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Some Aspects of the Action of Beta-Adrenergic Receptor Blockers in the Treatment of Arterial Hypertension

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Abstract

Arterial hypertension is a complex and multifactorial process. The pathophysiological factors involved in the pathogenesis of arterial hypertension include activation of the sympathetic nervous system, changes in the activity of adrenergic receptors, overproduction of hormones that regulate sodium metabolism and vasoconstrictors, activation of vascular growth factors, structural and functional disorders in the vascular network, inflammation, oxidative stress, endothelial dysfunction, blood clot formation. Despite many works dedicated to the research of the causes and mechanisms of the development of hypertension, its pathogenesis has not been completely determined, and the issue of choosing an effective treatment remains an actual problem. Hypertension is characterized by impaired sensitivity of the β-adrenergic system which causes the use of β-adrenergic blockers to treat hypertension. In the presented review the mechanisms of action of beta-adrenergic receptor blockers during treatment of hypertension and their effects are discussed.

Key words: arterial hypertension, beta-adrenergic receptor blockers, immune system, nitric oxide, erythrocyte.

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Introduction

Arterial hypertension is a complex and multifactorial process. The etiological factors of arterial hypertension include genetic factors, kidney disease, pheochromocytoma, hyperthyroidism, drug (hypertension induced by mineralocorticoids, glucocorticoids, cyclosporine), nutritional (salt intake) factors, and others. However, in the majority of patients, it is impossible to determine a specific hypertensive factor ("primary, ie essential hypertension"). Despite many works dedicated to the research of the causes and mechanisms of the development of hypertension, its pathogenesis has not been completely determined, and the issue of choosing an effective treatment remains an actual problem. Arterial hypertension is noteworthy in terms of the development of complications.

Today, the pathophysiological factors involved in the pathogenesis of arterial hypertension include activation of the sympathetic nervous system during psychological stress, overproduction of hormones that regulate sodium metabolism and vasoconstrictors, activation of vascular growth factors, changes in the activity of adrenergic receptors, structural and functional disorders in the vascular network, endothelial dysfunction, oxidative stress, blood clot formation, including enhancement of remodeling and reduction of elasticity of blood vessels.

Studies conducted on hypertensive patients and animal models of genetic hypertension confirm the important role of sympathetic (adrenergic) activity in its pathogenesis [1].

Adrenergic receptors are a class of G protein-coupled receptors that are the target of catecholamines (norepinephrine and epinephrine). Adrenoreceptors are found on the membranes of many cells andare involved in the pathogenesis of many diseasesand critical conditions. The mobilization of catecholamines in the blood takes place in such situations as hypoxia, anemia, and hypercapnia, during strenuous exercise, that is, in conditions when it is necessary to increase the intensity of oxygen transport. These hormones initiate the development of integrated physiological responses for modulation of cardiovascular and respiratory functions, and modification of metabolic pathways. The functional activity of adrenoreceptors provides regulation of the intensity and direction of the adaptive reactions in the living organism, it is an important marker of the outcome of the pathological process, and also an effective target forthe treatment of various diseases.

Functions and mechanism of action of β-adrenoceptors; β-adrenoceptors agonists and antagonists

Regulation of the sympathoadrenal system activity is important, and the β-adrenoceptor is a significant target in many diseases such as arterial hypertension, coronary heart disease, tumors, and inflammation [2-5] and other diseases [6,7]. β-adrenoreceptors belong to the family of G-protein coupled receptors (GPCR), they are involved in the regulation of cell membrane signaling systems through activation of heteromeric G-proteins and other signaling molecules (including GPCR kinases (GRKs)).

