Role of nitric oxide and other endothelium-derived factors

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Summary. *The endothelial cell layer displays the features of a distributed organ and has a variety of biological functions such as keeping the balance between coagulation and fibrinolysis, expression of adhesion molecules for cells in the immune system, metabolism of noradrenaline and 5-hydroxytryptamine, and conversion of angiotensin I and bradykinin. The endothelium also regulates the underlying smooth muscle layer and vascular tone by release of endothelium-derived relaxing factors such as nitric oxide (NO), prostaglandins, and endothelium-derived hyperpolarizing factor (EDHF) as well as vasoconstricting factors such as endothelin, superoxide (O_2^-), and thromboxane. We have reviewed the nature, mechanisms of action, and role of these factors in regulation of vascular tone, with special emphasis on NO. By a process catalyzed by NO synthase, NO and citrulline is formed from the substrates molecular O_2 and L-arginine. The main receptor for NO is guanylyl cyclase leading to formation of smooth muscle cyclic guanosinmonophosphate and relaxation. EDHF is an endothelium-derived factor causing vasorelaxation of the underlying smooth muscle layer by hyperpolarization. The nature of EDHF is still unknown, but several candidates for EDHF have been proposed such as potassium ions, hydrogen peroxide, and epoxyeicosatrienoic acids. Prostaglandins such as prostacyclin and prostaglandin E_2 binds to specific receptors followed by increases in cyclic adenosinmonophosphate and vasorelaxation, while contractile prostaglandins constrict vessels by activation of thromboxane and endoperoxidase receptors. Superoxide anions induce contraction of vascular smooth muscles cells by scavenging NO. Endothelin is a potent endothelium-derived contractile factor. The synthesis of endothelin-1 is induced by hypoxia, thrombin, interleukin-1, transforming growth factor-β1, vasopressin, and catecholamines. Cardiovascular risk factors like age, hypertension, and hyperlipidemia are associated with impaired endothelium-dependent vasodilation either as a consequence of increased inactivation of endothelium-derived vasodilators or increased formation of endothelium-derived contracting factors. This imbalance of endothelium-derived factors plays a role for development of atheroslerosis and ischemic vascular diseases.*

Introduction

In 1980 Furchgott and Zawadzki (1) reported that acetylcholine (ACh) causes relaxation of isolated blood vessels only in the presence of an intact endothelial cell layer. In 1977 Murad discovered that nitric oxide (NO) release caused by nitrates relaxes smooth muscle cells. In 1986 Ignarro proposed that endothelium-derived relaxing factor (EDRF) is identical to NO. For these achievements, Robert Furchgott, Ferid Murad, and Luis Ignarro were awarded the Nobel Prize in Physiology and Medicine in 1998. The involvement of endothelium in coordination of vasoactive factors and its important role in regulation of blood vessels tone has been recognized. Today several endothelium-derived substances such as NO, prostacyclin, and epoxyeicosatrienoic acids causing smooth muscle relaxation are known. Meantime the nature of endothelium-derived hyperpolarizing fac-

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tor (EDHF), causing smooth muscle membrane hyperpolarization followed by vasodilatation, remains unknown.

Recent development of the research techniques has allowed to measure NO release directly (2), as well as use certain NO releasing substances; proposals are made that NO by itself can be EDHF, but even in the presence of an NO scavenger, acetylcholine still causes relaxation and hyperpolarization in small arteries.

Endothelium-derived vasorelaxing factors

The endothelium plays a direct role in vasomotor function by integrating the controlling factors: reflexes, humoral, and local factors (3). Endothelial cells release substances acting directly on vascular smooth muscle cells, causing either contraction or relaxation. Several endothelium-derived substances causing smooth muscle relaxation have been isolated: nitric oxide (NO), prostacyclin (PGI_2), and epoxyeicosatrienoic acids.

Nitric oxide. Nitric oxide (NO) is a relatively stable gas, with ability to easily diffuse through the cell membrane. NO is capable to interact with various substances in the cell (4). NO plays an important role in many physiological processes and is important in regulation of vascular system, neurotransmission and various homeostatic events (4). Many pathological states are known, where NO synthesis dysfunction is one of the main problems. Diabetes, shock, infarction, neurodegeneration, arthritis and chronic inflammation are examples of diseases where NO production is altered (5).

Depending on protein structure, NO may have strong or weak connection with different proteins. NO interaction with proteins containing hem is weak and manifests itself by changing their activity (activates or inhibits). For example, NO inhibits cytochromoxidase, NO synthase, cytochrome P450, thromboxane synthetase, catalase, and peroxidase. As result of cytochromoxidase inhibition, oxidative phosphorylation in mitochondria is inhibited. NO activates cytosolic guanylyl cyclase. As a result, cyclic GMP is increased and leads to vascular smooth muscle relaxation, inhibition of thrombocyte activity and decreased cell proliferation.

The activation of prostacyclin synthesis by NO is confirmed by in vivo (6) and in vitro (7) experiments. It is thought, that prostacyclin synthesis is activated by activation of prostaglandin H synthase (7) and, possibly, by increasing cyclooxygenase activity by a cGMP-independent pathway.

