ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 611.018.74:616.12-008.331.1

Morphofunctional alterations in endothelium in the pathogenesis of essential hypertension

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Received 7 July 2017;
accepted 21 August 2017.

Abstract

Endothelium is a multilevel cellular structure that permeates all organs and systems of the body. A disorder of the regulation of the arterial tone underlies essential hypertension. However, its pathogenesis basis, despite intense efforts, remains unclear. The unfavorable role of emotional stress, hypodynamia, obesity and disorder of water-salt metabolism is obvious. However, the exact mechanisms and predictors of the development of arterial hypertension (HTN) are not currently defined. This opposes the prevention and detection of essential hypertension at an early stage. The investigation of endothelial function as a target and a predisposing factor for HTN development is promising and implies both scientific and applied clinical significance. Indeed, understanding of pathognomonic endothelial alterations for HTN development will clarify its pathogenesis and will help the development of the adequate treatment protocols. The paper reviews current data on the involvement of endothelial cells (EC) in the development of HTN. The role of lipid disorders in the physiological state of the endothelium is shown. The role of endothelial dysfunction in increasing production of active oxygen species and disorders in the nitric oxide metabolism is highlighted. The activity of the following enzyme is reviewed: NADPH (nicotinamide adenine dinucleotide phosphate) oxidase, cyclooxygenase, xantinoxydoreductase and endothelial NO synthase. The interaction of the endothelium and the extracellular matrix, as well as endothelium and smooth muscle cells, is also given according to the literature data. The role of ghrelin, produced by endothelium, in the regulation of vascular tone is highlighted. Methods of the EC assessment in vitro under hypoxia are presented. Based on the literature review, it is clear that the assessment of the endothelium under hypoxia is highly important, as well as the investigation of the influence of tissue and hemic hypoxia in vivo. These studies will help to establish the contribution of functional endothelial disturbances to the development of HTN.

Key words: arterial hypertension, essential hypertension, endothelium, endothelial cells

For citation: Sysoev KA. Morphofunctional alterations in endothelium in the pathogenesis of essential hypertension. Arterial'naya Gipertenziya = Arterial Hypertension. 2017;23(5):447–456. ***doi:10.18705/1607-419X-2017-23-5-447-456***

Морфофункциональные изменения эндотелия в патогенезе гипертонической болезни

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Статья поступила в редакцию 07.07.17 и принята к печати 21.08.17.

Резюме

Эндотелий представляет собой многоуровневую клеточную структуру, пронизывающую все органы и системы организма. Гипертоническая болезнь (ГБ) является заболеванием, в основе патогенеза которого лежит нарушение регуляции тонуса магистральных артерий. Патогенетические основы ГБ, несмотря на интенсивные усилия, остаются неясными. Бесспорна неблагоприятная роль эмоционального стресса, гиподинамии, ожирения и нарушений водно-солевого обмена. Вместе с тем точные механизмы и предикторы развития артериальной гипертензии (АГ) в настоящее время не определены. Это препятствует профилактике и выявлению эссенциальной гипертензии на ранней стадии. Изучение функции эндотелия как мишени и предрасполагающего фона развития ГБ является задачей, имеющей как исследовательское, так и прикладное, клиническое значение. Действительно, если удастся выявить патогномоничные для развития АГ изменения эндотелиальной функции,— это позволит прояснить патогенетические основы заболевания и разработать адекватные медикаментозные схемы терапии. В обзоре рассмотрены накопленные на настоящее время данные по участию эндотелиальных клеток (ЭК) в развитии ГБ. Показан вклад изменений липидного обмена в физиологическое состояние эндотелиальной выстилки. Освещена роль нарушений эндотелиальной функции в увеличении продукции активных форм кислорода и дефектов метаболизма оксида азота. Продемонстрирована изученная авторскими коллективами активность следующих ферментных систем: НАДФН (никотинамидадениндинуклеотидфосфат)-оксидазы, циклооксигеназы, ксантиноксидоредуктазы и эндотелиальной NO-синтазы. Взаимодействие эндотелия и внеклеточного матрикса, а также эндотелия и гладкомышечных клеток также приведено согласно литературным данным. Освещена роль грелина, продуцируемого эндотелием в регуляции сосудистого тонуса. Показаны методические подходы к изучению ЭК in vitro в условиях гипоксии. Основным итогом проведенного анализа литературных данных является необходимость исследования функции эндотелия в условиях гипоксии in vitro, а также влияние тканевой и гемической гипоксии in vivo, что позволит установить вклад функциональных нарушений эндотелия в развитие ГБ.

