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Review Article

The impact of selected vasoactive factors on vascular functions

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ABSTRACT

Introduction: The regulation of blood circulation is crucial for maintaining vascular homeostasis under physiological conditions, i.e. for precisely controlling the balance between vasodilators and vasoconstrictor action. Numerous studies show that both arteries and veins actively participate in the control process.

Aim: This paper discusses the regulation of the secretion of selected vasoactive factors in endothelial cells. The mechanisms of action of those factors, the effect of other regulators on the function of vascular smooth muscle cells and the impact of physiological and pathological factors on the vasoreactivity are also examined.

Discussion: The synthesis and release of most vasodilators, including nitric oxide, carbon monoxide and prostacyclin, as well as vasoconstrictors – endothelin and thromboxane, takes place in endothelial cells. Prostaglandins $F_{2\alpha}$ or E_2 produced both in endothelial and other cells of bodily organs also influence blood vessel function. Steroid ovarian hormones, estradiol, progesterone and testosterone, affect vascular function indirectly by modulating endothelial secretory function.

Conclusions: Blood vessel function largely depends on the activity of endothelial cells which release various vasoactive factors in response to stimulation. The resulting mutual interactions adjust vascular function to current needs. Endothelial dysfunction disrupts the activity of various organs, and it may contribute to cardiovascular diseases such as hypertension, atherogenesis or thrombotic lesions.

1. Introduction

The regulation of blood circulation is crucial for maintaining vascular homeostasis under physiological conditions, i.e. for precisely controlling the balance between vasodilators and vasoconstrictor action. Numerous studies show that both arteries and veins are part of an extensive, multifunctional system and that they are not merely passive canals responsible for blood flow to tissues, organs and systemic circulation. Arteries and veins play a vital role in the function of the body, as demonstrated by research into the development of blood vessels in prenatal life[29,30] and studies indicating that vascular

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system defects contribute to mortality.[16] The synthesis and release of biologically active factors which regulate vasomotorics of blood vessels, such as nitric oxide, carbon monoxide, prostacyclin, prostagladins $F_{2\alpha}$ and E_2, thromboxane A_2, endothelins, estradiol, progesterone and testosterone, takes place in endothelial cells. Endothelial cells also participate in the control of hemostasis, angiogenesis, inflammatory processes and immune responses. The endothelium can respond to changes in blood pressure, via nervous and humoral pathways, as well as changes in blood flow and gas concentration. The secreted factors regulate motor activity, migration, proliferation and cellular apoptosis of vascular myocytes.

2. Aim

This paper discusses the regulation of the secretion of selected vasoactive factors in endothelial cells. The mechanisms of action of those factors, the effect of other regulators on the function of vascular smooth muscle cells and the impact of physiological and pathological factors on the vasoreactivity are also examined.

3. Discussion

Nitric oxide (NO), initially described as EDRF, is a well-known endothelial-derived relaxing agent.[12] NO is produced in the blood vessels of various bodily organs from L-arginine with the participation of NO synthase (NOS). NADPH-diaphorase (NADPH-d) is a cellular marker for NOS. Constitutive isoforms of NOS in the endothelium (eNOS) and the nervous system (bNOS) are responsible for the continuous release of picomole amounts of NO. Their activity is dependent on the calmodulin-calcium ion complex. Small, highly lipophilic molecules of NO permeate the membrane of vascular smooth muscle cells where they activate guanylate cyclase to catalyze the formation of cyclic GMP which mediates the relaxation of both vascular and non-vascular smooth muscle cells via path-dependent protein kinase.[13,24] The activity of inducible NOS (iNOS) can be stimulated by vessel relaxing factors: acetylcholine, bradykinin, ADP, cytokines, insulin, substance P, estrogens and shear stress, to which endothelial cells are exposed during blood flow.[31] Shear stress not only increases the expression of mRNA for eNOS, but also stimulates endothelial cells to release NO.[43] Estradiol (E_2) supplied to the ovine uterine artery caused vessel relaxation which is triggered by NO release from endothelial cells and increased blood flow.[4] Similarly, estradiol benzoate increased NADPH-d activity in the endothelium of arteries and veins of the broad ligament of uterus in ovariectomized gilts and sheep.[48,49] The substrate for NO production (L-NMMA) administered intravenously to humans permanently raised blood pressure due to continuous production of vessel-relaxing NO.[22] Scientific advances of the 1980s have expanded our knowledge of NO produced by mammals in the presence of carbon monoxide (CO). CO is formed in the process of heme degradation under the influence of heme oxygenase (HO) in the microsomal fraction of cells. HO is found in endothelial and vascular smooth muscle cells as well as various neural structures in the central nervous system, sensory cells and erythrocytes.[21,47] There are three isoforms of HO: inducible HO-1, constitutive HO-2 and HO-3, an isoform with a low catalytic activity. HO-2 participates in hemoprotein metabolism, and it produces CO which is a mediator of various biological functions. CO formed in endothelial cells regulates vascular tension. In some vessels, such as the aorta and pulmonary vessels, the relaxing effect of CO is manifested through the activation of guanylate cyclase and increase in cGMP levels.[28,35] In cerebral,[19] muscle[50] and renal vessels,[15] CO does not enhance the synthesis of cGMP, but it directly activates calcium-dependent potassium channels in muscle cells by increasing open times.[44] There is evidence that CO may be a constricting factor in vessels with intact endothelium[14] – by binding to guanylate cyclase, CO inhibits NOS or blocks the action of NO. In addition, CO stimulates endothelial cell proliferation and angiogenesis; it inhibits the proliferation of vascular smooth muscle cells, platelet aggregation and the synthesis of growth factors in endothelial cells.[26] Until recently, CO and NO were considered to be gaseous transmitters produced exclusively for local use, but recent studies supplied new evidence of their activity outside the place of the secretion. NO is bound by thiol groups, mainly cysteine and glutathione, and hemoglobin molecules found near the erythrocyte membrane, and it produces nitrosohemoglobin which transports NO to microcirculatory vessels.[34,37] CO is also transported to the blood.[17]