NO affects cell metabolism. Endogenous NO inhibits mitochondrial respiration and ATP synthesis. This is a consequence of inhibition of cytochromoxidase or indirectly by NO metabolism products, such as peroxynitrite and reactive oxygen species. It is known that NO metabolism products inhibit Krebs cycle enzyme aconitase. It is also known that NO binds to the hem part of the cytochromoxidase occupying the oxygen binding site, thus allowing NO to regulate mitochondrial affinity for oxygen (8).

Nitric oxide inhibits glycolysis by inhibiting 3-phosphoglyceraldehyde dehydrogenase. The product of this reaction, peroxynitrite, causes peroxidation of lipids and other substances (e.g. DNA). This also leads to disturbance of energetic metabolism. DNA synthesis depends on ribonucleotide reductase. This enzyme has two subunits, each of which can bind NO. The increase in NO synthesis decreases DNA synthesis. Nitric oxide can influence transcription through a cGMP-dependent mechanisms leading to phosphorylation of transcription factors.

NO may interact with some of receptors, causing downstream effects. As an example could be N-methyl-D-aspartate (NDMA) receptor, action of which is influenced by nitrosothiol formation. Stimulation of this receptor is harmful because of Ca^{2+} overload in certain neurons. Ca^{2+} overload activates proteases and phospholipases, as well as free radical reactions.

As an example of biological effects of NO could be activation of vascular smooth muscle cells Ca^{2+} dependent K^+ channels (K_{Ca}) and possible involvement in endothelial K^+ channels.

Endothelium-derived hyperpolarizing factor. Endothelium-derived hyperpolarizing factor (EDHF), which provides strong relaxing action on smooth muscle, remains unidentified. The investigation of vasorelaxation component resistant to N^{ω}-nitro-L-arginine in bovine, pig and rat coronary arteries leads to conclusion that substance could be labile arachidonic acid metabolite released after stimulation with bradykinin. The structure of the source of this substance depends on cytochrome P450 monooxygenase activity (9). Further conducted experiments in other arterial beds did not confirm this hypothesis (10). Guinea pig carotid artery smooth muscle hyperpolarization level, evoked by acetylcholine and independent of NO, was not changed after applied cytochrome P450 monooxygenase inhibitors. Therefore rat mesenteric artery smooth muscle polarization using cytochrome

P450 inhibitors (proadifen, miconazole, 17-oktadecionic acid, and 1-aminobenzotiazole) was studied (11). As these studies gave negative results, the origin of EDHF remains unknown.

Another, possibly most convincing hypothesis, relates origin of EDHF with phospholipase A_2 (PLA_2). In perfused rat heart model with blocked NO and prostaglandin synthesis (nitroarginine and indomethacin), PLA_2 inhibitor abolished vasodilation caused by bradykinin (12). This shows the PLA_2 importance in EDHF synthesis. Similar results were acquired in studies with porcine coronary arteries, when relaxation caused by bradykinin was abolished by arachidonyl trifluoromethylketone, cytosolic phospholipase A_2 inhibitor (13). This repeatedly confirms that arachidonic acid, released by activating PLA_2, plays a role in EDHF formation.

In 1998, potassium ions (K^+) were identified as possible EDHF. This was investigated on rat hepatic arteries. Effect of acetylcholine, muscarinic receptor blocker, to smooth muscle relaxation in presence of ouabain (Na^+/K^+ ATPase blocker) was tested. The inhibition of relaxation by ouabain was decreased by increasing the extracellular K^+ concentration. Acetylcholine-induced hyperpolarization of endothelial cells and K^+ concentration increase in myoendothelial gap were significantly decreased by blocking medium and small size Ca^{2+} dependent K^+ channels (K^+_{Ca}) with charybdotoxin and apamin. EDHF-evoked smooth muscle hyperpolarization was also abolished by these blockers, but there was no effect of them in hyperpolarization caused by K^+ (14). Another study demonstrates that EDHF is not K^+ but could be a hyperpolarizing current, spreading from the endothelium to smooth muscle cells and relaxing arterioles (15).

Other studies indicate that hydrogen peroxide is EDHF (H_2O_2). In 1998, Barlow and White reported, that H_2O_2 activates highly permeable Ca_2^+ dependent and voltage gated K^+ channels (BK_{Ca}) in porcine coronary arteries (16). Two years later Matoba et al. announced hypothesis that hydrogen peroxide is endothelium-derived hyperpolarizing factor in small mesenteric arteries of NO synthase-deficient transgenic mice (17).

Epoxyeicosatrienoic acids (EETa's) are also endothelium-released relaxing factors. The first idea was that this could be the same EDHF, however, data showing different origin of these factors were reported. The experiments confirm that EETa's are synthesized from arachidonic acid with a help of epoxygenases, which are closely related to cytochrome P450. These acids activate Ca^{2+} dependent K^+ channels (K_{Ca}), causing hyperpolarization of smooth muscle cells (18). In bovine coronary arteries EETa activates ribolysation of ADP-dependent G protein α subunit. This kind of $G_s\alpha$ activation could be additive to direct EETa effect on G protein in further K_{Ca} activation pathway, leading to smooth muscle hyperpolarization (19).

