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Beta blockers, nitric oxide, and cardiovascular disease

Paul M Vanhoutte[1,2] and Yuansheng Gao[3]

The third generation β-blockers possess important ancillary properties besides inhibiting β-adrenoceptors. Among them, nebivolol activates nitric oxide synthase (NOS). Nebivolol and carvedilol preserve NOS activity by reducing asymmetrical dimethylarginine (AMDA) and enhance the bioavailability of nitric oxide (NO) because of their antioxidant properties. Concerning the treatment of hypertension and chronic heart failure, these third generation β-blockers show distinct advantages resulting from their NO-dependent effects (vasodilatation, anti-proliferation and cardioprotection), which may translate into a more effective clinical outcome than that obtained with the conventional β-blockers. Impaired NOS activity and reduced NO bioavailability are common initiators of cardiovascular dysfunction. Thus, owing to their NO-mediated actions, the new generation β-blockers should find more clinical applications in the treatment of cardiovascular diseases.

Addresses
[1] Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China
[2] Department of BIN Fusion Technology, Chonbuk National University, Jeonju, South Korea
[3] Department of Physiology and Pathophysiology, Peking University, Health Science Center, Beijing, China

Corresponding author: Gao, Yuansheng (ygao@bjmu.edu.cn)

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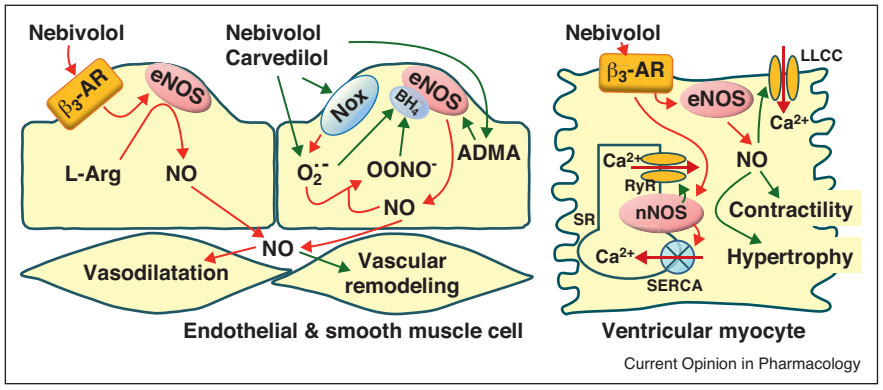
Introduction

β-Adrenergic receptors (β-ARs) play a pivotal role in the regulation of cardiovascular activities. At present three types of β-ARs have been identified, namely β_1-ARs, β_2-ARs, and β_3-ARs. All of them are present in the vasculature and cardiac muscle, with β_2-AR predominate in most vessel types and β_1-AR predominate in heart tissue [1–3]. In the blood vessels activation of β_1-ARs, β_2-ARs, and β_3-ARs stimulates the production of nitric oxide (NO) by eNOS in the endothelium [2]. Upon release, NO diffuses into the nearby smooth muscle cells where it stimulates soluble guanylyl cyclase (sGC) to generate cGMP and subsequently activates cGMP-dependent protein kinase (PKG). PKG causes vasodilatation by decreasing the intracellular calcium concentration ($[Ca^{2+}]_i$) and by reducing the sensitivity of myofilaments to calcium via the activation of myosin light chain phosphatase (MLCP) [4,5]. Activation of $\beta_{1,2,3}$-ARs on smooth muscle cells leads to elevated cAMP and PKA activation. PKA causes vasodilatation by reducing $[Ca^{2+}]_i$ and stimulating MLCP [1,5,6]. In cardiac myocytes activation of $\beta_{1,2}$-ARs stimulates the contractility via cAMP-PKA signaling while β_3-AR activation suppresses the contractility via cGMP-PKG signaling [1,3]. PKA acts through the stimulation of L-type voltage-dependent calcium channel (LTCC) on cell membrane and rynadine receptor (RyR) on the sarcoplasmic reticulum (SR), which leads to an increased $[Ca^{2+}]_i$ [7]. PKA also activate the SR calcium ATPase (SERCA), resulting in enhanced SR store loading and thereby enhanced contraction [7]. PKA also increases the calcium sensitivity of myofilaments by the phophorylation of troponin I (Tpn I) [5,8]. The underlying mechanisms for PKG action include the inhibition of LTCC and RyR, stimulation of SERCA, and phosphorylation of Tpn I [2,3,5] (Figure 1).

Under disease conditions when coronary blood flow cannot match the needs of cardiac workload the blockade of β-ARs, mainly β_1-AR, would prevent myocardial ischemia to occur. The reduced cardiac output may further lead to decreased blood pressure. β_1-AR antagonism also inhibits the release of renin and thereby suppresses vasoconstriction caused by angiotensin [9]. The first beta-adrenergic inhibitor (β-blocker), dichloroisoproterenol, was synthesized by Eli Lilly Laboratories in 1958. The first clinically significant β-blocker — propranolol — was developed by Sir James W. Black in 1962 [10]. Since then β-blockers evolved into three generations. The first and second generation β-blockers (conventional β-blockers) have no significant ancillary properties, with the former being nonselective and the latter selective for β_1-AR. The third generation β-blockers may be selective or nonselective for β_1 or β_2 ARs but possess important ancillary properties. Among them, nebivolol and carvedilol have been studied most intensively. Nebivolol is a highly selective β_1-blocker with the ability to stimulate nitric oxide synthases (NOSs) while carvedilol is a nonselective β-blocker with α_1-blocking properties. Nebivolol causes vasodilatation mainly by endothelium-derived NO while carvedilol by its α_1-adrenergic antagonist property. Both nebivolol and carvedilol possess antioxidant properties. Therefore, they may augment NO action via enhancement of NO bioavailability [11].