Vascular endothelial cells also produce prostanoids, including prostacyclin, prostaglandins and thromboxane. Prostacyclin (PGI_2) is synthesized from prostaglandins G_2 and H_2 through transformation of arachidonic acid with the involvement of prostacyclin synthase (PGIS). PGI_2 activates adenylate cyclase and increases cAMP levels in vascular smooth muscle cells to induce vessel relaxation. Similarly to NO, PGI_2 causes direct hyperpolarization of cGMP or cAMP by stimulating ATP-sensitive potassium channels. Under normal physiological conditions (intact endothelium), PGI_2 protects the inner surface of vessel walls against adhesion and clumping of blood platelets, and it prevents the shrinking of blood vessels. In this respect, it acts synergistically with NO.[42] The administration of estradiol benzoate increased the level of PGIS in the endothelium of uterine and renal arteries and in vascular smooth muscle cells of uterine and omental arteries, whereas progesterone elevated PGIS protein concentrations in vascular smooth muscle cells of uterine and omental arteries in ovariectomized sheep.[34]

Prostaglandins $F_{2\alpha}$ ($PGF_{2\alpha}$) and E_2 (PGE_2) are produced in many organs (lungs, kidneys, liver) and bodily fluids. $PGF_{2\alpha}$ contracts bronchial smooth muscles and arterial and venous vessels,[45] whereas PGE_2 has the opposite effect. Reproductive organs (ovary, oviduct, uterus), which regulate various functions, including blood flow, are an important site of $PGF_{2\alpha}$ and PGE_2 synthesis. According to general belief, $PGF_{2\alpha}$ decreases blood flow in the uterine artery, while PGE_2 increases blood flow in that vessel.[3] However, recent studies have demonstrated that while $PGF_{2\alpha}$ always contracts smooth muscles by acting through its only FP receptor, PGE_2 can deliver both relaxing and constricting effects through four types of its EP receptor (EP-1, EP-2, EP-3, EP-4). The above can be attributed to the distribution of EP receptor types in the vessels of reproductive organs as well as the stage of reproductive activity.[2] All types of prostanoid receptors are coupled to G proteins, but they differ in

the type of the effector and the signal transmission pathway. The effector of FP and EP receptors is phospholipase C which catalyzes the production of triphosphoinositol (IP_3) to release intracellular calcium and diacyloglycerol (DAG) – the activator of protein kinase C.[2] Adenylate cyclase, the effector of EP-2, EP-3 and EP-4 receptors, increases the concentrations of cAMP which activates protein kinase A. It is believed that retrograde and destination transfer of both prostaglandins, which locally increases $PGF_{2\alpha}$ and PGE_2 concentrations, significantly impacts their effect on reproductive organ vessels.[6,40] It has been recently demonstrated that increasing doses of $PGF_{2\alpha}$ and PGE_2 raise vascular tension in the branches of porcine uterine and ovarian arteries.[39] Both vessels were strongly contracted by $PGF_{2\alpha}$, and they produced a weaker contractile response to PGE_2. Vascular sensitivity to the examined prostaglandins was determined by the phase of the cycle and early pregnancy, but a stronger response was observed in the ovarian artery than in the uterine artery.