Prostaglandins. Prostacyclin (PGI_2) and prostaglandin E_2 are vascular smooth muscle relaxing substances. Prostacyclin was described as endothelium-derived relaxing factor in 1979. Vasorelaxing effect of this substance is determined by specific vascular smooth muscle cell receptors (20). Therefore, prostacyclin is not involved in endothelium dependent vasorelaxation in absence of these receptors.

Effect of prostacyclin is tightly connected with NO effects. It facilitates NO release from endothelial cells and in turn NO potentiates prostacyclin effects in smooth muscle. NO activates cyclic GMP synthesis and increases inhibition of phosphodiesterase, which degrades cAMP (21). Cyclic AMP prolongs effect of prostacyclin in smooth muscle cells.

Endothelium-derived vasoconstricting factors

Prostaglandins. Prostaglandin H_2 is formed in the endothelial cells during arachidonic acid metabolism pathway. Prostaglandin H_2 is a precursor of all prostanoids including thromboxane A_2. Prostaglandin H_2 and thromboxane A_2 binds to endoperoxidase and thromboxane receptors initiating vascular smooth muscle contraction (20). In normal physiological conditions action of this vasoconstrictor is overridden by endothelium-derived vasorelaxants.

Reactive oxygen radicals. Active oxygen radicals are formed in endothelial cells in response to increased blood pressure and endothelial agonists (22). Destruction of NO by superoxide ions causes vasoconstriction. Adjacent mechanism of action is believed to be oxygen effect on smooth muscle cytosol Ca^{2+}: increase in concentration of Ca^{2+} causes vasoconstriction. In addition, free radicals sensitize muscle contractile apparatus for Ca^{2+}, what also stimulates contraction.

Endothelin. Endothelin-1 produced by endothelial cells is one of the most potent vasoconstrictors. Its synthesis can be initiated by thrombin, interleukin-1, thrombocytes released factors, growth factor ā1, vasopressin and by effect of catecholamine on endothelial cells. Synthesis of this vasoconstrictor is inhibited by released NO (23).

Action of nitric oxide in vascular smooth muscle

L-arginine is a substrate for NO synthesis. NO and L-citrulline are produced after induction of L-arginine metabolism by NO synthase (NOS). During L-arginine splitting oxygen and NADHP are used; NH_2 group of L-arginine is transformed to NOH group, from which NO separates in the process of L-citrulline formation (Fig.1). L-arginine reserve is accumulated from extracellular space and by intracellular synthesis (24).

Endothelium released NO initiates smooth muscle relaxation (Fig.2). NO activates soluble guanylyl cyclase, which initiates guanosine triphosphate (GTP) transformation to cyclic GMP. Activation of cyclic GMP dependent proteinkinase G is followed by cytosolic Ca^{2+} removal from the cell and inhibition of contractile apparatus (25). Action of proteinkinase G has direct influence on phosphorylisation of gap junctions, activity of potassium and calcium channels. Phosphorylisation of potassium channels causes K^+ outflow from cell, when phosphorylated calcium channels decrease Ca^{2+} influx. If Ca^{2+} cytoplasmic concentration decreases below 500 nM, the contraction is stopped. It happens because of Ca^{2+} unbinding from calmodulin, followed by detachment from myosin light chain kinase, causing its inactivation. Dephosphorylated myosin light chain prevents from myosin head binding to actin, causing relaxation of smooth muscle.

Level of cyclic GMP is decreased via hydrolysis. In this process specific cyclic GMP phosphodiesterases 5th type (PDE5) is involved, resulting in cyclic GMP transformation to GMP. This is the action mechanism of drugs inhibiting PDE5. One representative substance from this family is sildenafil, which is known as specific PDE5 inhibitor potentiating relaxation caused by NO. This active substance is used for treatment of erectile dysfunction. PDE5 inhibitors are tested for their applicability in therapy of pulmonary hypertension (26) and effects on human hemodynamics (27).

Endothelial dysfunction

Endothelium and endothelium-released substances play an important role in maintaining vascular smooth muscle tone. The main role in endothelial dysfunction is thought to be played by vasorelaxing factors released after stimulation. This stimulation could be exerted via autonomic and sensory nerves (ACh, norepinephrine, ATP, substance P), circulating hormones (angiotensin II, insulin, catecholamine, vasopressin), coagulation derivates and thrombocyte-released substances (serotonin, ADP, thrombin). In addition, endothelial and smooth muscle cells can produce autacoids: bradykinin, angiotensin II, endothelin, ADP and ATP (28). Endothelium responses to shear stress and blood flow changes (29) and endothelium-released vasorelaxing factors control angiogenic and smooth muscle proliferation modifying factors. In healthy arteries endothelium has anti-adhesive and antithrombic properties. Age, hypertension, atherosclerosis, hyperlipidemia and critical conditions of organism may provoke endothelial dysfunction.

