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The biological role of the endothelium in normal conditions

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Abstract

The paper presents current data of domestic and foreign literature on the biological role of the vascular endothelium under normal conditions, the participation of the endothelium in the regulation of vascular tone, blood coagulation potential, regulation of leukocyte adhesion, regulation of vascular permeability and their re-endothelization due to growth factors.

Keywords: endothelium, vascular tone, coagulation potential

Endothelial cells have an extremely heterogeneous structure, with diverse functions and a violation of the structure and functions of the endothelium is the initiating factor for the development of various forms of pathology. The endothelial lining of vessels is very diverse, in a number of organs and tissues has dense cell – cell contacts, which is characteristic of the blood-brain barrier. In other organs and tissues, particularly in the kidneys, a number of endocrine glands, the endothelium is fenestrated, sinusoidal, and thus provides selective permeability for various substances. (Z. A. Lupinskaya, A. G. Zarifyan, T. Ts. Gurovich , S.G. Shleifer 2008)

According to a number of authors, the vascular endothelium is an endocrine organ, and performs numerous functions, in particular, the regulation of the coagulation potential of the blood, as well as vascular tone. Endothelial cells mediate inflammatory and immune processes; regulate leukocyte adhesion; modulate lipid oxidation; regulate vascular permeability, their re-endothelization due to growth factors.

The purpose of this work was to analyze the literature data of domestic and foreign authors on the role of the endothelium in the regulation of the functional activity of the vascular wall under normal conditions.

Endothelial factors that regulate vascular tone

Among the endothelial factors that affect vascular tone, vasodilating factors are identified, which include NO, EDHF (endothelial hyperpolarizing factor), prostacyclin, adrenomedullin, carbon monoxide, Na-uretic peptide C, kinins, and several others. The vasoconstrictor factors produced by endothelial cells include thromboxane A2, endothelin, 20-HETE (20-hydroxyeicosecotetraenic acid), angiotensin II. The balance between the factors of relaxation and constriction determines the vascular tone and, accordingly, the amount of local blood flow.

Vasodilator factors produced by endothelium

Regarding the biological effects of a number of vasodilating compounds synthesized in endothelial cells, one should first of all focus on the effects of NO.

NO is formed in endothelial cells from L-arginine by the action of the enzyme NO-synthetase. There are two levels of NO secretion - basal and stimulated. The tone of the vessels at rest is carried out by constant basal secretion. Some chemicals: acetylcholine, ATP, bradykinin, as well as hypoxia or mechanical deformation increase the synthesis of NO. By stimulating guanylate cyclase, NO increases the formation of cGMP in smooth muscle cells, platelets, which leads to vascular relaxation, inhibits the proliferation of smooth muscle cells and inhibits the activity of platelets and macrophages. (V. F. Kirichuk, A. P. Rebrov, S. I. Rossoshanskaya, 2005)

Prostacyclin is synthesized predominantly in the endothelium. The main mechanism regulating its formation is the activity of cyclooxygenase enzymes. Prostacyclin has a vasodilating effect by increasing the activity in vascular smooth muscle cells of adenylate cyclase and increasing the formation of cAMP in them. (Dzgoeva F. U., Kutyrina I. M. 2000)

When blocking the action of NO and prostacyclin, vasodilation causes endothelial hyperpolarization factor. This factor is released only under the action of certain stimuli: acetylcholine, bradykinin, thrombin, histamine, substance P, ADP, ATP.

Two more factors are known that are secreted by the endothelium and cause vascular dilatation: C-type natriuretic peptide (PPS) and adrenomedullin. Natriuretic peptide C causes relaxation of blood vessels and inhibits the proliferation of smooth muscle cells. Most of the NPC is synthesized in the endothelium, affects the receptors of smooth muscle cells, causing an increase in the formation of cGMP, leading to the expansion of the vessel. Adrenomedullin acts as a direct vasodilator by increasing the production of cAMP. As a result, activation of adenylate cyclase is formed from prepro-adrenomedullin in endothelial and smooth muscle cells of blood vessels. Proven. that the vasodilating action of adrenomedullin is associated with both endothelium-dependent and endothelium-independent mechanisms. It is assumed the presence of specific receptors for adrenomedullin. (Kitamura K. et al. Adrenomedullin, 1993)

Carbon monoxide is formed from heme by the action of two isoforms of hemoxygenase (HO-1 and HO2). CO is formed in various regions, but mainly in the endothelium of the brain vessels (Faraci F.M., Heistad D.D., 1998), where they participate in the regulation of blood flow, directly causing relaxation of the cerebral vessels. (Chertok V.M., Kotsyuba A.E., 2012)

Kallikrein-kininovaya system. The vasodilating effect of kinins is associated with the activation of B2 receptors on the endothelium and the formation of the main endothelial vasodilating factors — NO, prostacyclin, EDHF.

Vasoconstrictor factors produced by the endothelium

Endothelial factors cause vasoconstriction, which is due to the lack of release of relaxation factors and the production of constrictive agents. Endothelins, thromboxane A2, 20-HETE (20-hydroxyeicocycotetraenic acid), angiotensin II are referred to as vasoconstrictors synthesized in endothelial cells.

Endothelin is the most powerful vasoactive substances. The most studied representative of this class is endothelin-1. At physiological concentrations, it acts on endothelial receptors, causing the release of relaxation factors, and at higher levels, it activates receptors on smooth muscle cells, stimulating resistant vasoconstriction and proliferation of media.

Thromboxane A2 is predominantly synthesized in platelets, but some of it is produced in the endothelium. Specific receptors for it are located on the smooth muscle cells of the vascular wall. The reduction of smooth muscle cells during stimulation with thromboxane is associated with a decrease in the activity of adenylate cyclase and an increase in the content of intracellular calcium.