Vasodilators deliver an opposite effect to vessel constricting factors. The most notable vasodilators include thromboxane A_2 (TXA_2) and endothelins (ET). TXA_2 is synthesized from endogenous peroxides of prostaglandins G_2 and H_2 under the influence of thromboxane synthase. TXA_2 and PGI_2 have opposite effects. TXA_2 is produced mainly in platelets, but it may also by synthesized in the vascular endothelium after blood vessel rupture. Damage to the vessel wall leads to platelet activation, changes in platelet shape and secretion of substances stored in granules. TXA_2 is responsible for platelet adhesion and increased platelet aggregation, which narrows the lumen of the vessel and slows blood flow. Enhanced synthesis of TXA_2 contributes to atherosclerosis of major arteries.[23]

Endogenous ET from bovine aortic and pulmonary endothelial cells were characterized as vasoactive peptides.[46] They were localized in almost all tissues of the body. Three isoforms of ET encoded by three distinct genes with an extremely conservative nucleotide sequence have been identified to date. ET-1, the best known isoform, is produced by cells, including endothelial and vascular smooth muscle cells.[18] ET-1 plays an equally important role in circulatory regulation, and it controls the tension in the vascular endothelium. ET levels are very low in mammalian blood. In the lumen of vessels, ET is captured by the receptors of various cell types. In mammals, there are two types of the specific receptors for ET, ET_AR and ET_BR, which have opposite effects. The stimulation of ET_AR and ET_BR in vascular smooth muscle cells activates the phospholipase C pathway, and it leads to vessel stenosis. The stimulation of ET_BR, which is found mainly in endothelial cells, causes vasodilation through increased production of NO and PGI_2.[8] Furthermore, NO inhibits the production of ET-1, which limits iNOS. Shear stress has also been found to increase the synthesis of ET and ET_BR mRNA expression.[25]

Steroid hormones also exert a significant impact on blood vessel functions. E_2 has dilatory and protective effects on blood vessels. It reduces the tension of coronary, cerebral and uterine arteries, as well as arteries supplying skeletal muscles and femoral and radial veins. E_2 affects vessels via nuclear estrogen receptors (ER) α and β (genomic effect) as well as membrane receptors (non-genomic effect). After translocation to the nucleus, the estrogen-ER complex is bound to a specific DNA sequence in the promoter of the target gene, and the active receptor regulates the transcription. By regulating NO synthesis, estrogens are able to inhibit apoptosis, migration of endothelial cells and proliferation of vascular smooth muscle cells. The stimulation of ERα affects eNOS concentrations of and NO synthesis in murine coronary arteries.[27] A negative correlation between the number of ERα and the intensity of atherosclerosis in the aorta was observed in premenopausal women.[20] Non-genomic and transcription-independent action of E_2 generates a rapid response (seconds, minutes) to hormone exposure through the activation of regulatory proteins MAPK, PI3K, tyrosine kinase, ion channels and receptors coupled to G protein.[41] Vascular endothelial cells stimulate the immediate release of NO, causing vasodilatation,[38] closing L-type calcium channels and opening potassium channels in vascular myocytes.[7] Estrogens improve endothelial functions in coronary artery disease and stimulate rapid regeneration after mechanical damage.[32] There is ample evidence that a correlation exists between ER expression in endothelial cells and angiogenic activity. Angiogenesis was found to be impaired in mice lacking ERα, and it was specifically inhibited by ERα antagonists.[33] It was also demonstrated that gene expression of the vascular endothelial growth factor (VEGF) and its type 2 receptor can be regulated by estrogens.[1]

Progesterone (P_4) acts via nuclear receptors present in endothelial and vascular smooth muscle cells, including aorta, coronary and cerebral vessels, as well as via membrane receptors, and it may increase or decrease the vascular tone.[36] Recent studies indicate that P_4 connected to the PGRMC1/SERBP1 membrane receptor complex elevates cGMP levels, activates protein kinase G and decreases the levels of intracellular calcium ions. Through its non-genomic mechanism of action, P_4 may directly reduce the contractility of vascular smooth muscles by lowering membrane permeability for calcium ions and blocking calcium channels.[5] The highest expression of protein PGRMC1 was observed in smooth muscle cells of blood vessels.[9] Testosterone, a vasoactive steroid with relaxing effects, is also used in the treatment of coronary artery disease.[36]

Steroid hormones play a highly significant role in the blood vessels of reproductive organs where blood flow is involved in the regulation of cyclic functions. Blood flow in the uterine artery is determined by the ratio of E_2:P_4 concentrations. The predominance of E_2 increases blood flow in the vascular bed of the uterine artery, whereas the prevalence P_4 delivers an opposite effect.[11,10] Intra-arterial, intravenous and intramuscular estrogen infusions increase blood flow in mesomertial vessels of many animal species, and P_4 neutralizes the vasodilatating effect of E_2. A reverse correlation is observed between E_2:P_4 concentrations and blood flow in the ovarian artery which reaches the highest level during maximum secretory activity of the corpus luteum.[9]

4. Conclusions

Blood vessel function largely depends on the activity of endothelial cells which release various vasoactive factors in response to stimulation. The resulting mutual interactions regulate vasomotorics and determine blood flow. Endothelial dysfunctions disrupt the activity of various organs, and they may contribute to

cardiovascular diseases such as hypertension, atherogenesis or thrombotic lesions.

Conflict of interest

None declared.

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