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Abstract Beta-blockers are widely prescribed for the treatment of a variety of cardiovascular pathologies. Compared to traditional beta-adrenergic antagonists, beta-blockers of the new generation exhibit ancillary properties such as vasodilation through different mechanisms. This translates into a more favorable hemodynamic profile. The relative affinities of beta-adrenoreceptor antagonists towards the three beta-adrenoreceptor isotypes matter for predicting their functional impact on vasomotor control. This review will focus on the mechanisms underlying beta-blocker-evoked vasorelaxation with a specific emphasis on agonist properties of beta3-adrenergic receptors.

Keywords Hypertension · Beta-blockers · Beta1-blocker · Vasodilation · Beta3 agonism · Cardiovascular disease · Arteries

Introduction

Beta-blockers are widely prescribed for the treatment of a variety of cardiovascular pathologies including hypertension, heart failure, primary treatment of myocardial infarction, secondary prevention of ischemic cardiac events as well as for other non-cardiovascular diseases. Consistent with so many different beneficial effects, a large variety of beta-blockers exist, which differ in their receptor selectivity, their pharmacokinetic and pharmacodynamic properties. The first generation beta-blockers with propranolol are non-selective and block both beta1- and beta2-adrenoceptors. The second generation includes agents like metoprolol and atenolol, which are called cardioselective and preferentially block beta1-adrenoreceptors. More recently, beta-blockers with additional ancillary properties have been developed, among which are Nebivolol and Carvedilol. Compared to classical beta-antagonists, they promote a vasodilation through different mechanisms, which translate into a more favorable hemodynamic profile compared to non-vasodilating beta-blockers. This review will focus on the mechanism(s) behind this beta-blocker-evoked vasorelaxation.

Underlying Mechanisms of Vasodilation

Endothelium-Dependent Relaxation

The endothelium largely contributes to vascular homeostasis through the synthesis and release of several contracting and relaxing factors. Nitric oxide (NO) is the main vasodilator released from endothelial cells (ECs); the others are prostacyclin (PGI2) and endothelium-derived hyperpolarizing factor (EDHF).

In the vasculature, the predominant NOS isoform is eNOS, which is responsible for most of the NO production
Like other NOS isoforms, eNOS generates NO through the conversion of L-arginine to L-citrulline, and its activation relies on intracellular calcium concentration as well as on the presence of tetrahydrobiopterin (BH4) and NADPH [2]. NO synthesis is stimulated in response to shear stress or calcium-mobilizing agonists such as acetylcholine and dilates blood vessels by inducing the formation of cGMP from GTP in the underlying smooth muscle cells [3, 4]. In the context of this review, the beta-blocker, Nebivolol, was shown to activate both NO and cGMP production in different vascular beds (see Fig. 1) [5, 6]. The observation that, in a rat model of hypertension, carvedilol-induced decreases in blood pressure are associated with increased NO plasma levels also suggests that Carvedilol relaxation properties partly relate to the NO pathway [7]. Whether this relates to an improved NO production or a reduced oxidative stress-dependent NO degradation remains to be resolved. In addition to its vasodilating effect, NO inhibits platelet aggregation and adhesion, leukocyte activation and smooth muscle proliferation. Thus, NO is an important actor in the endogenous defense against vascular injury, inflammation and thrombosis [8]; these latter properties should be taken into account when considering the...