Angiotensin || is formed as a result of activation of the renin-angiotensin system and it is also one of the most powerful vasoconstrictors. Activation of this system can occur both at the systemic level when renin is secreted by the cells of the juxtaglomerular complex of the kidneys, or locally, at the endothelium level, in which renin and angiotensin-converting enzyme are formed. (Babak O. Ya., Kravchenko N. A. 2005)

The vasoconstrictor function is performed by 20-hydroxyeicosecotetraenoic acid (20-HETE), which is a product of the arachidonic acid exchange along the monooxygenase pathway. 20-HETE, acting on vascular smooth muscle cells, causes depolarization of cell membranes. Its formation increases under the action of angiotensin 2 and endothelin-1, as well as during hyperoxia, and is one of the leading factors of high blood pressure. An increase in its formation is accompanied by the inclusion of inhibitory regulatory mechanisms by the activation of the synthesis of prostacyclin, i.e. the principle of antagonistic regulation is preserved.

The role of the endothelium in the regulation of blood coagulation potential

One of the important functions of the endothelium is to ensure thromboresistance of the vascular wall, and on the other side of its thrombogenicity. Among thrombogenic factors stimulating the processes of adhesion and platelet aggregation refers vWF (von Willebrand factor), PAF (platelet activating factor), ADP, thromboxane A2, platelet adhesion to the endothelium - this is the initial stage of the hemostatic processes and thrombosis, which leads to the formation of platelet thrombus formation, activation plasma procoagulants with the subsequent formation of thrombin. Thrombin synthesis inhibitors include: thrombomodulin, proteoglycans that prevent excessive fibrin formation. Thromboregulators affect not only hemostasis, but also vascular permeability, vasomotor reactions, angiogenesis, cell proliferation. (Petrishchev N.N., Vlasov ETC. 2003)

As mentioned above, during hypoxia and the action of mediators that increase the synthesis of NO, prostacyclin is synthesized in endothelial cells, media, and adventitia. Prostacyclin activates adenylate cyclase, resulting is an increase of cAMP, which, in addition to performing the vasodilating function, prevents platelet activation and causes vascular relaxation. Violation of the synthesis of prostacyclin or a decrease in its release into the blood creates a thrombogenic hazard. NO inhibits platelet adhesion and aggregation. This process is associated with an increase of cGMP platelet count.

Thrombogenic risk increases with decreasing content in the blood plasma of active antithrombin, primarily AT III, with the simultaneous presence of predisposing factors - hyperlipidemia, obesity, diabetes, heart failure. (Suck G., Traut W. 2000)

Endothelium plays an important role in the development of fibrinolysis due to the secretion of tissue and urokinase plasminogen activators and its inhibitors, which can either quickly neutralize plasmin or inhibit the activation of plasminogen. Under the influence of hemodynamic factors, near-wall shear stress, transmural pressure and a number of other factors, a dynamic change occurs in the synthesis and secretion of thrombogenic and atrombogenic substances of the endothelium. Under physiological conditions, the release of atrombogenic substances prevails over thrombogenic. (Petrishchev N.N., Vlasov ETC. 2003)

The physiological anticoagulant complex is a protein C system (Pr C), which includes thrombomodulin, protein C, protein S, thrombin (Pr C activator) and Pr C. inhibitor. The function of this system is to inhibit blood coagulation factors Va and VIII, inactivating tissue inhibitor plasminogen activator. (Aylamazyan E. K., Mozgovaya E. V. 2008)

In the regulation of the hemostatic function of the endothelium hormones vasopressin, estrogens, cytokines: interleukin-1, TNF-α, hemodynamic factors are of great importance. The factors of endothelial origin that inhibit adhesion and platelet aggregation include prostacyclins, E2 prostaglandins, and NO.

The value of the endothelium in the regulation of leukocyte adhesion

The endothelium plays a crucial role in the development of leukocyte adhesion. Adhesive endothelial molecules include P-selectin, GMP-140, ELAM-1, ICAM. Increased adhesion of the endothelium is of great importance in the pathogenesis of inflammatory processes, atherosclerosis, and septic shock. However, until now, the value of the violation of the adhesive properties of the vascular wall in the pathogenesis of neoplasias of various localization and the development of metastasis of malignant cells remains unexplored.

The value of endothelial cells in the process of angiogenesis

The endothelium plays a significant role in the process of angiogenesis under conditions of pathology. In a stable state, endotheliocytes proliferate only once every 10 years. Under the action of angiogenic factors, proliferation of endotheliocytes occurs, which ends with their differentiation and re-endothelization of the vessels. The endothelium is actively involved in the process of cooperation between endotheliocytes and surrounding cells, highlighting growth factors (VEGF, FGF-2), causing taxis and proliferation of smooth muscle cells and fibroblasts.

Endothelial dysfunction is one of the universal pathogenetic factors in the development of such forms of pathology as atherosclerosis, hypertension, diabetes mellitus, thrombohemorrhagic syndrome and carcinogenesis. The causes of endothelial dysfunction can be ischemia, tissue hypoxia, free radical damage, cytokines, and a number of other factors.

Conclusion

In the pathogenesis of numbers diseases of various genesis, dysfunction of the vascular wall, is particularly endothelial dysfunction plays enormous role. Therefore, for the prevention and competent treatment of these pathologies, deep knowledge of the functional significance of the vascular wall in health and pathology is necessary. Monitoring of blood levels of endothelial dysfunction markers can be used as objective diagnostic, predictive criteria for various diseases, as well as an assessment of the effectiveness of complex therapy.

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