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New Views on the Role of Endothelin in the Regulation of Cell Functions

(Minireview)

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The endothelin family consists of isoforms endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3). ET-1 is the main isoform which was synthetized in endothelial cells, muscular cells in arterial walls and in heart, as well as in the kidney and the central nervous system. Endothelins affect functions of multiple cells, tissues and organ systems and are involved in the pathogenesis of many diseases.

Key words: endothelin (ET-1), endothelial cells, muscular cells of cardiovascular system, ovarian granulosa cells, cell function regulation.

Endothelin was detected as a cell factor produced by endothelial cells and causing smooth muscle contractions in 1985 [10]. Three years later (1988/1989), the biologically active substance — endothelin-1 (ET-1), has been isolated and identified by Yanagisawa et al. [16] from the *in vitro* cultivated pig arterial endothelial cells.

ET-1 is a peptide composed of 21 amino acids, including two disulphide bonds (the loss of these bonds between the amino acids 1—15 and 3 — 11, leads to the reduction of ET-1 biological activity).

In man, the endothelin gene encoding 212 aminoacid pre-pro-ET is localized in chromosome 6 and consists of 5 exons and 4 introns. Endothelin is formed by cleaving 164 amino acids from the pre-pro-ET by means of specific endopeptidase (s), resulting in big endothelin.

In further studies endothelin isomers, called endothelin-2 (ET-2) and endothelin-3 (ET-3) — encoded by independent genes were identified, which are different in their chemical structure and potency to contract the smooth muscle cells [11].

ET-1 is produced by vascular endothelial cells, vascular smooth muscle cells and less by astrocytes and neurons in the central nervous system (CNS), by Sertoli cells, hepatocytes in the liver and mesangium.

ET-2 is produced mainly within the kidney and intestines. The high levels of ET-3 have been found in the brain — probably involved in the regulation of neuronal functions.

Some cellular factors stimulate and others inhibite the endothelin synthesis and production by endothelial cells. The stimulating substances are thrombin, Ca ions, epinephrine, angiotensin II, vasopressin, dopamine, erythropoietin, cytokines (IL-1, IL-6), growth factors (fibroblastic, epidermal, insulin-like, GTF-beta), endothoxines, lipids (low density lipoproteis — LDL, and high density lipoproteis — HDL) and stress as well.

Inhibitors of the endothelin synthesis are nitrogen oxide (NO), cyclic guanosine monophosphate (cGMP), atrial natriuretic peptide (ANP), bradykinin, prostacyclin.

The blood levels of ET-1, AT-2 and ET-3 range from 0,3 to 3 pg/ml. [5, 14]. Endothelin concentrations in other body fluids, e.g. in milk, saliva, urine and cerebrospinal fluid are several times higher than the plasma concentrations.

Endothelin receptors are found in many internal organs and organ systems — heart, adrenal glands, kidneys, lungs, CNS [7]. The receptors to ET-1 are existing mainly in the vascular smooth muscle cells. Other type of receptors — responding equally well to ET-1 and to ET-3, are localized on the surface of endothelial cells.

Acting via the ET-1 receptors, ET-1 contributes to the blood vessels vasoconstriction and endothelial dysfunction [6, 9]. The mechanism of vasoconstriction (including of coronary blood vessels — coronary vasospasm), caused by endothelin, may be associated with calcium inflow into the cells and directly correlates with the functional and morphological status of endothelial cells [8, 12, 16]. Endothelin causes a marked and sustained vasoconstriction, exceeding in molar values the vasoconstricting properties of angiotensin II or catecholamines [16].

In this field, the involvement of endothelin in the ethiopathogenesis of arterial hypertension aroused the interest of medical scientists in ET-1 receptor blockers and their hypotensive effects [4, 9, 15]. These ET-1 antagonists also prevent the mitogenic effect of ET on vascular smooth muscle cells.

ET-1 is a potent cell growth factor for cardiomyocytes, exerting direct long term effects (such as myocardial hypertrophy) and causing cellular injury in the cardiac muscle cells [12].

ET-1 reduces the production of rennin in isolated juxtaglomerular cells *in vitro* [13]. Additionaly, endothelin controls some kidney functions: elevated blood concentrations of ET-1 have been observed in patient with acute and chronic renal failure [4]. Exerting a mitogenic effect, ET-1 increases as well a renal interstitial proliferation of fibroblasts in humans [15].

ET-1 stimulates also pulmonary fibroblasts to produce collagen, increases mucus secretion of bronchial mucous glands and contracts bronchial smooth muscles. ET-1 regulates the fibroblast functions in the process of wound healing. At the levels of cells and tissues, the involvement of ET-1 has been also demonstrated in the CNS pathology (cerebral vasospasm) as well as in the methabolic diseases such as atherosclerosis and diabetes mellitus [14]. Some cellular mechanisms of the ET-1 induced *in vitro* inhibition of progesterone synthesis in human ovarian granulosa cells have been demonstrated [1-3] by electron microscopical and histochemical methods.

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