated and characterized in 1989 and showed pleiotropic effects on brown fat thermogenesis, ileal relaxation, and soleus muscle glycogen synthesis [1]. Earlier studies on human tissues found that B3ARs are highly expressed in adipose tissue but are not detected in quadriceps or abdominal muscles, heart, liver, lung, kidney, thyroid, and lymphocytes [2]. B3AR and its traditional role in lipolysis has been studied over the past decades as a potential target of antidiabetic and anti-obesity drugs [3]. Since its discovery, little is known about the effects of B3AR stimulation and/or blockade. Its molecular mechanisms, particularly in the cardiac myocyte, are poorly understood in contrast to beta-1 adrenergic (B1AR) and beta-2 adrenergic receptors (B2AR)—both of which are widely utilized in guideline-directed medical treatment of heart failure [4,5]. One study demonstrated that activation of the cardiac B3AR by endogenous catecholamines led to depression of left ventricular contraction and relaxation in chronic heart failure [6]. However, a recent study refuted these findings, and showed that B3AR agonism has a cardioprotective effect through its coupling with other molecular events that involve the nitric oxide (NO) pathway [7]. NO is a well-known vasodilating substance beneficial in heart failure. In smooth muscle cells, NO causes relaxation while it increases left ventricular distensibility and myocardial performance in cardiac myocytes [8,9].

Majority of beta-adrenergic receptors in healthy human cardiac myocytes are composed of beta-1 and beta-2 subtypes—with a 4:1 ratio—and minimal expression of the beta-3 subtype [10]. There is growing evidence that there is an increased expression of B3AR in heart failure [6,11]. A recent systematic review discussed the downregulation of beta-1 receptors, with overexpression of B3AR in heart failure and hypertension [12].

Newer studies on the structure and function of the B3AR, as well as pharmacologic agonists, are underway—with the goal of providing novel therapeutic strategies in managing patients with heart failure [13].

Structure and Function of Beta-3 Adrenergic Receptor

Unlike its two other counterparts, the B3AR lacks the particular amino acid sequences targeted by protein kinase A (PKA) and G-protein coupled receptor kinase 2 (GRK2), making it resistant to catecholamine-induced downregulation [14]. Furthermore, B3AR are coupled to two different isoforms of G-proteins—Gα stimulatory (Gαs) and Gα inhibitory (Gαi) subunits. The B3AR is mainly coupled with the Gαi subunit, with downstream pathways leading to activation of the nitric oxide synthase (NOS) pathway to promote myocyte relaxation and endothelial smooth muscle cell vasodilation [10,14]. Activation of the nitric oxide synthase by the upregulation of B3AR will lead to production of the vasodilatory nitric oxide in the endothelium and myocardium. It also suppresses the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, bringing about its antioxidant effects, downregulating the reactive oxygen species that cause endothelial inflammation and myocardial fibrosis (Figure 1) [13,15].

Figure 1: Graphic representation summarizing the mechanism behind the upregulation of B3AR and hemodynamic improvement in heart failure. NOS, Nitric Oxide Synthase; cGMP, Cyclic Guanosine Monophosphate; PKG, Protein Kinase G; ROS, Reactive Oxygen Species [13-16,20].
In a healthy human heart, 80% of adrenergic receptors are composed of B1AR subtype while 20% are composed of B2AR (Figure 2). On the other hand, heart failure results in the downregulation of B1AR and the ratio between B1AR and B2AR becomes equal. In heart failure and hypertension, beta-3 receptors—present both in the atria and ventricles—are overexpressed in heart failure and hypertension [12].

**Beta Receptors in Heart Failure**

In patients with heart failure, the increased sympathetic activity causes phosphorylation of B1AR and B2AR by cAMP-dependent protein kinase or beta-adrenoreceptor kinase resulting in their decreased expression in cardiac myocytes [16]. The receptor downregulation causes decreased inotropic response to catecholamines. In contrast, B3AR lacks phosphorylation sites for cAMP-dependent protein kinase or beta-adrenoceptor kinase, preventing its downregulation [14]. B3AR signalling is coupled with the inhibitory subunit of adenyl cyclase (Gai) thereby countering the overstimulation from downregulation of B1AR and B2AR, making the failing heart sensitive to catecholamine stimulation to increase its inotropy [14]. Furthermore, another advantage of the B3AR in endothelial cells is the activation of the Nitric Oxide Synthase (NOS) pathway. The increase in NO production and guanylate cyclase activation generates cyclic guanosine monophosphate (cGMP) and Protein Kinase G (PKG). In effect, endothelial function increases, leading to vasodilation and improvement of coronary perfusion (Figure 1) [14,17].