Ключевые слова: артериальная гипертензия, гипертоническая болезнь, эндотелий, эндотелиальные клетки

Для цитирования: Сысоев К. А. Морфофункциональные изменения эндотелия в патогенезе гипертонической болезни. Артериальная гипертензия. 2017;23(5):447–456. ***doi:10.18705/1607-419X-2017-23-5-447-456***

Introduction

Hypertensive disease (HD), also called essential hypertension, or arterial hypertension (AH), represents a serious medical and social problem. The age of the debut disease is steadily declining. Despite intensive efforts, the pathogenesis of HD remains unclear. The risk factors include emotional stress, hypodinamy, obesity and violation of the water-salt balance. However, the variety of clinical manifestations and variants of HD dictates the search for factors directly triggering the pathological process. The state of the endothelium is critically important for the regulation of the effect of humoral substances and blood cells on the tone of the vascular wall. It is obvious that a physiologically consistent endothelial barrier contributes to the effective regulation of vascular tone through selective permeability for blood cells and a selective response to stimulating stimuli. Of particular importance is the adhesive capacity of endothelial cells (EC), as excessive adhesiveness leads to disruption of transendothelial migration, and the lack of adhesion disturbs the intercellular interaction. Endothelium has a number of features that distinguish it from other types of cells: a wide range of synthesized substances (hemostasis regulators, vascular tone, permeability, and cytokines), morphological features (caveolae, vesicles, lipid rafts, Weibel-Palade bodies) and the ability to form gap junctions via the sophisticated receptor machinery. It is noteworthy that the endothelium is under constant influence of hemodynamic forces (shear stress), blood cells (adhesion, aggregation, transendothelial migration), and also participates in intermolecular and intercellular interactions with structures located in the depth of the vascular wall.

A significant effect on the endothelium has a state of lipid metabolism. ECs carry receptors for low-density lipoprotein (LDL), being a natural reservoir for binding an excess of LDL. Constantly interacting with cells of peripheral blood, the endothelium controls the migration of cells into the depth of the vascular wall. Since the blood flow depends on the width of the lumen of the vascular bed, the balance of thrombotic and antithrombotic factors produced by the endothelium is essential, which is necessary for the regulation of platelet adhesion.

An important aspect is the production of endothelium components of extracellular matrix components (ECM): fibronectin, laminin, collagen and proteoglycans. The stiffness of the vascular wall directly depends on the structure of the ECM. The predominance of elastin increases the flexibility of the vascular wall, and the excess collagen leads to rigidity.

The production of EC growth factors (TGF-β, IGF, G-CSF and GM–CSF) promotes the restructuring of the vascular wall with disturbed regulation. Inflammatory cytokines (IL-1β, TNF-α, IL-6) and chemokines (MCP-1, eotaxin-3, IL-8, RANTES), synthesized by the endothelium, promote activation and penetration of leukocytes (monocytes, lymphocytes, neutrophils, and eosinophils). The endothelial production of reactive oxygen species with a vasoconstrictive effect provides an increased tonus of the muscular layer of the vascular wall.

All of the above processes contribute to the development of hypertension. At the same time, a difficult problem arises in the process of research, namely: is endothelial dysfunction the cause or consequence of hypertension.