The inhibitory effect of propranolol (a non-selective β-adrenergic receptor blocker) on norepinephrine-induced expression of vascular endothelial growth factor (VEGF) in adipose tissue [8] and on the norepinephrine-induced release of a functional angiogenic factor in nasopharyngeal carcinoma tumor cells has been described [9], which indicates the participation of β-adrenoreceptors in the regulation of the angiogenesis process. The last circumstance indicates the participation of adrenoreceptors in the modulation of the functioning of various systems of the living organism and the pathogenesis of many diseases (tumor growth, development of metastases, rheumatoid arthritis, diabetic retinopathy, ischemic heart disease, damage to peripheral blood vessels [10-17]. They affect the expression of cytokines, and chemokines [18], VEGF, and fibroblast growth factor [19-21], hepatocyte growth factor (HGF), placental growth factor, stromal cell factor-α [22-24], matrix metalloproteinases (MMP – a group of enzymes that play an important role in the degradation of extracellular matrix macromolecules and remodeling of connective tissue)[25].

β-adrenoceptor agonists are known to cause vasodilation. Their vasodilatory effect is caused by activation of the β-AR/Gs protein/adenylyl cyclase/cAMP/PKA pathway in smooth muscle cells [26-28]. However,

in addition to Gs, β2-AR can activate the Gi protein (G_s and G_i families regulate adenylyl cyclase activity) leading to stimulation of the Src/Ras/MAPKs signaling pathway. Continuous stimulation of β-adrenoreceptors has been shown to lead to phosphorylation of the vascular MAPK ERK1/2 activation in vascular cells [29] and increases the expression of pro-inflammatory cytokines in the aorta even during sustained acute isoproterenol-induced vasorelaxation and PKA expression [30-32] This pro-inflammatory effect leads to a decrease in NO content, accompanied with increase in the local expression of pro-inflammatory factors (ICAM-1, VCAM-1 and interleukin (IL)-6), blockade of NF-κB activity restores aortic endothelial dysfunction. Based on this observation, it was hypothesized that overstimulation of β-adrenoreceptors can initiate endothelial dysfunction and inflammation.

β-adrenoceptors antagonists (β-adrenoceptorsblockers) are widely used in the treatment of cardiovascular diseases , and their antitumor and anti-inflammatory effects are well known [33-35]. Hypertension is characterized by impaired sensitivity of β-adrenergic system [36,37] which causes the use of β-adrenergic blockers to treat hypertension.Despite the widespread use of β-adrenoceptor blockers in the treatment of hypertension and cardiovascular diseases, the mechanisms of their clinical effects have not been fully established. β-blockers can be divided into three groups: first-generation non-selective β-blockers, second-generation selective β-blockers, and third-generation β-blockers that additionally have a vasodilating effect [38 39].

Studies have shown that propranolol, a first-generation non-specific β-blocker inhibits ERK1/2 activation and has protective properties. Propranolol treatment can lead to a decrease in systolic pressure, improved endothelium-dependent relaxation, activation of eNOS, and an increase in NO content in the blood. It also leads to a reduction in the expression of inflammatory markers, including C-reactive protein [32].

The main component of ьecond generation selective β-blockers, Egilok and Betaloc-zok, is metoprolol (Egilok - metoprolol tartrate, Betaloc Zok - metoprolol succinate). Activation of eNOS by the β-adrenergic system is mediated by two mechanisms: phosphorylation of Ser 1177 via the PI3K/Akt signaling pathway and calcium-dependent translocation of eNOS from plasma membrane caveolae to cytosolic calmodulin. Although Akt phosphorylation is increased by metoprolol exposure, eNOS phosphorylation is not altered, suggesting an inability of this drug to regulate nitric oxide generation and any subsequent negative inotropic effects [40].

Nebivolol is a third-generation selective β1-adrenergic receptor blocker with unique vasodilating action. The third-generation β-blocker Nebivolol is a highly selective β1-adrenoceptor antagonist with vasodilating effects. Studies in vitro and in vivo, in animals and humans, have shown that Nebivolol provides vasodilation of resistance arteries and veins by a NO-dependent mechanism. Intravenous infusion of Nebivolol resulted in improvement of forearm blood flow in healthy subjects and hypertensive patients. In addition, the NO synthase inhibitor NG-monomethyl-L-arginine can block Nebivolol-induced vasodilation. The exact mechanisms by which Nebivolol increases endothelial NO viability are not fully established but may involve activation of endothelial NO synthase through stimulation of β3-adrenoreceptors expressed in endothelial cells, reduction level of asymmetric dimethylarginine, and reduction of reactive oxygen species content [41].