In addition to its vascular effects, NOS pathway activation causes myocardial relaxation, preventing excessive oxygen demand and ventricular remodelling[15]. PKG activation reduces calcium oscillations to prevent arrhythmia, hypercontracture, and sarcolemmal rupture which lead to cell death [18-20]. Lastly, through the B3AR, the NOS pathway decreases NADPH oxidase activity, thereby decreasing reactive oxygen species which deactivate the Na/K ATPase pump [14,15,17]. Hence, the restoration of Na/K ATPase pump activity leads to improvement of myocardial contractility. Targeting the B3AR in cases of heart failure can be a promising point of interest in terms of pharmacological management.

**B. Review of Selected Beta Blockers Beneficial In Heart Failure and Their Effects on B3AR**

In a recent publication, it was emphasized that the use of beta blockers prevents the excessive sympathomimetic activity and downregulation of B1AR and B2AR, with upregulation of B3AR [12]. Specifically, four beta blockers have been identified to have novel mechanisms in reducing the effects of heart failure—Metoprolol, Nebivolol, Bisoprolol and Carvedilol (Figure 3). These beta blockers provide varied expression with different mechanistic beneficial effect in heart failure.

**Figure 2:** Difference in the amount of beta receptors in a (A) normal heart and a (B) diseased heart. In a previous study, it was established that the number of B1AR and B2AR are closely equal in heart failure [12].

**B. Review of Selected Beta Blockers Beneficial In Heart Failure and Their Effects on B3AR**

In a recent publication, it was emphasized that the use of beta blockers prevents the excessive sympathomimetic activity and downregulation of B1AR and B2AR, with upregulation of B3AR [12]. Specifically, four beta blockers have been identified to have novel mechanisms in reducing the effects of heart failure—Metoprolol, Nebivolol, Bisoprolol and Carvedilol (Figure 3). These beta blockers provide varied expression with different mechanistic beneficial effect in heart failure.

**Figure 3:** Effects of four beta blockers to the B3AR. Metoprolol and Nebivolol upregulates B3AR; Bisoprolol has a neutral effect on the B3AR; while Carvedilol downregulates the B3AR [12].

**Metoprolol**

Metoprolol is a cardio-selective inhibitor of the B1AR, with minimal to no effects on B2AR [21]. Likewise, Metoprolol causes upregulation of the B3AR expression [12] in cases of heart failure. This mechanism activates the NOS pathway in the vessels and in the myocardium. The vasodilating effect decreases the total peripheral resistance which improves the cardiac output. On the other hand, myocardial relaxation, prevention of cell death and restoration of Na/K-ATPase pump activity occur in effect. Hence, causing improvement of heart failure hemodynamically.

Human studies on the effect of Metoprolol and B3AR are distinctly limited. Apparently, only researches using animal models were available, metoprolol has shown beneficial effect using B3AR upregulation by enhancing the NOS pathway leading to improved cardiac function [14].

**Nebivolol**

Nebivolol is a beta-1 selective beta blocker that antagonizes sympathetic effects of myocardial contraction and exerts protective effect along the endothelial lining, through its metabolic effects, which contribute to enhanced cardiovascular functions [22]. The additional vasodilatory effect of Nebivolol is the consequence of its B3AR agonistic action, promoting endothelial NO production [22]. In effect, there is a reduction in the peripheral vascular resistance with an increase in stroke volume without causing deleterious effect in the left ventricular function [12]. In addition, it also has a capacity to exert protective metabolic effects, thereby preventing the formation of atherosclerosis along the vascular lining. This mechanism promotes greater vascular compliance and improved cardiac output [12].
**Bisoprolol**

Bisoprolol is a highly selective blocker of the B1AR [23]. In one review, it showed neutral effect to the B3AR in terms of upregulatory or downregulatory mechanisms. Its property of being highly cardiac selective could explain its neutrality on the B3AR [12]. Bisoprolol has no effect on NO generation, yet it is still an effective beta blocker for heart failure by providing agonistic effect on the downregulated B1AR in cardiac myocytes by promoting vasodilation [12].

**Carvedilol**

Carvedilol is a non-selective adrenergic blocker, with alpha-1 adrenergic receptor antagonist properties [21]. It is known as a beta blocker with peripheral vasodilating effects thereby decreasing total peripheral resistance [24]. This favorable hemodynamic profile improves cardiac output, stroke volume, and left ventricular function. In addition to its antihypertensive properties, carvedilol has antiproliferative effects on smooth muscle cells and inhibits oxygen free radicals [24]. In addition, this drug has advantage in the setting of congestive heart failure by blocking the beta-adrenergic receptors, thereby protecting the heart from chronic sympathetic stimulation, while its vasodilating activity counterbalances any acute adverse effect of beta blockade on hemodynamics [25].

Limited studies on human tissues have been conducted to demonstrate the effects of Carvedilol on the B3AR. Carvedilol is known to downregulate B3AR expression, alongside B1AR and B2AR [12]. Despite this, the drug still works as an effective therapeutic agent for heart failure due to its activity on the alpha receptor [12].

**Conclusion and Recommendations**

The beneficial effects of the four identified beta-blockers on heart failure patients are well-established, but their effects on B3AR are varied with different mechanistic beneficial effect. Further studies are still needed to elucidate the role of different beta blockers on B3AR in therapeutics.