Effects of lipid metabolism disorders for the endothelium

As mentioned above, the vascular endothelium represents a reservoir for excess binding of low density lipoprotein (LDL). The study V. Lubrano and S. Balzan [1] was indicated the role of lectin receptor for low density lipoprotein (LOX-1) in the pathogenesis of vascular disorders including essential hypertension. LOX-1 is a receptor selective for the endothelium [2]. Increased concentration of LDL leads to a decrease in NO production due to suppression eNOS activity [3]. There is the point of view that bioavailability of NO is reduced under the influence of hypercholesterolemia, increases the activity of arginase, which in turn leads to a decrease in the substrate for eNOS [4]. Level sLOX-1 (soluble form of LOX-1) in serum of patients with hypercholesterolemia significantly combined with decreasing NO-dependent vasodilation [3]. Elevated LOX-1 expression on endothelial cells in hypertensive patients increases vasoconstriction and leads to the progression of hypertension due to stimulated tissue hypoxia.

Disturbance of NADPH oxidase activity is a factor of AH progression

The emphasis in the regulation of blood pressure bears the NADPH oxidase (NOX). Presently, there are 7 known NOX isoforms. Endothelium is one of the main sources of NOX in normal and with AH, producing NOX1, NOX2, NOX4 and NOX5. Superoxide anion, which is formed during the oxidation of NADPH, has a pronounced signal effect, affecting the weakening of the vascular tone. Vasorelaxation is mediated by nitric oxide produced by eNOS. Lipophilicity allows NO to diffuse, penetrating into the cytoplasm of smooth muscle cells, where the

level of cGMP increases, which leads to a decrease in the level of intracellular calcium and relaxation. The superoxide anion interacts with NO, forming peroxynitrite, which causes vasoconstriction. Several studies have been performed, where the role of NOX in the development of AH has been demonstrated [5–7]. Mice with knockout of the NOX2 gene ($NOX2^{-/-}$) proved to be resistant to angiotensin-2-induced hypertension [5]. Also, $NOX2^{-/-}$ mice showed better bioavailability of NO compared to the control. Experimental studies were conducted on the study of inhibitors of NOX2. In SHR rats, a specific inhibitor of NOX2 (VAS 2870) reduced the level of ROS in the aortic tissue, improving endothelial function [5].

Increased synthesis of superoxide anion according to T. R. Nurkiewicz et al. [8] leads to disruption of signaling mechanisms in endothelial and smooth muscle cells by reducing the level of tetrahydrobiopterin, a key cofactor necessary for the production of nitric oxide. The increased formation of peroxynitrite during the interaction of the superoxide anion with nitric oxide contributes to the formation of a vicious circle: an increase in the superoxide anion content leads to an increase in the level of peroxynitrite, which reduces the activity of endothelial NO synthase (eNOS), reducing the synthesis of nitric oxide [9]. It is important that the healthy endothelium has an anti-inflammatory effect due to inhibition of leukocyte adhesion. The suppression of eNOS activity leads to an increase in the expression of adhesion molecules and the activation of such a chemokine as MCP-1 [10]. An important source of ROS besides the endothelium is smooth muscle cells, since the oxidation of NADPH is an indispensable condition for muscle contraction.

Cyclooxygenase indicates the state of the endothelium

Another important aspect of increasing the level of reactive oxygen species is the activity of the cyclooxygenase enzyme (COX). There are two isoforms of cycloxygenase: COX-1 and COX-2 [11]. While COX-1 is expressed constitutionally, COX-2 activates various stimuli, including inflammatory and growth factors [12]. The most important source of COX is the endothelium. According to the data of A. Virdis and S. Taddei [13], in the endothelium of arterioles of patients with HD there is an increase in COX-2 activity, which is a factor in suppressing the effect of NO, and, according to the authors, serves as the main source of ROS production in hypertensive patients.