Age influence. Endothelium-dependent relaxation of the arteries decreases with the age, as it was proved by experiments performed on human endothelium (30). In arteries of rats, relaxation decreases due to increased production of

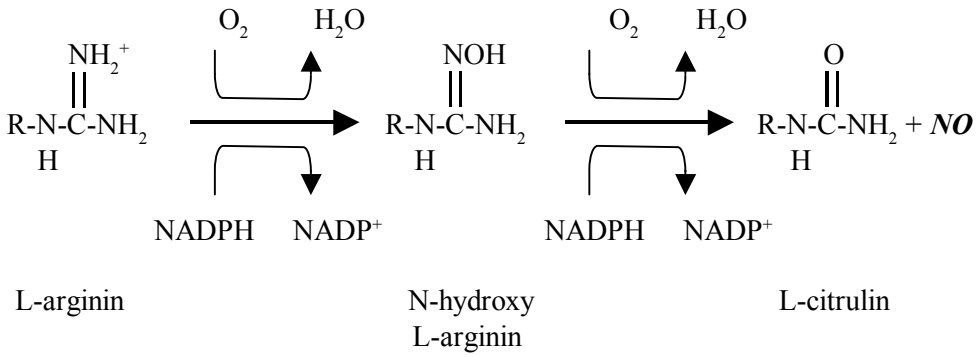

Fig.1. **Nitric oxide (NO) formation from L-arginine by NO synthase**

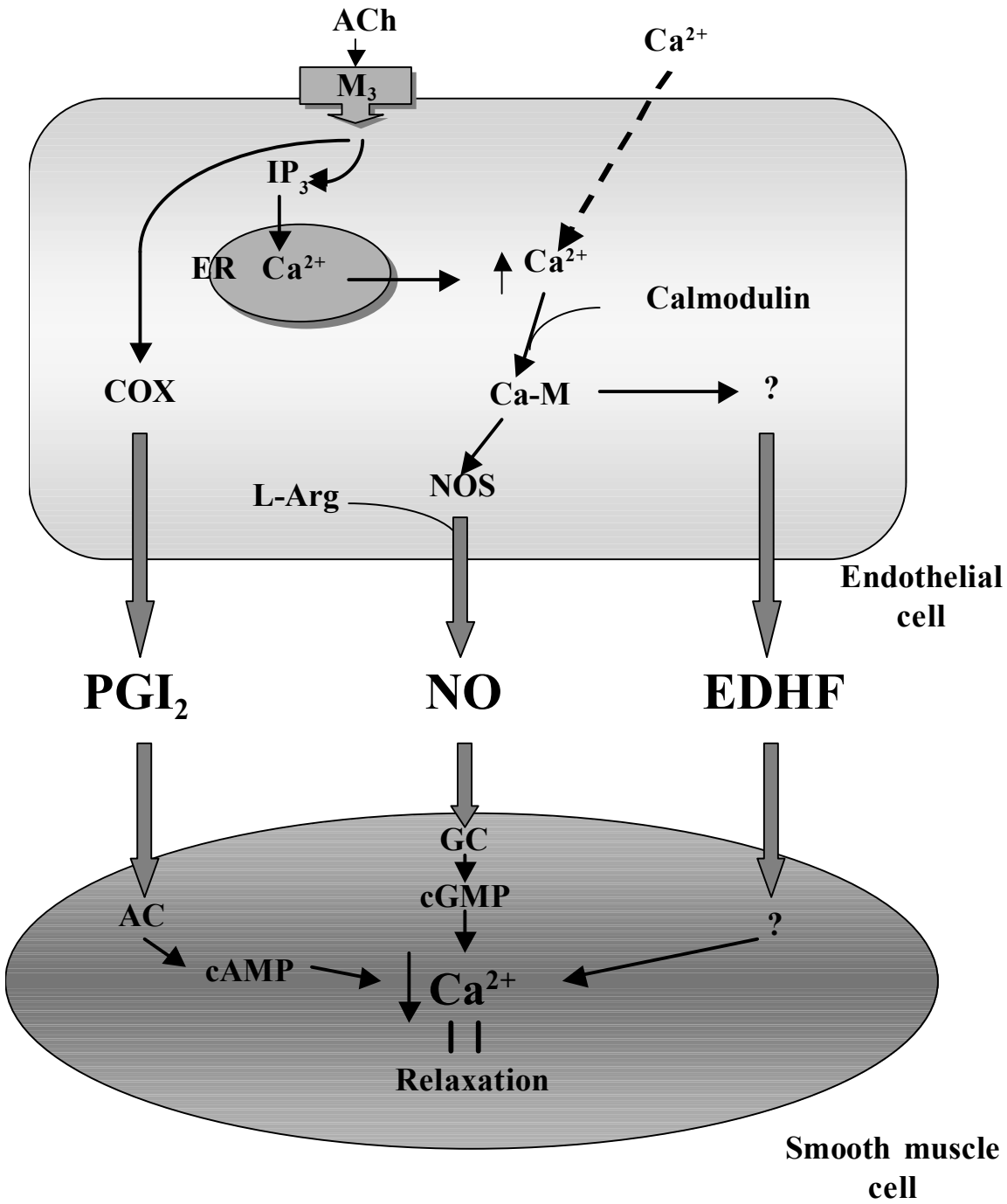

Fig.2. **Mechanism of the endothelium-dependent vascular smooth muscle relaxation**