Interaction of β-adrenergic receptors and NOSs system

Nitric oxide (NO) is an essential component of the human body, a biological messenger participating in the regulation of vascular tone, vasodilatation, platelet aggregation, and leukocyte adhesion. An increasein NO content causes vasodilatation and inhibitionof the proliferation of smooth muscle cells, stimulation of hormone release, signaling, and regulation of neurotransmission [42-44]. It has also been shown that NO synthesized in endothelial cells spreads not only to the surrounding smooth muscle cells but also to the vascular lumen [45-46]. NO is synthesized by NO-synthases (NOSs – endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS)) as a result of the conversion of L-arginine to L-citrulline. The main source of NO is endothelial cells, blood cells (platelets, monocytes, and erythrocytes) also can produce NO.

It is known that in the vasoregulation of blood vessels participates the β-adrenergic system, which is mediated by activation of the L-arginine/NOS pathway through cAMP-dependent mechanisms (PKA or PI3K-ACT signaling pathway),this mechanism provides phosphorylation of serine-177 of eNOS, consequently, its Ca^{2+}-independent activation[47]and intensification of NO synthesis. Increased level of NO synthesis, in turn, promotes hyperpolarization of the plasma membrane, activation of CAT-1 (a carrier of cationic amino acids), increase in arginine consumption by eNOS, and, therefore, further intensification in NO production [47,48].

Alterations in the neuronal NOS (nNOS) activity have been detected in areas of the central and peripheral autonomic nervous system, involved in regulating blood pressure[49]. An increase in the content of NO in the paraventricular nuclei of the hypothalamus leads to a decrease in sympathetic outflow; NO plays an important role in lowering blood pressure during recovery from psycho-emotional stress [50].

As already noted, continuous stimulation of β-adrenoreceptors leads to MAPK ERK1/2 activation in vascular cells and expression of pro-inflammatory cytokines. This pro-inflammatory effect causes a decrease in NO content [30]. Blockade of NF-κB activity restores endothelial dysfunction. Based on this observation, it was hypothesized that overstimulation of β-adrenoreceptors can initiate endothelial dysfunction and inflammation. Long-term use of beta-adrenergic blockers in hypertension and chronic congestive heart failure increases life expectancy. From this point of view, studying the mechanisms of interaction and interdependence between β-adrenergic and NO-ergic systems is interesting.

β-adrenoreceptors on the erythrocyte membrane

The β-adrenoreceptors are also found on the erythrocytes and lymphocyte membranes [54,55]. Erythrocytes are multifunctional cells; in addition to gas transport, they are involved in regulating the rheological parameters of the blood, transport of medicinal, biologically active substances and immune complexes, and vascular dilatation, they play an important role in the regulation of vascular tone, and arterial, and venous blood pressure, and affect platelet function. Erythrocytes can regulate lymphocyte-endothelium interaction, immune response, and intensity of apoptosis in activated T cells, they also inhibit neutrophil apoptosis[56].

It is established that β-adrenoreceptors play an important role in the regulation of erythrocyte function - they participate in the regulation of their pH, hemoglobin's affinity for oxygen, oxygen transport, and rheological properties (deformability, aggregation, adhesion) [57].

Regulation of the blood fluidity may be mediated through the sympathetic adrenergic nervous system. The investigations of the effects of adrenergic receptor agonists and antagonists on blood fluidity show that adrenergic receptor-modulating drugs alter blood fluidity through changes in both platelet aggregation and erythrocyte deformability [58].