Xanthine oxidoreductase increases the ROS production by endothelium

The ratio of endothelial-produced ROS and NO is also determined by the activity of xanthine oxidoreductase (XOR) [14]. XOR metabolizes purine bases, catalyzing the oxidation of hypoxanthine to xanthine, with the further formation of uric acid. Structurally, XOR is a homodimer, each subunit of which consists of four redox regions: a molybdenum-containing cofactor (Mo-co), a flavinadenine dinucleotide (FAD), and two iron-sulfur sites (Fe/S). Mo-co consists of a peter derivative and one molybdenum atom, which is bonded to dithiolene, two oxygen atoms and a sulfur atom. Mo-co is the site of oxidation of hypoxanthine and xanthine, whereas the reduction of NAD^+ and O_2 occurs in FAD. Two Fe/S clusters provide a channel for the flow of electrons between Mo-co and FAD. Differences in the spectra of their specific electron paramagnetic resonance (EPR), these Fe/S centers are both ferredoxin type, but not identical [15]. Over the past 40 years, the opinion has been formed that an increase in the activity of xanthine oxidase in ischemia, hypoxia or inflammation leads to an increase in the production of ROS, mediating adverse clinical manifestations. However, recent research has shown that xanthine oxidase stimulates production of NO in pathological conditions. Indeed, in the absence of oxygen and at an acidic pH, xanthine oxidase demonstrates nitrite-reductase activity, catalyzing the reduction of NO_2- in •NO in the presence of xanthine or NADH as substrates (electron donors) [16].

The production of ghrelin by endothelium promotes vasodilation

Recently, data have appeared on the role of ghrelin in the development of endothelial dysfunction. Originally, ghrelin was described as a substrate secreted by the cells of the stomach [17]. Then, there were data on ghrelin products by endothelial cells [18], as well as on the expression of receptors on the surface of endotheliocytes [19]. A proof of the special role of ghrelin in patients with metabolic syndrome was obtained. With intra-arterial administration, ghrelin contributed to a reduction in endothelial dysfunction, increasing the availability of NO [20]. The antioxidant properties of ghrelin were also studied: the inhibitory effect of ghrelin on the production of NADPH oxidase was observed [21]. Evidence of the action of the genes on the tone of the vascular wall in patients with metabolic syndrome is obtained. The introduction into the artery of the forearm ghrelin docked endothelial dysfunction by increasing availability of NO [20] and eliminating

imbalance between NO and ET-1 [22] that way to allow equilibrium between the tonic and dilated effects.

Disorder of the interaction of the endothelium and smooth muscle cells — the pathway of the progression of hypertension

For the pathogenesis of hypertensive disease, the interaction of endothelium and smooth muscle cells of blood vessels (SMC) is of great importance. Polarization of the SM determines the state of vascular tone. In view of the presence of gap junctions between the EC and the SMC, the magnitude and sign of the charge of the EC membrane determines the polarization of the SMC. The main driving force of hyperpolarization of EC is an increase in the concentration of intracellular calcium, which leads to the discovery of calcium-bound potassium channels [23]. Further, there is hyperpolarization of SMC, which can be stimulated either directly due to the gap contact, or indirectly by the release of NO, H_2O_2 and K^+ [25].

Disturbances of endothelial function in spontaneously hypertensive rats

One of the approaches to the study of the role of endothelial dysfunction in the pathogenesis of arterial hypertension is the use of a strain of spontaneously hypertensive rats (SHR). When studying the NO level in SHR rats by several scientific groups, a wide range of data on the metabolite amount was revealed. There was a reduced [26], normal [27] and even elevated [28] NO levels produced by the vascular wall endothelium.

In a recent study, S. Al-Gburi et al. [29] studied the role of the endothelium in the development of adrenergic regulation of the vascular wall tone in SHR rats depending on the sex of animals. In females of SHR-rats, an α-adrenergic increase in the tonus of the aortic vascular wall was observed in comparison with males, while β-adrenergic receptor-induced relaxation of the aortic vascular wall was significantly more effective. By the immunohistochemistry, the authors found that the expression of α-adrenergic receptors was mainly observed on smooth muscle cells of the vascular wall, whereas β-adrenoreceptors were mainly present on EC. The data did not differ between males and females. The authors conclude that β-adrenergic vasodilatation of the vascular wall is mediated by NO produced by EC. At the same time, the authors found no evidence of the effect of estrogens on β-adrenergic regulation of the vascular wall tone. Thus, it remains unclear what is the main factor of sexual differences in adrenergic regulation of vascular tone.