Stimulation of the receptor, i.e. M_3-cholinoreceptor by acetylcholine (ACh), on the membrane of endothelial cell causes formation of inositol triphosphate (IP_3), which releases calcium from endoplasmic reticulum (ER). An increase in cytosolic calcium concentration leads to calcium binding to calmodulin. After the calcium-calmodulin complex is formed (Ca-M), NO synthase (NOS) is stimulated, which in turn activates formation of NO from L-arginine (L-Arg). In smooth muscle cell NO activates soluble guanylyl cyclase and increases intracellular cyclic guanosine monophosphate (cGMP) concentration. An increase of cGMP level leads to a decrease of calcium concentration in smooth muscle cell, which is followed by relaxation. Prostacyclin (PGI_2), which is synthesized by cyclooxygenase (COX), activates adenyl cyclase (AC). As a result, intracellular concentration of cyclic adenosine monophosphate (cAMP) increases, which leads to a decrease of intracellular calcium concentration in smooth muscles. The origin of endothelium-derived hyperpolarizing factor (EDHF) is not known yet and its formation depends on the calcium concentration in the endothelial cell.

endoperoxidases. Endothelium-dependent NO production in old rats disappears due to age-related changes in endothelium and the vasoconstrictive action, caused by endothelin-1 in small concentrations, is left without contrabalance (31). In this case NO role in relaxation is very important as it was shown in series of experiments (32).

It was found that response of the artery to ACh decreases but it remains unchanged to sodium nitroprusside (33). Similar results were obtained in studies of essential hypertension, proving the direct influence of the age on the decreased endothelial function. Age-related differences in NO and prostaglandins secretion were investigated using L-arginine as a substrate for NO synthesis and indomethacin as a cyclooxygenase inhibitor. In the group of young (up to 30 years old) normotensive humans the above mentioned substances did not increase ACh-induced vasodilatation, however in the group of older individuals L-arginine potentiated response to ACh that gives a proof that decrease in NO secretion was due to age-related changes. Indomethacin had influence on relaxation only in the group of 60 years old and older humans.

Influence of hypertension. During the hypertension endothelium-dependent relaxation of the arteries is decreased. In the rats with genetic hypertension NO production is markedly decreased. Studies of endothelial NOS have shown that the amount of it is decreased in coronary arteries, but there is no significant decrease in aorta. At the same time there is a vasodilative dysfunction in both vessel types. In rats with spontaneous hypertension (SHR) increased production of free radicals was found, which is not present in genetic hypertension. During hypertension due to aortic banding, slightly increased endothelial NOS expression was found (34). In experiments performed two weeks after aortic banding there were no changes in endothelium-dependent vasodilatation, but production of O^{2-} was increased. After six weeks, increased concentration of endothelial NOS and O^{2-} was found. Hyperproduction of these factors stimulates formation of peroxynitrites and consequent nitrosylation of tyrosine proteins in vascular wall. Soluble guanylyl cyclase (NO target in smooth muscle) amount was significantly decreased in adult SHR rats (35).

In one-kidney one-clip hypertension rats (non renin-dependent hypertension model) release of NO and relaxation of the artery to ACh is decreased (36).

Synthesis of vasoconstrictors such as angiotensin II which is produced from angiotensin I due to action of angiotensin converting enzyme (ACE) is increased during hypertension (37). It was shown that level of ACE is increased in hypertensive rats' blood vessels, therefore ACE inhibitors normalize blood pressure in spontaneous hypertensive rats. Inhibition of this enzyme was successfully employed in clinical practice for the treatment of hypertension (captopril, enalapril, quinaprilat, and other ACE inhibitors).

Atherosclerosis and hyperlipidemia. An increase of low-density lipoproteins (LDL) and cholesterol in blood plasma are two main factors in development of atherosclerosis (28). Hypercholesterolemia in humans decreases pertussis toxin-sensitive vessel response to ACh, but bradykinin relaxation remains unchanged. It was found that combining endothelium removal and hypercholesterolemia, endothelium-dependent relaxation was lost first in response to pertussis toxin *in vivo* (on animals) and then after a prolonged period of time relaxation of the arteries in response to all endothelium-released relaxing factors is markedly reduced. Lysophosphatidylcholine and oxidized lipoproteins, being atherosclerosis mediators, stop NO and EDHF production. After oxidation LDL's have suppressive action on endothelial NO synthase (38). Due to diminished production of endothelium-derived relaxing factors the activity of thrombocyte released vasoconstrictive and growth-stimulating factors (angiotensin II, endothelin-1) is increased. Lowered production of NO decreases anti-aggregative and anti-adhesive properties of the endothelium to thrombocytes and leucocytes what in turn stimulates formation of atherosclerosis. Many pathways to decrease cholesterol level in blood are being tested; it could be statins, hormone replacement therapy, vitamin E, and L-arginine therapy (39).