**Fig. 1** Schematic overview of adrenoreceptor distribution in endothelial and smooth muscle cells illustrating the potential target pathways inducing vasomotion. Relevant interrelationships (→ = activators, = inhibitors) between adrenoreceptors and some of the vasodilator substances produced by the endothelial cell (EC) and second messenger vasodilator pathways in the vascular smooth muscle cell (VSMC) are represented. AA arachidonic acid, α-AR alpha-adrenoreceptors, Akt protein kinase B, ATP adenosine triphosphate, β-AR beta-adrenoreceptors, Ca²⁺ calcium from both voltage- and agonist-dependent channels, CAMKK calmodulin-dependent protein kinase kinase, cAMP adenosine 3',5'-cyclic monophosphate, cGMP cyclic guanosine 3',5'-monophosphate, COX cyclooxygenase, DAG diacylglycerol, EDH(F) endothelium-derived hyperpolarization (or hyperpolarizing factor), Gi inhibitory regulative G-protein, Gq heterotrimeric G protein subunit q, Gs stimulative regulative G-protein, GTP guanosine triphosphate, IP₃ inositol 1,4,5-triphosphate, K⁺ potassium from both voltage- and agonist-dependent channels, L-arg L-arginine, NADPH nicotinamide adenine dinucleotide phosphate, NO nitric oxide, NOS nitric oxide synthase, PGH₂ prostaglandin H₂, PGI₂ prostacyclin, PI3K phosphoinositide-3-kinase, PIP₂ phosphatidylinositol bisphosphate, PKA protein kinase-A, PKG protein kinase-G, PL (C, D, A₂) phospholipase (C, D, A₂), ROS reactive oxygen species, S.R. = sarcoplasmic reticulum
potential beneficial effects of drugs (beta-blockers in this case) that promote the NO pathway.

Prostacyclin is a product of cyclooxygenase (COX) formed from arachidonic acid in ECs and causes relaxation via activation of an IP receptor (prostaglandin I2 receptor) [9] stimulating adenylate cyclase and increasing the intracellular cAMP level [10]. Despite the fact that its contribution to endothelium-dependent relaxation is not preeminent, prostacyclin, like NO, has antiplatelet and antithrombotic activity. They act synergistically, and both effects are tightly related since PGI2 potentiates NO release and NO potentiates PGI2’s effect on vascular smooth muscle cells (VSMCs) [11]. The link between beta-adrenoceptors and prostacyclin production in the endothelium is ambiguous as beta-adrenergic stimulation promotes prostacyclin synthesis, which is countered by a cAMP-dependent inhibition of phospholipase D activity [12].

A third pathway that is independent of the two previously cited is termed “endothelium-derived hyperpolarizing factor” (EDHF). The name may be confusing since both NO and/or PGI2 are able to hyperpolarize the underlying smooth muscle cells [13, 14], and the phenomenon is increasingly described as simply “endothelium-dependent hyperpolarization” (EDH) [15]. What is meant with EDH(F) is the hyperpolarization of both ECs and VSMCs, which requires an intracellular Ca2+ increase in ECs, a subsequent opening of small and intermediate calcium-activated potassium channels (SKCa and IKCa) and the spread of hyperpolarization throughout the media via myoendothelial gap junctions toward VSMCs [16]. Despite remaining controversies regarding the mediators involved, an increasing amount of experimental evidence suggests that EDH(F) contributes to control blood flow, especially in resistance arteries, and systemic blood pressure [17–19]. EDH(F) is a potential, still under-explored, pharmaceutical target that participates in the beta1-adrenoceptor-mediated vasodilation (see below for details and Fig. 1).