Diminished NO production and bioavailability are common initiators and independent predictors of

Figure 1



Regulation of cardiovascular activities by β-Adrenergic receptor (β-AR). In the vasculature (left panel) activation of $\beta_{1,2,3}$-ARs stimulates the conversion of nitric oxide (NO) from L-arginine (L-Arg) by eNOS in the endothelial cells. NO then diffuses into the underlying smooth muscle and activates soluble guanylyl cyclase (sGC), resulting in increased cGMP from GTP and activation of cGMP-dependent protein kinase (PKG). PKG causes vasodilatation by reducing the intracellular calcium concentration ($[Ca^{2+}]_i$) and by decreasing the calcium sensitivity of myofilaments via activating myosin light chain phosphatase (MLCP). Activation of $\beta_{1,2,3}$-ARs on smooth muscle cells stimulates adenylyl cyclase (AC) with resultant cAMP elevation and PKA activation. PKA can also causes vasodilatation by decreasing $[Ca^{2+}]_i$ and activating MLCP. In cardiac myocytes (right panel) activation of $\beta_{1,2}$-ARs stimulates the contractility via cAMP-PKA signaling. PKA may increase $[Ca^{2+}]_i$ by stimulating L-type voltage-dependent calcium channel (LTCC) on cell membrane and activating rynadine receptor (RyR) on the sarcoplasmic reticulum (SR). PKA-mediated activation of the SR calcium ATPase (SERCA) enhances SR store loading and thereby enhances contraction. PKA also increases the calcium sensitivity of myofilaments by the phophorylation of troponin I (Tpn I). β_3-AR exerts an inhibitory effect on the contractility of cardiac muscle via cGMP-PKG signaling, the underlying mechanisms include the inhibition of LTCC and RyR, stimulation of SERCA, and phosphorylation of Tpn I. The red arrow lines denote stimulatory and green arrow lines inhibitory effects.

cardiovascular events [4,12]. Substantial evidence implicates a critical role of NO in the favorable therapeutic effects of the third generation β-blockers on cardiovascular diseases [13]. This brief review will summarize the NO-related actions of these compounds including NO-mediated vasodilatation and cardiacprotection, inhibitory effects on endogenous NOS inhibitor asymmetrical dimethylarginine (ADMA), and antioxidant properties. The role of the NO-related actions of these β-blockers in the treatment of hypertension, heart failure and some other cardiovascular disorders will also be discussed.

NO-mediated vasodilatation

Nebivolol is the only β-adrenergic antagonist that causes vasodilatation primarily by the activation of NOS. The first study on endothelium-derived NO (EDNO)-dependent vasodilatation induced by nebivolol was conducted in isolated canine coronary arteries [14]. The important role of EDNO in the vasodilator effect of nebivolol has been subsequently confirmed in various species including the human, in conductance and resistance arteries as well as in veins, and under both *in vitro* and *in vivo* conditions [13]. It is now generally recognized that nebivolol exert its dilator effect by activating eNOS after its binding to the receptors on the endothelial cell membrane. Nebivolol is a racemic mixture of D-enantiomers and L-enantiomers. Its β_1-antagonistic properties reside almost entirely in D-nebivolol while both D-enantiomers and L-enantiomers are capable of activating eNOS, although the L-isomer is more potent [13].

Activation of β_3-AR is an important mechanism for nebivolol to stimulate eNOS and cause vasodilatation. In contrast, carvedilol, another third-generation β-blocker, is an antagonist of β_3-AR [15]. Nebivolol dose-dependently relaxes rodent coronary resistance microarteries, an effect which is sensitive to NOS inhibition and prevented by the nonselective β-blocker bupranolol but unaffected by the $\beta_{1\text{-}2}$-blocker nadolol. Nebivolol fails to relax microarteries from β_3-AR-deficient mice [16]. In an isolated blood-perfused juxtamedullary rat nephron preparation nebivolol but not metoprolol (a conventional β_1-blocker) markedly increased afferent and efferent arteriolar diameters. The effect was prevented by inhibitors of NOS and soluble guanylyl cyclase as well by a β_3-blocker, suggesting that nebivolol causes vasodilatation via a mechanism that is dependent of activation of β_3-AR and is mediated by EDNO-cGMP signaling [17]. The EDNO-dependent relaxation of rat aortae caused by the L-enantiomer of nebivolol is mediated by β_3-ARs while the D-enantiomer causes relaxation by activating β_2-ARs and β_3-ARs and antagonizing α_1-AR [18]. Shear stress play an important role in circulatory homoeostasis. The role of ARs including β_3-AR in shear stress-induced vascular responses is not well studied. In Goto-Kakizaki rat, a non-obese type 2 diabetes model, β_3-AR inhibitor