It is known, that the deformability of the erythrocyte's membrane depends on the viscoelastic properties (related to lipids composition), properties of their membrane peripheral (cytoskeletal, adhesive proteins), and integral (pumps an channels) proteins, fluidity of the cytoplasm, and the cell's shape and size (surface area/volume ratio)[59]. In the regulation of erythrocyte diameter and volume, membrane transport systems are involved – channels and pumps (Na^+/K^+-ATPase and Ca^{2+}-ATPase) maintaining cellular osmotic balance and low concentration of intracellular Ca^{2+}. β-adrenoceptors agonist-induced modification of membrane transport proteins (L-type Ca^{2+}-channels, Ca^{2+}-dependent K^+-channels (Gardo channels), Na+/K+-ATPase, Ca^{+2}-ATPase, $Na^+/K^+/2Cl^-$cotransporter, Na^+/H^+-antiporter) activity can cause changes in the osmotic balance and volume of erythrocytes, which can affect their deformability [60].

β-adrenoceptors activity mediated by a receptor-coupled G protein leads to adenyl cyclase activation, and the formation of a secondary messenger, cyclic adenosine monophosphate (cAMP) inside the cell, which through cAMP-dependent protein kinases (PK-A, PK-C) promotes modification of membrane transport proteins (L-type Ca^{2+}-channels, Ca^{2+}-dependent K^+ channels (Gardo channels), Na+/K+-ATPase, Ca^{+2}-ATPase, $Na^+/K^+/2Cl^-$cotransporter, Na^+/H^+-antiporter, CAT-1 **(**a carrier of cationic amino acids)), AMP-

dependent L-arginine/NOS system, and erythrocyte NOS (erNOS) activity, intensity of NO synthesis and ATP reliase, and therefore modulate the cells pH, osmotic balance, volume [61-66]. that is reflected in the erythrocytes rheological properties (deformability, aggregability), regulate cellular clearance [67]. Therefore, it seems reasonable to suppose that alterations of erythrocyte deformability mainly are associated with activation of the AC-cAMP-PKA pathway, and with a decrease of Ca^{2+} entry into cells.

The findings suggest that beta-adrenergic agonists may increase mechanical fluctuations of the cell membrane in human erythrocytes, the bending deformability of the membrane-skeleton complex and therefore improve the passage of erythrocytes through microvasculature, enhancing oxygen delivery to tissues, especially under situations of reduced oxygen tension for periods 20 -60 min [51]. Study results suggestthe long-term and short-term beneficial effects of beta-blockade in various prethrombotic conditions (e.g., hypertension, angina pectoris, reinfarction) may be partly due to the interference of these drugs with the normal and abnormal adhesive and rheological properties of human erythrocytes [68]. A study showed that treatment with β-blockers (propranolol)increased erythrocyte deformability and decreased adhesion [69,70].

The deformability of erythrocytes is crucial for microcirculation, as well as for maintaining the normal intensity of blood flow in large vessels: it allows erythrocytes to pass through narrow capillaries and also reduces blood viscosity in large vessels [71]. It was shown that a decrease in the deformability of erythrocytes leads to a violation of microcirculatory perfusion [72] especially important during various critical situations [73-78].

β-adrenoceptors mediated alterations in the activity of erythrocyte membrane transport systems also leadto alterations **of** their acidity, metabolism level, NOS activity, and intensity of NO synthesis.

There is evidence that human erythrocytes are positive for both inducible (iNOS) and constitutive (NOS) NO synthase (NOS) and can also synthesize their NO [79]. The effects of NO are known to be mediated by cGMP produced by soluble guanylate cyclase. The presence of soluble guanylate cyclase in erythrocytes has been established, which confirms the role of guanylate cyclase and related metabolic pathways in the regulation of erythrocyte functions [80]. The CAT-1 protein is also found in the erythrocytes membrane[81], which indicates the possibility of participation in the above-mentioned β-adrenergic regulatory mechanism of NO synthesis in erythrocytes.

According to Stamler (1996), erythrocytes can absorb NO synthesized by endothelial cells, and transport nitrosylated hemoglobin. NO interacts with the heme moiety of erythrocyte hemoglobin to form S-nitroso hemoglobin and participate in the regulation of its bioactivity [82-84].