Circulatory shock. Circulatory shock can be evoked by systemic hypotension caused by NO hyperproduction in blood vessels. This is considered to be a main cause during septic and cytokine initiated shocks. It occurs because of increased stimulation of soluble guanylyl cyclase, as it influences cyclic GMP increase and vascular smooth muscle relaxation. This mechanism helps lipopolysaccharides and tumor necrosis factor to affect microcirculation by NO hyperproduction. Low NOS inhibitor doses have stabilized blood circulation in experimental animals with evoked septic shock and this was confirmed in humans too (28).

Ischemia and reperfusion. Using ischemia-reperfusion model in rats mesenteric bed with decreased NO production, it was noticed that leuko-

cyte adhesion, albumin extravasation, mastocytes degranulation and thrombocytes-leukocytes aggregation were decreased by stimulating release of NO (40). During coronary microcirculation, NO decreases area of necrosis and recovers endothelium-dependent relaxation. In rat brain, following ischemia caused by occlusion of middle brain artery, rapid increase in NO synthesis has been found. This could be an effort of organism to decrease area of necrosis.

Long-term hypothermic ischemia and normothermic reperfusion of rat isolated heart causes endothelial dysfunction of the coronary arteries that is not affected by addition of NO synthase substrate L-arginine (41). The endothelium-dependent smooth muscle relaxation is more impaired in the distal part (intramyocardial) of coronary arteries in comparison to the proximal part (epicardial) of these arteries. Natural antioxidant - reduced glutathione protects the endothelium of coronary arteries from ischemic damage (42, 43).

Conclusion

Investigation of vascular structure and function successfully drew up basic sciences and clinical practice (44). Results of joint investigations opened up many new directions, gave new possibilities to better understand and correct pathological states of organism, in development of which dysfunction of vasomotorics plays a big role. Establishment of endothelial significance was a major breakthrough in investigation of blood vessels, clinical practice, as well as changed understanding about drug treatment of cardiovascular diseases.

There still is no full understanding about origin of endothelial factors, their interactions, and involvement in physiological functions, which raises increasing interest in further investigations of this area.

Azoto oksido ir kitų endotelio išskiriamų medžiagų svarba

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Raktažodžiai: azoto oksidas, endotelis, hipertenzija, aterosklerozė, išemija.

Santrauka. Endotelis atlieka integruojančiąją funkciją ir palaiko daugelį biologinių funkcijų: reguliuoja koaguliacijos ir fibrinolizės pusiausvyrą, turi įtakos adhezijos aktyvavimui dėl imuninės sistemos sužadinimo, palaiko pusiausvyrą tarp noradrenalino ir 5-hidroksitriptamino, angiotenzino I ir bradikinino susidarymo. Be to, endotelis reguliuoja kraujagyslių lygiųjų raumenų veiklą išskirdamas juos atpalaiduojančių medžiagų: azoto oksido, prostaglandinų, endotelio išskiriamos hiperpoliarizuojančios medžiagos, bei kraujagyslių lygiuosius raumenis sutraukiančių medžiagų, t. y. endotelino, superoksido, tromboksano. Šiame straipsnyje apžvelgiama šių medžiagų kilmė, veikimo mechanizmai ir svarba, daugiausiai dėmesio skiriant azoto oksidui. Katalizuojant azoto oksido sintazei, susidaro azoto oksidas ir citrulinas iš molekulinio deguonies ir L-arginino. Guanililciklazė yra pagrindinis azoto oksido taikinys, sužadinantis ciklinio guanozinmonofosfato formavimąsi lygiuosiuose raumenyse ir jų atsipalaidavimą. Endotelio išskiriama hiperpoliarizuojanti medžiaga sukelia kraujagyslių lygiųjų raumenų atsipalaidavimą hiperpoliarizacijos būdu. Endotelio išskiriamos hiperpoliarizuojančios medžiagos kilmė nėra ištirta. Manyta, kad tai galėtų būti kalio jonai, vandenilio peroksidas, epoksieikosatrieninės rūgštys. Prostaciklinas ir prostaglandinas E_2 veikia specifinius receptorius, sukeldami ciklinio adenozinmonofosfato koncentracijos padidėjimą ir kraujagyslių lygiųjų raumenų atsipalaidavimą, o jų susitraukimą sukeliantys prostaglandinai aktyvuoja tromboksano ir endoperoksidazių receptorius. Superoksido anijonai sukelia kraujagyslių lygiųjų raumenų susitraukimą, ardydami azoto oksidą. Endotelinas yra stiprus endotelio išskiriamas vazokonstriktorius. Endotelino-1 sintezė sužadinama trombino, interleukino-1, transformuojančio augimo faktoriaus β_1, vazopresino, katecholaminų ir hipoksijos metu. Amžius, hipertenzija ir hiperlipidemija yra širdies ir kraujagyslių sutrikimų rizikos veiksniai, tiesiogiai susiję su kraujagyslių gebėjimu atsipalaiduoti. Tai priklauso nuo endotelio išskiriamų atpalaiduojančiųjų medžiagų sintezės susilpnėjimo ar kraujagysles sutraukiančių medžiagų sintezės padidėjimo. Tokia sutrikusi pusiausvyra tiesiogiai veikia aterosklerozės ir išeminių kraujagyslinių sutrikimų atsiradimą.