Endothelium-Independent Relaxation

In addition to endothelium-dependent relaxation, vasodilation also occurs through a direct effect on smooth muscle cells. VSMC tone is highly dependent on the membrane potential, which is essentially determined by K+ channel activity. The general working of these channels is as follows: once activated, the resultant increased K+ efflux causes membrane potential hyperpolarization, which closes voltage-dependent Ca2+ channels and therefore decreases Ca2+ entry, leading to VSMC relaxation. Among these channels, voltage-gated potassium channels (Kv), high conductance Ca2+-activated channels (BKCa) as well as ATP-sensitive K+ (KATP) channels contribute to the majority of the K+ current [18]. In the context of the present review the latter are of highest interest as several reports implicated KATP channel activation in beta-adrenoreceptor-mediated vasodilation. Indeed, using isoprenaline together with the KATP channel inhibitor glibenclamide on rat mesenteric arteries, Randall and McCulloch showed that the vasodilator potency of this beta-adrenoreceptor agonist is coupled to the opening of KATP channels. They additionally demonstrated that both beta1- and beta2-adrenoreceptors are implicated since dobutamine and terbutaline (beta1 and beta2-agonists, respectively) gave similar results [19]. Notably, the underlying pathway was described by Wellman, Quayle and Standen. They showed that KATP channel activation by beta-adrenoreceptors occurs via stimulation of PKA, resulting from adenyl cyclase-mediated cAMP generation [20, 21] (see Fig. 1). In opposition to the endothelium-independent process, a very recent study demonstrated that following focal beta-adrenoreceptor stimulation, a KATP and endothelium-related hyperpolarization underlies the ability of vasodilation to spread along the artery wall [22]. This latter mechanism might also be of physiological and pharmacological relevance when considering vasorelaxing properties of beta-adrenoreceptor modulators. Of note, it has been shown in cat atrial myocytes that beta1-adrenoreceptor exclusively couples via Gi-protein to adenylate cyclase to stimulate cAMP synthesis, while beta2-adrenoreceptor also couples, via Gi-protein and PI3K/Akt signaling, to NO production and cGMP activation [23]. This finding is of particular interest as it suggests that the vasodilation provided by beta-adrenoreceptor stimulation may involve both endothelium-independent (cAMP pathway) and -dependent (eNOS stimulation and cGMP pathway activation) mechanisms. This point will be developed later on.

Adrenoreceptor Distribution in Heart and Vessels

Adrenoreceptors belong to the family of G-protein coupled receptors stimulated by catecholamines and are found in nearly all peripheral tissue membranes. When after their discovery divergent pharmacological characteristics and molecular differences were rapidly observed, adrenoreceptors were first divided into two major types, namely alpha and beta [24]. Subsequently, both types were subdivided into alpha1, alpha2, beta1 and beta2 subtypes and further divided into at least three groups [25]. Finally, the beta-adrenoreceptor family was enriched with a third member cloned in 1989 [26]: the beta3-adrenoreceptor, which is of particular interest in the present review as it has been linked to beta-associated vasodilation.

The Alpha-Adrenoreceptors

As the common and most described function of alpha-adrenoreceptor is the vasoconstriction of arteries and veins,
they will only briefly be considered here. It has been widely
demonstrated in animals and humans that both alpha1- and
alpha2-adrenoreceptors contribute to coronary vasoconstric-
tion. Using large and small canine coronary arteries, Heusch
and coworkers interestingly showed that alpha1-adrenorecep-
tor rather induces vasoconstriction of conduit vessels, whereas alpha2-adrenoreceptor is predominant in mediating
microvascular contraction of resistance vessels [27]. Addi-
tionally, both alpha-adrenoreceptor subtypes have been ob-
served in endothelial and smooth muscle cells in various
vascular beds with perhaps a preferential location of alpha1-
adrenoreceptors in smooth muscle cells, whereas alpha2-
adrenoreceptors may be more expressed in the endothelium
[28, 29]. Importantly, both subtypes can interact, as illus-
trated in rat tail arteries by Xiao and Rand, who showed that
alpha2-adrenoreceptor enhances the agonist response to al-
pha1-adrenoreceptor through a Ca2+-dependent mechanism
[30].

Perhaps more relevant is the fact that despite extensive
description of their contracting properties, alpha-
adrenoreceptors are also proposed as indirect vasodilators.
Although the underlying mechanisms may still be somewhat
disputed [31, 32], endothelial alpha2-adrenoreceptors were
clearly shown to couple to NOS activation [33]. The above
properties help interpreting the effect of combined alpha1
and beta-agonists of Carvedilol [34]. With the same method, they examined the distribution of beta-adrenoreceptor subtypes to membrane subdomains
such as caveolae has also been investigated. Rybin et al. for
instance identified the caveolae as a site to assemble func-
tionally active beta-adrenoreceptor complexes in rat cardio-
myocytes. Using subcellular fractioning they evidenced that
beta2-adrenoreceptors are confined to the caveolae, whereas
beta1-adrenoreceptors are detected across the sucrose gradi-
ent, thus also located in non-caveolar plasma membrane
fractions [38]. These results were further confirmed using
filipin, a caveolar-disrupting agent that selectively affected
the functional properties of the beta2-adrenoreceptor in car-
diac myocytes [39].