It is suggested that NO synthesized in erythrocytes can modulate the physiological behavior of erythrocytes [79-85]. It has been shown that NO may have a regulatory effect on RBC deformability and aggregation essential for the transport of these cells in narrow capillaries, and this effect depends on NO concentration[86-89]. Chronic inhibition of NOS by N ω-nitro-l-arginine methyl ether (l-NAME) was found to significantly reduce erythrocyte deformability in rats [90]. The mechanical properties of erythrocytes from these animals were normalized in vitro by a low dose (10 μM) of sodium nitroprusside (SNP), whereas higher doses were ineffective [91].

β-adrenoreceptors on the lymphocyte membranes

The sympathetic nervous system integrates the functions of many organ systems, including the immune system, with their autonomic physiological regulation mechanisms. The existence of an autoregulation mechanismbetween the nervous and immune systems ensures the maintenance of homeostasis and modification of the immune response in various diseases [92,93].

Neuroimmune communication mechanisms involve the interaction of immune cells with signaling molecules of the nervous and endocrine system via activation ofmembrane adrenergic receptors, including β-adrenoreceptors, which are expressed on various (innate and adaptive) immune cells. Pharmacological analyses using various β-agonists and antagonists indicate the presence of specific beta-

adrenergic receptors on the lymphocyte membrane [94] (about 2000 specific β-adrenergic receptors per 1 lymphocyte). Adrenergic signaling through the β-adrenoreceptor-Gs-adenylyl cyclase system regulates a variety of immune cell functions, from cell migration to cytokine secretion.

Epidemiological and experimental studies have revealed a relationship between biochemical markers of systemic inflammation and cardiovascular diseases such as atherosclerosis, heart failure, and hypertension [95]. A link between the regulatory systems of arterial hypertension, such as the renin-angiotensin system and the sympathetic nervous system, and proinflammatory cytokines has been identified. Proinflammatory cytokines affect vascular function by regulating the release of vasoactive factors by the endothelium, thereby participating in the regulation of blood pressure. Both TNF- and IL-6 have been shown to induce structural and functional changes in endothelial cells and enhance the release of vasoactive substances by endothelial cells such as endothelin, nitric oxide, and NOS-m-RNA [96].

Thus, endothelial dysfunction associated with many forms of hypertension may be partially mediated by changes in proinflammatory cytokines, suggesting a potential role for cytokines in the regulation of arterial hypertension.

During hypertension, the enhanced expression of adhesion molecules on the blood vessels of the heart and kidneys contributes to the accumulation of inflammatory cells, increasing the extravasation of leukocytes, and infiltration of macrophages and T cells. Infiltrating mononuclear cells induces the expression of pro-hypertensive cytokines, including IL-6, IL-10, IL-17, IL-4, IFN-γ and TNF-α [97]. It has been established that T lymphocytes are involved in the process of increased blood pressure, which sheds light on the involvement of innate and adaptive immunity in the pathogenesis of hypertension [98-100]. In severe combined immunodeficiency mice or Rag1 knockout mice, functional T cells have been shown to increase renal sodium retention and intravascular volume expansion, leading to a sustained increase in blood pressure [101]. Treg cells suppress cellular immune responses. Accordingly, Treg cells limit the development of atherosclerosis, and the adaptive response of Treg cells in hypertensive mice dramatically attenuates the degree of cardiac hypertrophy. CD4 + CD25 + Treg have been shown to improve vascular function and limit blood pressure increases in response to angiotensin II or aldosterone[101]. IL-10 is the main effector cytokine of Treg cells, consistent with its immunosuppressive function. Administration of exogenous IL-10 improves blood pressure and endothelial function Normalization in a rodent model of pregnancy-induced hypertension. Thus, as in other cardiovascular diseases, in hypertension T regulatory cells exert a protective function, in part through the action of IL-10. According to the data, it may be assumed that the change in the mitogenic response of lymphocytes in essential hypertension is due to changes in the distribution of lymphocyte subclasses.