**References**

1. Emorine LJ, Marullo S, Briend-Sutren MM, et al. Molecular characterization of the human beta 3-adrenergic receptor. Science. 1989; 245: 1118-1121.
2. Krief S, Lonqvist F, Raimbault S, et al. Tissue distribution of β3-adrenergic receptor mRNA in man. Journal of Clinical Investigation. 1993; 91: 344-349.
3. Arch JR, Ainsworth AT, Cawthorne MA, et al. Atypical beta-adrenocceptor on brown adipocytes as target for anti-obesity drugs. Nature. 1984; 309: 163-165.
4. Yancey CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Journal of the American College of Cardiology. 2017; 70: 776–803.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. 2016; 18: 891-975.
6. Morimoto A, Hasegawa H, Cheng HJ, et al. Endogenous β3adrenoreceptor activation contributes to left ventricular and cardiomyocyte dysfunction in heart failure. American Journal of Physiology - Heart and Circulatory Physiology. 2004; 286: 2425-2433.
7. Niu X, Watts VL, Cingolani OH, et al. Cardioprotective effect of beta-3 adrenergic receptor agonism: Role of neuronal nitric oxide synthase. Journal of the American College of Cardiology. 2012; 59: 1979-1987.
8. Chirinos JA, Akers SR, Trieu L, et al. Heart failure, left ventricular remodeling, and circulating nitric oxide metabolites. Journal of the American Heart Association. 2016; 5: 6-8.
9. Singh P, Vijayakumar S, Kalogeroupoulos A, et al. Multiple Avenues of Modulating the Nitric Oxide Pathway in Heart Failure Clinical Trials. Current Heart Failure Reports. 2018; 15: 44-52.
10. Claudio de Lucia, Akito Eguchi, Walter J. Koch. New insights in cardiac β-Adrenergic signaling during heart failure and aging. Frontiers in Pharmacology. 2018; 9: 1-14.
11. Bristow MR, Hershberger RE, Port JD, et al. Beta-adrenergic pathways in nonfailing and failing human ventricular myocardium. Circulation. 1990; 82: 112-125.
12. Go JG, Santiago LD, Miranda AC, et al. Effect of Beta-blockers on Hypertension and Heart Failure with Reduced Ejection Fraction: A Systematic Review of Randomized Controlled Trials. Hypertension Journal. 2019; 5: 1-6.
13. Balligand JL. Cardiac beta3-adrenergic receptors in the clinical arena: the end of the beginning. European Journal of Heart Failure. 2017; 19: 576-578.
14. Cannavo A, Koch WJ. Targeting β3-adrenergic receptors in the heart: Selective agonism and β-blockade. Journal of Cardiovascular Pharmacology. 2017; 69: 71-78.
15. Bachus E, Ponikowski P. Beta-3 Receptor Agonists. International Cardiovascular Forum Journal. 2019; 18: 15-18.
16. Gauthier C, Tavernier G, Charpentier F, et al. Functional β3adrenoreceptor in the human heart. Journal of Clinical Investigation. 1996; 98: 556-562.
17. Balligand JL. Cardiac salvage by tweaking with beta-3-Adrenergic Receptors. Cardiovascular Research. 2016; 111: 128-133.
18. Abdallah Y, Gkatzoflia A, Gligorievski D, et al. Insulin protects cardiomyocytes against reoxygenation-induced hypercontracture by a survival pathway targeting SR Ca2+ storage. Cardiovascular Research. 2006; 70: 346-353.
19. Abdallah Y, Gkatzoflia A, Pieper H, et al. Mechanism of
cGMP-mediated protection in a cellular model of myocardial reperfusion injury. Cardiovascular Research. 2005; 66: 123-131.

20. Inserte J, Garcia-Dorado D. The cGMP/PKG pathway as a common mediator of cardioprotection: Translatability and mechanism. British Journal of Pharmacology. 2015; 172: 1996-2009.

21. Benjamin W. Van Tassell. A Systematic Review of the Beta-Blockers Carvedilol and Metoprolol for the Treatment of Chronic Heart Failure. Journal of pharmacology & clinical research. 2017; 3: 1-9.

22. Cohen Arazi H, Gonzalez M. Nebivolol: Does the key lie in β3 agonism?. Vascular Diseases and Therapeutics. 2017; 2: 1-6.

23. Pascal de Groote, Pierre-Vladimir Ennezat, Frédéric Mouquet. Bisoprolol in the treatment of chronic heart failure. Vascular Health and Risk Management. 2007; 3: 431-439.

24. Moser M, Frishman W. Results of therapy with carvedilol, a β-blocker vasodilator with antioxidant properties, in hypertensive patients. American Journal of Hypertension. 1998; 11: 15-22.

25. McTavish D, Campoli-richards D, Sorkin EM. Carvedilol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs. 1993; 45: 232-258.