Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/poamed

Review Article

# The impact of selected vasoactive factors on vascular functions

*Jolanta Muszak**

*Department of Local Physiological Regulation, Institute of Animal Reproduction and Food, Research of the Polish Academy of Sciences, Olsztyn, Poland*

ARTICLE INFO

*Article history:*
Received 26 February 2013
Accepted 11 September 2013
Available online 16 September 2013

*Keywords:*
Endothelium
Vasoactive factors
Vasomotorics
Vasodilators
Vasoconstrictors

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

*Correspondence to: Department of Local Physiological Regulations, Bydgoska 7A, 10-243 Olsztyn, Poland. Tel.: +4889 539 31 25.
*E-mail address:* j.muszak@pan.olsztyn.pl

1230-8013/$ - see front matter 
http://dx.doi.org/10.1016/j.poamed.2013.09.001

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