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References

1. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells an the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373-6.
2. Simonsen U, Wadsworth RM, Buus NH, Mulvany MJ. In vitro simultaneous measurements of relaxation and nitric oxide concentration in rat superior mesenteric artery. J Physiol 1999;516:271-82.
3. Cohen AR, Vanhoutte PM. Endothelium-dependent hyperpolarization beyond nitric oxide and cyclic GMP. Circulation 1995;92:3337-49.
4. Nathan C, Xie QW. Regulation of the biosynthesis of nitric oxide. J Biol Chem 1994;269:13725-8.
5. Gross SS, Wolin MS. Nitric oxide: pathophysiological mechanisms. Annu Rev Physiol 1995;57:737-69.
6. Sautebin L, Ialenti A, Ianaro A, Dr Rosa M. Modulation by nitric oxide of prostaglandin biosynthesis in the rat. Br J Pharmacol 1995;114:323-8.
7. Davidge ST, Baker PN, McLaughlin MK, Roberts JM. Nitric oxide produced by endothelial cells increases production of eicosanoids through activation of prostaglandin H synthase. Circ Res 1995;77:274-83.
8. Fleming I, Busse R. NO: primary EDRF. J Mol Cell Cardiol 1999;31:5-14.
9. Hecker M, Bara AT, Bauersachs J, Busse R. Characterization of endothelium-derived hyperpolarizing factor as a cytochrome P_{450}-derived arachidonic acid metabolite in mammals. J Physiol 1994;481:407-14.
10. Corriu C, Félétou M, Canet E, Vanhoutte PM. Inhibitors of the cytochrome P450 mono-oxygenase and endothelium-dependent hyperpolarizations in the guinea-pig isolated carotid artery. Br J Pharmacol 1996;117:607-10.
11. Vanheel B, Van de Voorde J. Influence of various cytochrome P450 on hyperpolarizations and relaxations in the main mesenteric artery of the rat. In: Vanhoutte PM, editor. Endothelium-dependent hyperpolarizations. The Netherlands: Harwood Academic Publishers; 1999. p. 85-96.
12. Fulton D, McGiff JC, Quilley J. Role of phospholipase C and phopholipase A_2 in the nitric oxide-independent vasodilator effect of bradykinin in the rat perfused heart. J Pharmacol Exp Ther 1996;278:518-26.
13. Weintraub NL, Stephenson AH, Sprague RS, Lonigro AJ. Role of phospholipase A_2 in EDHF-mediated relaxation of the porcine coronary artery. In: Vanhoutte PM, editor. Endothelium-dependent hyperpolarizations. The Netherlands: Harwood Academic Publishers; 1999. p. 97-108.
14. Edwards G, Dora KA, Gardener MJ, Garland CJ, Weston AH. K^+ is an endothelium-derived hyperpolarizing factor in rat arteries. Nature 1998;396:269-72.
15. Coleman HA, Tare M, Parkington HC. EDHF is not K^+ but may be due to spread of current from the endothelium in guinea pig arterioles. Am J Physiol 2001; 280: H2478-83.
16. Barlow RS, White RE. Hydrogen peroxide relaxes porcine coronary arteries by stimulating BKCa channel activity. Am J Physiol 1998; 275: H1283-9.
17. Matoba T, Shimokawa H, Nakashima M, Hirakawa Y, Mukai Y, Hirano K, Kanaide H, Takeshita A. Hydrogen peroxide is an endothelium-derived hyperpolarizing factor in mice. J Clin Invest 2000;106(12): 1521-30.
18. Campbell WB, Gebremedhin D, Pratt PF, Harder DR. Identification of epoxyeicosatrienoic acids as endothelium-derived hyperpolarizing factors. Circ Res 1996;78:415-23.
19. Miura H, Gutterman DD. Human coronary arteriolar dilation to arachidonic acid depends on cytochrome P-450 monooxygenase and Ca^{2+}-activated K^+ channels. Circ Res 1998; 83:501-7.
20. Coleman RA, Smith WL, Narumiya S. International union of pharmacology classification of prostanoid receptors and their subtypes. Pharmacol Rev 1994;46:205-29.
21. Delpy E, Coste H, Gouville AC. Effects of cyclic GMP elevation on isoprenaline-induced increase in cyclic AMP and relaxation in rat aortic smooth muscle: role of phosphodiesterase 3. Br J Pharmacol 1996;119:471-8.
22. Shimizu S, Ishii M, Yamamoto T, Kawanishi T, Momose K, et al. Bradykinin induces generation of reactive oxygen species in bovine aortic endothelial cells. Res Commun Chem Pathol Pharmacol 1994;84:301-14.
23. Lüscher TF, Oemar BS, Boulanger CM, Hahn AWA. Molecular and cellular biology of endothelin and its receptors. In: Lindpainter K, Ganten D, editors. Molecular rewievs. London: Chapman & Hall; 1996. p. 96-104.
24. Hecker M, Billiar TR. Detection of L-arginine, related metabolites and guanidino compounds. In: Feelisch M, Stamler JS, editors. Methods in nitric oxide research. John Wiley & Sons Ltd; 1996. p. 465-78.
25. Lincoln TM, Komalavilas P, Cornwell TL. Pleiotropic regulation of vascular smooth muscle tone by cyclic GMP-dependent protein kinase. Hypertension 1994;23:1141-7.
26. Dukarm RC, Russell JA, Morin FC 3rd, Perry BJ, Steinhorn RH. The cGMP-specific phosphodiesterase inhibitor E4021 dilates the pulmonary circulation. Am J Respir Crit Care Med 1999;160(3):858-65.
27. Jackson G, Benjamin N, Jackson N, Allen MJ. Effects of sildenafil citrate on human hemodynamics. Am J Cardiol 1999;83(5A):13C-20C.
28. Mombouli JV, Vanhoutte PM. Endothelial dysfunction: from physiology to therapy. J Mol Cell Cardiol 1999;31:61-74.
29. Fleming I, Bauersachs J, Fisslthaler B, Busse R. Ca^{2+}-independent activation of the endothelial nitric oxide synthase in response to tyrosine phosphatase inhibitors and fluid shear stress. Circ Res 1998;82:686-95.
30. Taddei S, Virdis A, Mattei P, Ghiadoni L, Fasolo CB, et al. Hypertension causes premature aging of endothelial function in humans. Hypertension 1997;29:736-43.
31. Nakashima M, Mombouli JV. Age-dependent decrease in endothelium-dependent hyperpolarizations to endothelin-3 in the rat mesenteric artery. J Cardiovasc Pharmacol 1993; 22(8):S352-4.
32. Panza JA, Casino PR, Badar DM, Quyyumi AA. Effect of increased availability of endothelium-derived nitric oxide precursor on endothelium-dependent vascular relaxation in normal subjects and in patients with essential hypertension. Circulation 1993;87:1475-81.
33. Gerhard M, Roddy MA, Creager SJ, Creager MA. Aging progressively impairs endothelium-dependent vasodilatation in forearm resistance vessels of humans. Hypertension 1996; 27:849-53.
34. Bouloumie G, Fleming I, Busse R. Endothelial dysfunction coincides with an enhanced NO synthase expression and superoxide anion production. Hypertension 1997;30:934-41.
35. Bauersachs J, Bouloumie A, Mülsch A, Wiemer G, Fleming I, et al. Vasodilator dysfunction in aged spontaneously hypertensive rats: changes in NO synthase III and soluble guanylyl expression and in superoxide anion production.