Endothelium and C-type natriuretic peptide

In the study, C. Caniffi et al. [30] the role of C-type natriuretic peptide (CNP) in Wistar and HRS rats was investigated. CNP is one of the endothelium-allocated hyperpolarizing factors. The role of CNP in the pathogenesis of essential hypertension is important due to a relaxing effect on the tone of the vascular wall. The authors demonstrated that CNP-induced relaxation of the aortic wall in both non- and a hypertensive rats is mediated by NO production and the opening of potassium channels. Increasing peripheral resistance and rigidity of the vascular wall are the main factors contributing to the growth of blood pressure. In addition to structural changes, the stiffness of the walls of the vessels depends on the functional usefulness of the endothelium. The authors summarize that, in the case of hypertension, there is a failure of the mechanisms of CNP-mediated relaxation.

K. Nakao et al. the effect of CNP produced by endothelium on the activity of smooth muscle guanylyl cyclase B (GCB) was studied [31]. The authors studied in vivo these interactions in mice knocked out by endothelial CNP and smooth muscle GCB [31]. Mice with an absent endothelial CNP gene showed a significant increase in blood pressure and a pronounced acute hypertensive response to the introduction of an NO synthase inhibitor [31]. In the test with acetylcholine in the study of the mesenteric artery rings, vasorelaxation in $CNP^{-/-}$ mice was impaired in comparison with littermate mice. Also $CNP^{-/-}$ mice differed significantly in the level of ET-1 and significantly reduced response to the introduction of the antagonist of the receptor ET-1. In contrast, in mice $GCB^{-/-}$ there was no increase in blood pressure in comparison with mongrel mice. Vasorelaxation with acetylcholine in the mesenteric arteries was similar to that of the control group. At the same time, the induction of vasorelaxation with CNP in $GCB^{-/-}$ mice was negative compared to mongrel mice. The authors concluded that endothelium-derived CNP promotes regulation of vascular tone and systemic BP, supporting endothelial function regardless of smooth muscle GCB [31].

Endothelium and stiffness of the vascular wall

The rigidity of the vascular wall is a factor in the progression of arterial hypertension. Endothelium directly contacts the components of the extracellular matrix. Extracellular matrix (ECM) — the main structural element that provides rigidity of the vascular wall. The lumen of the main vessels widens during systole to accommodate the volume of the blood of the ejection fraction, after which, tissue diastole is perfused [32]. To a large extent, the effectiveness of blood fill-

ing is determined by the elasticity, extensibility and susceptibility of arterial vessels [32]. Decreased elasticity and increased stiffness lead to increased efforts to distribute blood flow, increase systolic pressure, volume overload, hypertrophy of the myocardium and cardiovascular disorders. Stiffness of the aortic wall affects microcirculation and vice versa [32]. The transforming growth factor-β (TGF-β) is one of the main stimuli for the restructuring of the extracellular matrix. Endothelial cells significantly produce TGF-β in the activated state. Activating events are hypoxia, shear stress and increased blood viscosity. The increase in TGF-β activity directly leads to an increase in the synthesis of fibronectin and collagen, and also indirectly stimulates the production of ECM through inhibition of collagenase and stimulation of the formation of TIMP: a tissue inhibitor of matrix metalloproteinases [32]. Endothelin-1 (ET-1) peptide, secreted by EC, has a powerful vasoconstrictor effect. In addition to mitogenic and hypertrophic action, ET-1 is able to activate the rearrangement of ECM and stimulate the production of collagen fibroblasts [32].

Disturbances of microcirculation and arterial hypertension

Particular importance for endothelial function in the development of hypertension has a state of microcirculation. Traditionally, the role of microcirculation of the arteries is reduced to regulation of vascular resistance and maintenance of metabolism by blood flow [33]. Muscle contraction of the arterial wall protects the underlying vessels from damage due to increased pressure, prevents excessive perfusion of tissues and creates a reserve of blood flow [33]. Also, the vascular tone is regulated by the intercellular electrical connection and the substances synthesized by the endothelium: nitric oxide, prostacyclin, endothelin-1 and thromboxane A2. Each of the mediators released by the endothelium penetrates into the depth of the vascular wall, acting on the SMC, causing dilation, hypertrophy or fibrosis. Also these mediators are able to penetrate into the depth of the parenchyma. This particularly applies to the capillary bed with its large area in the absence of SMC, where the endothelium has a paracrine effect on the parenchyma tissue. Tissue hypoxia, observed with AH, increases the disturbances of microcirculation, which leads to the progression of the disease.