Concerning the location of the beta1-adrenoreceptor on a
vascular level, many studies concur to propose its endothe-
lial location as the removal of the endothelium strongly
impairs beta3-adrenoreceptor activation. This was shown in
several models, such as in rat thoracic aorta [40], in human
coronary microarteries [41, 42] and in human mammary
arteries [43]. Endothelial expression of the beta3 isotype
was also confirmed by transcription-polymerase chain reac-
tion assay in endothelial cells isolated from human cardiac
tissue by laser capture [41]. Conversely, Viard and col-
leagues, using similar transcription-polymerase chain reac-
tion assays, showed that beta3-adrenoreceptors were
expressed in rat portal vein myocytes together with beta1-
and beta2-adrenoreceptors [44]. The presence of functional
beta3-adrenoreceptors has also been demonstrated in the rat
retinal vascular bed. As in other vascular beds, their stimu-
luation mediates a vasodilation; however, their specific loca-
tion (endothelium versus smooth muscle cells) was not
completely characterized [45].

In the heart, the anatomical location of beta3-adrenore-
ceptor has been little studied so far; beta3-adrenoreceptors
are clearly expressed in cardiac myocytes, including in
humans [46, 47] and several other species [47]: although we
did not find any difference of beta3 expression among
the different layers of the human ventricular muscle, the
abundance of beta3-adrenoreceptor strikingly increases in
several forms of cardiomyopathies (compared with non-
diseased hearts) [48].

A summary of the beta-adrenoreceptor location in the
vascular compartments is proposed in Fig. 1, which helps
to interpret the effects of integrated molecular and pharmacological events resulting from the diverse abundance and locations of beta-adrenoreceptor in normal and disease states.

Pharmacology of Beta-Blockers and Incidence on Vasodilatation

As outlined above, the relative affinities of beta-adrenoreceptor antagonists towards the three beta-adrenoreceptor isotypes matter for predicting their functional impact on vasomotor control. This in turn will influence both the efficacy of any specific beta-blocker on cardiovascular disease and the incidence of side effects, particularly on tissue perfusion.

Since the early development of beta-adrenoreceptor antagonists following the pioneering work of Sir J. Black [49], the therapeutic armament has been enriched from non-specific pan-beta-adrenoreceptor antagonists to beta-adrenoreceptor-specific blockers that mostly target the beta1-adrenoreceptor. This is indeed the isotype that has mainly been involved in the anti-anginal and anti-hypertensive effect of beta-blockers by opposing the inotropic effect of catecholamines on cardiac muscle. The same effect was subsequently demonstrated to confer beneficial effects in the setting of heart failure, probably by preventing from adverse myocardial remodeling, protecting failing cardiac myocytes from the toxicity of neurohormonal overstimulation, as well as by restoring beta-adrenoreceptor expression and density, resulting in restoration of heart rate variability [50].

The use of the first beta1-adrenoreceptor “preferential” antagonists, however, has exposed patients to common side effects due both to the expected beta1-adrenoreceptor blockade (e.g., bradycardia), but also to off-target effects attributable to targeting of the other isotypes [51]. Accordingly, blockade of beta2-adrenoreceptor (and possibly beta3-adrenoreceptor) is classically associated with bronchospasm as well as peripheral vasoconstriction due to loss of beta2 (and, possibly beta2)-adrenoreceptor-mediated relaxation of smooth muscles [51].