Cardiovasc Res 1998;37:772-9.
36. Stankevicius E, Martinez AC, Mulvany MJ, Simonsen U. Blunted acetylcholine relaxation and nitric oxide release in arteries from renal hypertensive rats. J Hypertension 2002; 20:1571-9.
37. Gibbons GH. Cardioprotective mechanisms of ACE inhibition. The angiotensin II-nitric oxide balance. Drugs 1997; 54(5):1-11.
38. Vidal F, Colome C, Martinez-Gonzalez J, Badimon L. Atherogenic concentrations of native low-density lipoproteins down-regulate nitric oxide synthase mRNA and protein levels in endothelial cells. Eur J Biochem 1998;252:378-84.
39. Richard OC. Cardiovascular benefit of cholesterol-lowering therapy. Does improved endothelial vasodilator function matter? Circulation 2000;102:820-2.
40. Kurose I, Wolf R, Grisham MB, Granger DN. Modulation of ischaemia/reperfusion-induced microvascular dysfunction by nitric oxide. Circ Res 1994;74:376- 82.
41. Kevelaitis E, Mouas C, Menasché P. Poststorage diastolic abnormalities of heart transplants: is vascular dysfunction or myocardial contracture the culprit? J Heart Lung Transplant 1996;15:461-9.
42. Kevelaitis E, Nyborg NCB, Menasché P. Protective effect of reduced glutathione on endothelial function of coronary arteries subjected to prolonged cold storage. Transplantation 1997;64:660-3.
43. Kevelaitis E, Nyborg NCB, Menasché P. Coronary endothelial dysfunction of isolated hearts subjected to prolonged cold storage: patterns and contributing factors. J Heart Lung Transplant 1999;18:239-47.
44. Alexander RW, Dzau VJ. Vascular biology. The past 50 years. Circulation 2000;102:IV-112-6.

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