Endothelium and peroxisome proliferator activated receptors

A special group of signal molecules expressed in the cytoplasm of EC are peroxisomal proliferator activated receptors (PPARs). PPARs belong to the first superfamily of nuclear hormonal receptors. These receptors are involved in a variety of homeostatic and protective processes, including the functioning of the cardiovascular system, regulation of metabolism, immunity, inflammation, thrombosis, angiogenesis and tumor growth. Three types of PPAR are described: PPAR-α, PPAR-β/δ and PPAR-γ. For each of the receptors, there is a way of regulating blood pressure. PPAR-α regulates the transport and oxidation of fatty acids and the reverse absorption of cholesterol [34]. According to S. Glineur et al., Fenofibrate, which is a PPAR-α agonist, reduces the production of ET-1 by the endothelium due to various mechanisms [35]. First, the activity of the ET-1 promoter is suppressed [35]. Secondly, the activity of TGF-β, which stimulates the production of ET-1, decreases [35]. Third, the production of the transcription factor KLF-11 is stimulated [35]. In the paper Š. Jichova et al. An experimental study of the effect of fenofibrate on the course of malignant hypertension in rats of the TGR line was carried out [36]. The authors concluded that the antihypertensive effect of fenofibrate is based on the inhibition of RAAS activity, particularly the ANH-II. Moreover, both systemic and intracentular transformation of ANG-I into ANG-II was suppressed [36].

The participation of PPAR-γ in the regulation of blood pressure is carried out in three ways: the activation of signaling pathways of MAPK (mitogen-activated protein kinase) and PI3K (phosphoinositide-3 kinase), modulation of RAAS and stimulation of eNOS formation [37].

The effect of hypoxia on the functional activity of the endothelium

Of particular importance in the pathogenesis of hypertension is the state of microcirculation of the main arteries. The effectiveness of angiogenesis processes in the capillary bed of large vessels determines the adequacy of metabolism. Under hypoxic conditions, disturbance of oxidation-reduction mechanisms of vascular tone maintenance occurs: excessive formation of ROS, accumulation of degradation products of extracellular matrix, reduction of bioavailability of nitric oxide. All these events lead to the formation of a vicious circle: hypoxia, increased vascular wall tone, smooth muscle hypertrophy, ROS production, endothelial damage, deterioration of microcirculation and increased hypoxia. EC are an important source of production of a specialized group of proteins called hypoxia-inducible factors (HIF). Although hypoxia is the most potent factor inducing angiogenesis, with a chronic lack of oxygen in the tissues, the newly formed capillary network does not have a full-fledged efficacy. In the T. D. Nauta et

al. [38] studied the effects of hypoxia in vitro on the endothelial cells of the microvasculature (hMVEC), as well as the production of HIF-2α hMVEC. Under normal culture conditions (20 % O_2) supplemented with VEGF-A and TNF-α, endothelial cells sprouted 3D fibrin matrix after 7 days. While under hypoxic conditions (1 % O_2), the germination of hMVEC was severely hampered. Turning off the HIF-2α gene with si-RNA partially restored germination under hypoxic conditions and increased the effect in normoxia, indicating the inhibitory role of HIF-2α in endothelial germination, both with normal oxygen content and hypoxia. In a study by C. Befani and P. Liakos [39], the effect of hypoxia on the endothelial cells of the microcirculatory bed (line HMEC-1), as well as the production of HIF-1α and HIF-2α, was assessed in vitro. The authors noted that for HIF-1α, the maximum exposure to hypoxia (a fourfold increase over the control) was observed after 16 hours of cultivation; Later, after 24–48 hours, a gradual decrease in the effect occurred (twofold growth). While production of HIF-2α increased 30-fold after 8 hours of cultivation and remained elevated 20-fold after 48 hours. The authors evaluated the transcription activity of HIF genes under the influence of hypoxia and under normal conditions after 4 and 24 hours of cultivation. It was revealed that under hypoxic conditions in HMEC-1 cells, transcription activity of HIF increased by cultivation for 4 hours 10-fold, and after 24 hours-70-fold compared with the control. In the same experiment, the hypoxia-induced expression of mRNA PAI-1 (well known as the target for HIF-2α) remained elevated 48 hours after culturing. The expression of VEGF mRNA, which is regulated by HIF-1α and HIF-2α, also increased under the influence of hypoxia and remained increased after 48 hours of culture. The proliferative activity of HMEC-1 has also been studied under conditions of hypoxia. The authors noted a 30 % decrease in proliferation after 48 hours of culture and 60 % after 72 hours. The chemotactic activity of HMEC-1 was also evaluated in hypoxic conditions. To assess the chemotaxis, filters (pore size 8 μm) coated with laminin-1 and collagen IV were used. The chemotactic activity of HMEC-1 under conditions of hypoxia significantly (by 50 %) increased 24 hours after culture, regardless of the type of matrix [39].