Further drug development led to the introduction of beta-blockers with either better selectivity for the beta1-adrenoreceptor, ancillary vasodilating properties or both. Among the first, drugs such as metoprolol have proven their better beta1-adrenoreceptor selectivity with lower vascular or bronchial side effects, without compromising efficacy [51]. Other less (or non-) selective beta-blockers, such as carvedilol, are endowed with additional properties that compensate for the lack of selectivity, e.g., through alpha-adrenoreceptor blockade and possibly antioxidant properties, both of which may preserve vasodilatation (on top of antagonizing adverse effects of adrenergic tone on oxidant stress and tissue remodeling) [7].

In this context, drugs that improve endothelial function have received recent renewed attention, especially in the context of evidence demonstrating the prognostic value of endothelial dysfunction and its pathophysiologic role in the development of cardiovascular disease, e.g., atherosclerosis, ischemic cardiovascular disease and heart failure. Some “third-generation” beta-adrenoreceptor blockers were indeed shown to influence endothelial function through either targeting of specific beta-adrenoreceptor isotypes or other receptors on the endothelial cells.

Celiroprol, a beta1-specific antagonist, was shown to exert agonist properties on beta2-adrenoreceptors, which have been implicated in enhanced endothelial NO synthesis, vascular anti-oxidant effects and preserved vasodilatation [52]. Whether this translates into better protection from cardiovascular morbidity/mortality in patients remains an unanswered question.

Endothelial function involves more than NO synthesis and production (as outlined in the previous sections). In this regard, another recent beta-blocker, Nebivolol, may present the most pleiotropic vasculoprotective properties. It is highly selective for beta1-adrenoreceptor blockade (>200-fold over beta2) [53]; in addition, in several animal but also human vessels, it activates beta3-adrenoreceptor [42], which (as outlined above) is expected to activate not only NO production from eNOS, but also to recruit additional components of endothelium-derived vasodilatation, such as “EDH(F)(s).” Importantly, these vasodilatory properties were demonstrated in human coronary microvessels, but also in human mammary arteries from diseased patients [41–43], emphasizing their potential therapeutic relevance. Finally, as beta2-adrenoreceptors were also shown to be expressed in cardiac myocytes from human ventricles [47], their activation of myocardial NO production would promote NO-cGMP-mediated relaxation as well as protection against excessive catecholamine stimulation that, together with coronary vasodilatation, would combine beneficial effects on the myocardial oxygen supply and demand to preserve ventricular function [54*].

Again, whether this translates to superior protection from morbidity/mortality in patients needs to be demonstrated with a “head-to-head” comparison of Nebivolol with a pure beta1-adrenoreceptor blocker in a prospective, randomized trial. So far, the SENIORS trial in elderly patients with moderate heart failure only compared Nebivolol with placebo, and showed an improvement in clinical symptoms [55] (as previously demonstrated with other beta-blockers in HF trials). This suggests that if beta2 agonist properties are operative in vivo, they at least do not negate the expected beneficial effects of beta1-adrenoreceptor blockade.

Moreover, the comparative efficacy of Nebivolol and the “pure” beta1-adrenoreceptor blocker, Metoprolol, has been
tested on the protection against adverse remodeling and mortality in a mouse model of myocardial infarction. This showed the superior efficacy of Nebivolol against hypertrophic remodeling of the remaining viable myocardium, better preserved endothelium-dependent relaxation ex-vivo and endothelial progenitor cells function [56]. Importantly, the use of a mouse model allowed the direct comparison of Nebivolol protection in wild-type mice and mice with genetic deletion of eNOS; Nebivolol’s effect was lost in the latter, showing an obligatory role of eNOS, at least in the mouse [57]. This could be correlated with Nebivolol’s properties to prevent oxidative stress in isolated endothelial cells that were lost upon full beta_{1,2,3} blockade [58•].

In the next section, we will outline the experimental evidence for these ancillary properties of Nebivolol (as well as other specific beta_{3}-adrenoceptor agonists) on endothelial function in animal and human vessels.

