

3.29 The role of endothelium in the reactivity of the vascular smooth muscle

Contractility of vessels is regulated by nervous, hormonal, but also local humoral regulatory mechanisms. The sympathetic adrenergic nervous system is regarded as the main regulatory mechanism of the vascular tonus. Activation of this system which locally releases a neurotransmitter (in particular noradrenaline), leads to contraction of the smooth vascular muscle.

Currently, great attention is paid to the study of vascular endothelium cells which play an important role in modulation of the vascular tonus.

Endothelial cells are responsible for a variety of physiological functions, as for example uptaking and metabolism of noradrenaline or serotonin, conversion of angiotensin I to angiotensin II, bradykinin metabolism, prostacyclin (PGI₂) biosynthesis. They affect the vascular wall permeability, blood coagulation, and thrombocytes activity.

Since the discovery of prostacyclin Mondacom, great attention has been paid to vasoactive substances produced in the vascular wall. The Furchgott's discovery of the role of vascular endothelium in vasodilatation induced by acetylcholin (1980), and evidence that this response takes place due to participation of a substance called *endothelium-derived relaxing factor*, stirred interest and attention to the forthright role of endothelium in modulation of vascular responses.

Endothelium cells produce **vasodilatory and vasoconstrictive factors**.

1. Vasodilatory factors include:

- PGI (prostacyclin)
- Endothelium-derived relaxing factor (EDRF)
- Endothelium-derived hyperpolarizing factor (EDHF)

PGI₂ (prostacyclin) – is a metabolite of arachidonic acid. It stimulates adenylatecyclase and increases the amount of cAMP in cells of vascular smooth muscle.

Endothelium-derived relaxing factor (EDRF) – is being synthesized from L-arginine in endothelium cells due to the impact of arginine oxidase.

Chemically, EDRF is nitrogen oxide (NO) or other labile nitroso compounds (R-NO). EDRF stimulates guanylatecyclase and increases the amount of cGMP in the vascular smooth muscle. EDRF is released under basal conditions and stimulation. The variety of physiological stimulations capable of evoking the augmentation of EDRF liberation includes the thrombocytes products (serotonin, ADP), thrombin, hormones, neurotransmitters (acetylcholine), changes in partial oxygen tension and increased blood flow. The release of EDRF owing to the increased blood flow plays an important role in alteration of the size of arterial lumen. Rapid elevation of intraluminal pressure stimulates the EDRF release or leads to an increased release of EDCF (endothelium-derived contracting factor).

2. **Vasoconstricting factors** are produced by endothelial cells (EDCFs). They function as intermediaries of endothelium-dependent vasoconstriction. It has been experimentally confirmed that the removal of endothelium reduces constriction caused by antagonists. Endothelium-dependent vasoconstriction can be stimulated by naturally present substances (noradrenaline, arachidonic acid (AA), thrombin, prostaglandin H₂), by pharmacological substances (nicotine, increased K⁺ ions), physical stimuli (stress, pressure) and hypoxia (see fig. 3.55 on page 254).

EDCFs which modulate the endothelium-dependent vasoconstriction include three categories:

- (a) EDCF₁ – vasoconstricting metabolites of arachidonic acid or oxygen radicals (e.g. superoxide anion)
- (b) EDCF₂ – which is released due to hypoxia. Its chemical structure has not yet been identified.

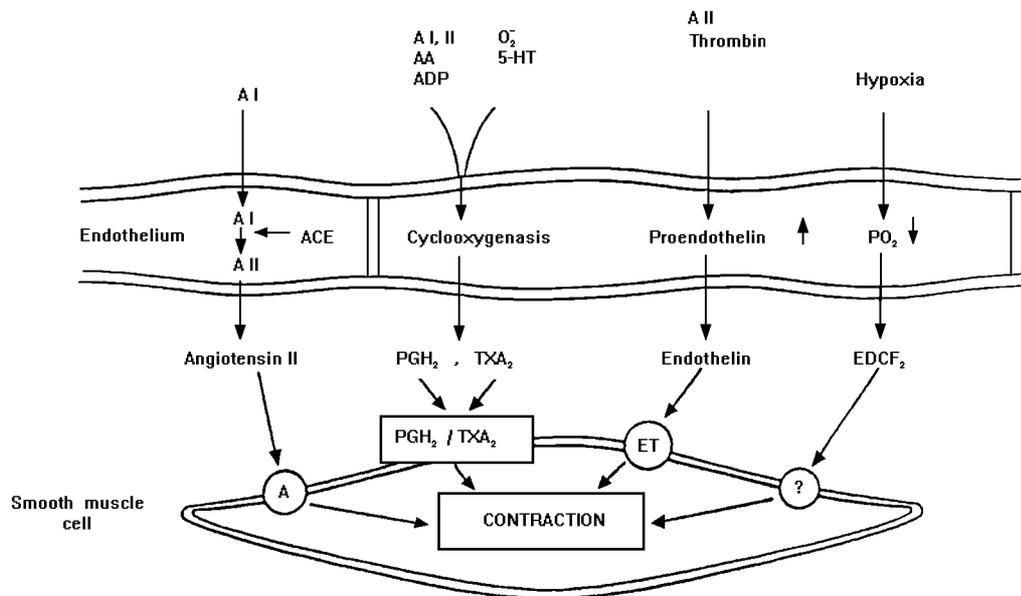


Figure 3.55: Endothel and some other vasoconstrictors

- (c) EDCF₃ – endothelin – substance which in contrast to the rapid contraction caused by other EDCFs, causes a long-term slowly developing vasoconstriction

Endothelin – is a peptide comprising 21 aminoacids. It has a strong vasoconstricting effect. A significant resemblance between endothelin and sarafatoxin which is a compound of snake venom has been revealed. Sarafatoxins, similarly as endothelin, have a strong coronaconstricting, hence cardiotoxic lethal effect.