For the production of NADPH oxidase by endothelial cells, there is a stimulation mechanism associated with endothelin-1 [40]. Thus, ET-1 induces the expression of NOX2 by endothelium in vitro, as well as the production of ROS ex vivo EC isolated artery by activating the receptor for ET-1 [40]. ET-1 also stimulates the formation of superoxide anion in the experimental model of mild hypertension [40]. There is also an inverse relationship: as a result of the activity of ET-1, the superoxide anion produced by NOX2 causes vasoconstriction [40].

It is known that in the EC, mitochondria are the main source of superoxide anion. In the study A. Koziel and W. Jarmuszkiewicz, an observation was made of the effect of chronic hypoxia on the oxidative metabolism of mitochondria EC [41]. The umbilical vein endothelial cells (HUVEC) were cultured for 6 days at an oxygen amount of 1 %. The effect of hypoxia was studied both at the cell level and in the isolated mitochondria. In EC, hypoxia inhibited tissue respiration during the oxidation of amino acids, fatty acids and carbohydrates, at the same time, stimulating the oxidation of ketogenic amino acids. Hypoxia increased the production of ROS both in mitochondria and in the cytoplasm, although the antioxidant system (SOD 1 and SOD 2) and cell viability did not change. In mitochondria of EC, subjected to hypoxia, the activity of the electron transport chain of the II complex (succinate) increased, and the I complex (NADPH) was suppressed. The activity of the II complex was increased due to succinate-resistant products of ROS, mainly due to reverse electronic transport. In general, the authors made an obvious conclusion that chronic hypoxia causes a switch from aerobic to anaerobic metabolism [41]. In the work of P. Hernansanz-Agustín et al. the effect of acute hypoxia on tissue respiration EC was studied. The authors found suppression of the first electron transfer complex [42]. According to the author, the consequence of acute hypoxia is the activation of the Na^+/H^+ exchanger, which leads to an increase in the production of ROS [42]. It seems that a significant factor in the progression of AT is tissue hypoxia, which contributes to the production of ROS and leads to a steady increase in vascular tone.

The AT-II, acting via AT-1R, promotes the activation of NOX, stimulating the production of ROS [43]. With hypertension with the participation of AT-II, ROS produced by NOX-1, contribute to kidney damage [43].

Endothelium, immune disorders, and hypertension

According to P. R. DeBatista et al. expression of the receptor of innate immunity TLR 4 on endothelial cells, is enhanced by RAAS, contributing to the maintenance of hypertension [44]. In addition, an increase in the expression of TLR 4 leads to the activation of oxidative stress. Essential hypertension is interpreted by the authors as an inflammatory process of low intensity [44].

According to G. F. Bomfim et al. activation of TLR 4 on EC leads to mild inflammation and increases vascular tone in spontaneously hypertensive rats [45].

Also, the activating effect of AT-II on TLR-4 led to endothelial dysfunction, including oxidative stress and activation of MyD 88 JNK/NF-κB signaling pathways [46]. In turn, suppression of TLR-4 reduced the production of ROS and stimulated MyD 88 production of IL-6 on the endothelium of spontaneously hypertensive rats [47]. Mitochondrial extracellular DNA also promotes hypertension due to the activation of TLR-9 [48].