**Beta_{3}-Adrenoceptor and Vasorelaxation**

The observation that Nebivolol dose-dependently relaxed preconstricted rodent coronary resistance microarteries but failed to do so in microarteries isolated from beta_{3}-adrenoceptor-deficient mice demonstrates a beta_{3} agonism for Nebivolol [42]. Additional pharmacologic evidence supports this hypothesis as Nebivolol-induced relaxation of human coronary microvessels was insensitive to beta_{1,2,3} blockade [42]. Similarly, Nebivolol-induced relaxation of the rat thoracic aorta is resistant to beta_{2} blockade, but inhibited by S-(−)-Cyanopindolol or by L-748,337, a selective beta_{3}-adrenoceptor antagonist [59, 60 and 61•]. As described earlier, the beta_{3}-adrenoceptor-subtype is mainly expressed on the vascular endothelium, consistent with functional evidence. Indeed, several studies described the loss of beta_{3}-dependent vasodilation in endothelium-denuded vessels [42, 60]. However, BRL 37344, a selective beta_{3}-adrenoceptor agonist, was shown to evoke a relaxation of endothelium-denuded human internal mammary arteries, suggesting that in some vascular beds, an endothelium-independent pathway may exist [62]. NOS inhibition strongly reduces the relaxation of human coronary microvessels and rat aorta to Nebivolol or BRL37344 [42, 60]; likewise L-NAME attenuated vasorelaxing responses to both the beta_{3}-adrenoceptor agonist BRL 37344 and non-specific isoprenaline in rat carotid arteries [63]. In cultured endothelial cells, beta_{3}-adrenoceptor stimulation with Nebivolol increased NO release as measured by electron paramagnetic resonance spin trapping. In parallel, fura-2 calcium fluorescence was increased and endothelial NOS was dephosphorylated on threonine(495/497) [42]. Similarly, epinephrine-dependent eNOS activation through beta_{3}-adrenoceptor signaling is accompanied by an increase in phosphorylation of eNOS at Ser(1179) and with decreased eNOS phosphorylation at the inhibitory phosphorylation sites Ser(116) and Thr(497) [64], confirming that beta_{3} adrenoceptor vasodilation is associated the endothelial synthesis/release role of nitric oxide. In the context of NO-mediated response to Nebivolol, it is also worth mentioning that Nebivolol promotes angiogenesis in a NOS/beta_{3}-dependent manner, which could be of particular interest in the course of treatment of ischemia-associated diseases. Besides, in human coronary resistance arteries, in the presence of NOS and Cox inhibition, an endothelium-dependent relaxation to beta_{3}-adrenoceptor stimulation persists. BRL37344-mediated hyperpolarization of smooth muscle cell membrane and the inhibitory effect of the combination of apamin and charybotoxin concur to suggest that beta_{3}-adrenoceptor stimulation with BRL37344-evoked relaxation is partly mediated via an endothelium-derived hyperpolarization (EDH(F)). This could be a real advantage in pathological situations associated with reduced NO bioavailability.

Of note, Nebivolol is used as a racemate mixture of the two enantiomers D-Nebivolol (+SRRR nebivolol) and L-Nebivolol (−RSSS neivbolol), which present different pharmacological properties. Both Nebivolol enantiomers produced a vasorelaxation through activation of beta_{3}-adrenoceptors. However, D-Nebivolol-produced vasorelaxation is also mediated by activation of beta_{2}-adrenoceptors and antagonism of alpha_{1}-adrenoceptors [61•]. This could broaden the clinical interest of Nebivolol as beta_{3} agonism could alleviate the contraindication of beta-blockade in obstructive respiratory disease.

**Conclusion**

In conclusion, beta-blockers are widely used for the treatment of hypertension. The latest generation of beta-blockers exhibits ancillary properties, such as Nebivolol, which demonstrates additive pleiotropic vasculoprotective effects in comparison to traditional beta-antagonists. In particular, Nebivolol exerts agonist activity on beta_{3} adrenoceptors, which mediates endothelium-dependent modulation of vascular tone. As nitric oxide release promotes vasodilation and angiogenesis, this suggests that beta_{3}-adrenoceptors could represent a new therapeutic target to improve the hemodynamic profile in hypertension.

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