Three different endothelin genes, and consequently three different endothelins were confirmed in man. Endothelin 1 (ET-1 in pigs, human endothelin), endothelin 2 (ET-2 differs from ET-1 by two aminoacids) and endothelin 3 (ET-3 differs from ET-1 by six aminoacids).

Endothelin 1 is formed from a precursor protein, the so-called big endothelin by the effect of endothelinconvertase. ET-1 is the only endothelin contained in vascular endothelium cells, additionally it was dis-

covered in cells of nonvascular type, as for example in kidneys, lungs and other tissues. ET-2 and ET-3 are contained in tissues of the brain, lungs, kidneys, adrenal glands, and small intestine.

3.29.1 Effects of endothelin

Endothelin had been formerly identified as a strong vasoconstricting substance, later a wider spectrum of its effects was discovered.

1. Vasoconstricting effects of endothelin - in dependence on dosage endothelin evokes contractions of arteries and veins, already in doses of $10^{-11} - 10^{-8}$, regardless of anatomical localisation of blood vessels. In general, the veins are more sensitive to endothelin than arteries. The onset of the coronary vessels response to the ET constricting effect is slow and of prolonged duration (several hours).
2. Pressoric and depressoric ET effects – intravenous administration of endothelin causes a

short-term (0,5–2 min.) depressoric response which is followed by elevation of arterial pressure dependently on the dosage. The mechanism of the initial depressoric response can be explained by the fact that endothelins, mainly ET-1 and ET-3, induce a release of prostacyclin or EDRF from the vascular endothelium. The pressure elevation in the vascular network lasts for 2–3 hours. This extremely prolonged effect represents one of the most important vascular effects of endothelin.

3. Contraction of nonvascular smooth muscles – endothelin causes contraction of the small intestine, tracheal and bronchial smooth muscles. The endothelin effect is comparable with that of histamin and exceeds that of leucotrien D₄.
4. Endothelin has a positive inotropic and chronotropic effect on myocardium.
5. Endothelin stimulates secretion of atrial natriuretic peptide (ANP) in myocardium
6. Renal effects – endothelium participates in regulation of renal functions by inhibiting the release of renin in kidneys. It decreases renal blood flow accompanied by reduction of glomerular filtration, urine volume and excretion of Na⁺ and K⁺ by the kidneys.
7. Endothelin decreases aggregation of thrombocytes, assumedly by cAMP decreasing.
8. Proliferation of smooth muscle cells

In addition, endothelin has trophic effects on the smooth muscle cells of vessels, the effect being of importance in regard to its role in both pathogenesis of atherosclerosis and vascular hypertension, and in elevated blood flow.

3.29.2 The mechanism of endothelin effect

Endothelin can be released due to the effect of vasopressin, adrenaline and thrombin. It is active via endothelin receptors of several subtypes, whilst the affinity of ET-1, ET-2 and ET-3 to these receptors is variable. The binding loci for endothelin are situated in the media of variously calibrated vessels and

parenchyma organs (heart, kidneys, lungs, small intestine, suprarenal glands, brain). Endothelin effect is based on the increased influx of Ca²⁺ via calcium canals in target cells.

It can also mobilize Ca²⁺ from intracellular depot sites by induction of the phosphatidylinositol system.

The evidence of endothelin effects, other than vasoconstrictive, as well as of endothelin receptors existence in various nonvascular tissues, draws attention to the fact that endothelin affects regulatory functions of various cardiovascular and non-cardiovascular tissues. Endothelin participates in regulation of the systemic arterial pressure and local blood distribution, formation and composition of urine, release of circulating hormones (e.g. renin, ANP, adrenaline) from kidneys, atrium and suprarenal glands, tonus of bronchial smooth muscles, small intestine motility, various CNS functions including autonomous regulation and higher functions.

There are two different models of endothelin formation in relation to the cardiovascular system regulation:

1. Endothelin participates in maintainance of the systemic and local circulation under physiological conditions. It functions similarly as a number of vasoactive substances, e.g. catecholamins, angiotensin II, vasopressin and ANP. Plasmatic concentration of endothelin in man is in average cca. 1 pmol·l⁻¹, which is a too small amount for it to be classified as a circulating hormone. It is quickly eliminated from circulation by the lungs. Endothelin has a local impact. Inhibition of renin-angiotensin system by means of endothelin, as well as stimulation of ANP secretion (strong vasorelaxing factor) represent examples of negative feed-back between endothelin and other hormonal systems.
2. A greater amount of endothelin is produced in damaged tissues due to their lesion or protective reactions (e.g. healing of wounds, inflammation), its formation being induced by thrombin.

Abrogation of regulatory mechanism which participate in endothelin formation, leads to various pathological states, e.g. coronary and cerebral vasospasms, bronchospasms, atherosclerosis and hypertension.

Endothelin is to a greater extent produced within the site of endothelial impairment and has contrac-

tile and proliferative effects on cells of the vascular smooth muscle representing the pathogenic factors of atherosclerosis and vasospasm pathogenesis.

Undoubtful is the role of endothelin especially in the pathogenesis of cardiocascular diseases. An increase of plasmatic ET-1 concentration was observed

in people with essential hypertension, vasospastic angina pectoris, and in acute myocardium infarction (IM).

From the clinical point of view, the changes in plasmatic ET concentration could be regarded as indices of IM course.