Adrenergic receptors on the surface of Th1 are almost exclusively ADRB2, whereas Th2 are fairly devoid of ADRB receptors on their cell membrane [102]. The effect of receptor stimulation depends on different factors and is not the same for each CD4 + T cell subset or culture condition: ADRB2 engagement on activated naïve T cells in the presence of IL-12 leads to increased production of IFN-γ per cell in comparison to naïve cells activated alone without ADRB stimulation [103]. Similar results were obtained by engagement of ADRB2 on activated naïve T cells in the presence of IL-4, which increased the cytokine release per cell by differentiated Th2 cells. If ADRB stimulation occurred before, during, or after activation, cells produced less, unchanged, or increased amounts of IFN-γ, respectively, than control cells that were activated alone [104].

IL-17-deficient mice have been shown to have impaired hypertensive responses to chronic angiotensin II infusion, suggesting that Th17 cells contribute to increased blood pressure. Administration of antibodies neutralizing IL-17 or IL-23, a cytokine that promotes Th17 differentiation, stabilized blood pressure under angiotensin II infusion. Moreover, in a saline (sodium-dependent) hypertension model, IL-17- or IL-23-deficiency caused kidney damage, suggesting a protective role of Th17 cells as well [105].

Stimulation of sympathetic neurons innervating secondary lymphoid organs is known to suppress inflammation in various chronic diseases by blocking cytokine secretion (locally and systemically) [96].

Regulation of the functional activity of lymphocytes, and protective and harmful effects of T cell antibodies, it is necessary to take into account several autoregulatory mechanisms [93,106], which ensure the interaction of immune cells with mediators of the nervous and endocrine systems, maintaining the homeostasis of these systems and regulating the immune response during various diseases. This mechanism is quite powerful and has been used to treat various chronic inflammatory diseases.

To control "inflammation", the neuro signaling system via β-adrenoreceptors limits the release of inflammatory cytokines by macrophages and dendritic cells, as well as the activation of T cells. Blocking inflammatory stimuli is used to treat various chronic diseases. It has been shown that β-blockers can change the mitogenic response of lymphocytes (IL-2 production and, therefore, the proliferation of T cells, (LPS)-induced TNF-alpha, interleukin 6, interleukin 1-beta production) [107,108], enhance their proliferation and differentiation, and therefore change the distribution of lymphocytes in subpopulations [109].

Administration of propranolol before the stressful stimulus has been shown to inhibit acute lymphocyte and monocyte mobilization induced by the activation of the biological stress response or catecholamine infusion [110]. The nonselective ADRB antagonist nadolol prevents the norepinephrine-induced increase in IFN-γ [102].

Furthermore, T-cell differentiation is regulated by ADRB2, and the stimulation of ADRB2 on naïve T lymphocytes favors Th1 differentiation, which may be blocked by β-antagonists [111]. The study revealed that propranolol restores homeostasis and normalizes the function of T-cell subsets. However, to complete the understanding of the impact of BB on the T-cell population, more studies are needed.

European Society of Hypertension upgraded β blockers, putting them on equal footing with thiazide diuretics, renin–angiotensin system blockers (eg, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), and calcium channel blockers. In most current national and international hypertension guidelines, β blockers are only considered to be an alternative when there are specific indications. Compared with the other first-line antihypertensive drug classes, β blockers are significantly less effective in preventing stroke and cardiovascular mortality [112].

Primary/essential hypertension in younger/middle-aged is underpinned by high sympathetic nerve activity. In this age group, high resting heart rates and high plasma norepinephrine levels (independent of blood pressure) are linked to premature cardiovascular events and death. Beta-blockers perform well in reducingthe risk of death/stroke/myocardial infarction in younger (<60 years) hypertensive subjects and are a reasonable first-line choice of therapy (certainly in men) [113]. Beta-blockers also have an anti-inflammatory effect, improve the rheological properties of blood, and reduce thrombus formation.

Conclusion

Much remains to be done to develop a perfect clinical/pharmacological management of hypertension. To improve clinical results, it is necessary to develop new improved methods of prevention and therapy of hypertension. For this, it is necessary to identify and specify the mechanisms of vasomotor function regulation (including immune, adrenergic, and NO-ergic), reveal new pharmacological targets, and search for new treatment methods.

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