T-regulatory lymphocytes (Tregs) are also involved in the pathogenesis of AH. In the study M. O. Mian et al. the effect of AT-II on endothelial dysfunction and remodeling in $Rag1^{-/-}$ mice was studied in the deficit of FOXP3-positive Tregs. In such animals, there was an enhanced response to AT-II in the form of inflammatory polarization of monocytes/macrophages and damage to microvessels compared to $Rag1^{-/-}$ mice without Treg deficiency.

Conclusion

Thus, the endothelium in hypertension plays a dual role: on the one hand reflects the functional disorders, and on the other — a factor of disease progression. Exact mechanisms of the involvement of endothelial cells in the initiation, development of the disease and maintenance of vicious circles of the pathological process require further study. However, there is a significant body of data indicating the leading role of endothelial dysfunction in the development of arterial hypertension. First of all, it is a defect in the regulatory mechanisms of products of ROS and NO. Indeed, the increased NO production at the strengthened formation of superoxide anion does not lead to a weakening of the tone and vasoconstriction due to increased peroxynitrite synthesis. Products EC growth factors (TGF-β) stimulates the synthesis of collagen and lead to an increase in rigidity of the main wall of the arteries, which exacerbates the HD.

In light of the identified lesions endothelial function at HD seems most reasonable following sequence of activation events: lack of exercise, which is characteristic for patients with hypertension leads to tissue hypoxia, which gives microcirculation resistive arteries, increases the activity of vasoconstrictors (endothelin-1) stimulates angiogenesis, which is due to inadequacy de novo formed capillary network leads to the progression of functional disorders (increases vasoconstriction). To further study the role of the endothelium in the initiation and development of HD, studies on both experimental and clinical material are required. In particular, it is necessary to study the interaction of blood cells with endothelium in vitro and in vivo in both spontaneously hypertensive rats and patients with HD. The analysis of the obtained data will help to reveal the exact mechanisms of the role of endothelium in the pathogenesis of arterial hypertension.

Abbreviations

AT-1R receptor of angiotensin-1
CNP C-type natriuretic peptide
COX cyclooxygenase
eNOS endothelial NO synthase
FAD flavin adenine dinucleotide
FOXP3 forkheadboxP3 (transcriptional protein of T-regulatory lymphocytes)
GCB guanylate cyclase B
G-CSF granulocyte colony stimulating factor
GM–CSF granulocyte-mononuclear colony stimulating factor
HD hypertensive disease (Russian traditional name of essential hypertension)
HIF hypoxia inducible factor
HMEC-1 endothelial cells of the microvascular bed of a human (cell line)
HMVEC endothelial cells of human microvascular bed
IGF insulin-like growth factor
IL-1β interleukin-1 beta
IL-6 interleukin-6
IL-8 interleukin-8
JNK c-junN-terminal kinase
KLF-11 Krueppel-likefactor-11 (transcription protein of embryonic development)
LOX-1 lectin-like receptor for low-density lipoproteins
MAPK mitogen-activated protein kinase
MCP-1 monocyte chemotactic protein-1
MyD 88 primary myeloid differentiation gene 88
NF-κB nuclear factor κB
NOX NADPH oxidase
PAI-1 plasminogen inhibitor activator
PI3K phosphoinositide-3-kinase
PPAR peroxisome proliferator activated receptor
Rag1 gene that activates recombination-1
RANTES [chemokine], regulated after activation, secreted and expressed by normal T cells
SHR spontaneously hypertensive rats (rat strain)
Si-RNA small interfering RNA
sLOX-1 soluble form LOX-1
SOD superoxide dismutase
TGF-β transforming growth factor beta
TLR toll-like receptor
TNF-α tumor necrosis factor alpha
Treg T-regulatory lymphocytes
VEGF vascular endothelial growth factor
XOR xanthine oxidoreductase

The work is supported by the program of the Presidium of the Russian Academy of Sciences I.19P, project 0134–2015–0002.

Conflict of interest
The paper is supported by the Program of the Panel of the Russian Academy of Sciences I.19P, project # 0134–2015–0002.

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