

# ENDOTHELIN IN HEALTH AND DISEASE

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## Abstract

Endothelin is a recently discovered peptide composed of 21 amino acids. There are three endothelin isomers: endothelin -1 (ET-1), endothelin -2 (ET-2) and endothelin -3 (ET-3). In humans and animals levels of ET-1, ET-2, ET-3 and big endothelin in blood range from 0,3 to 3 pg/ml. ET-1, ET-2 and ET-3 act by binding to receptors. Two main types of the receptors for endothelins exist and they are referred to as A and B type receptors. Different factors can stimulate or inhibit production of endothelin by endothelial cells. Mechanical stimulation of endothelium, thrombin, calcium ions, epinephrine, angiotensin II, vasopressin, dopamine, cytokines, growth factors stimulate the production of endothelin whereas nitric oxide, cyclic guanosine monophosphate, atrial natriuretic peptide, prostacyclin, bradykinin inhibit its production. Endothelins have different physiological roles in human body but at the same time their actions are involved in the pathogenesis of many diseases.

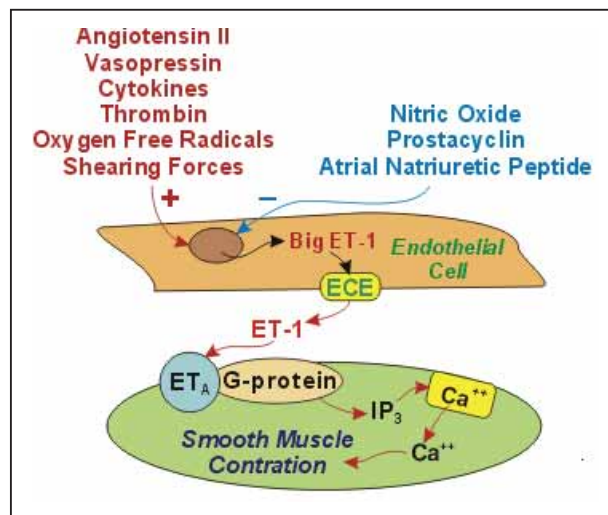
The aim of this review was to present some of, so far, the best studied physiological roles of endothelin and to summarize evidence supporting the potential role of ET in the pathogenesis of certain diseases.

**Key words:** endothelin, physiological and pathophysiological effects

## Introduction

Yanagisawa et al. were the first to isolate and identify endothelin from the pig arterial endothelial cell culture in 1988 (1). Endothelin (ET) is a peptide composed of 21 amino acids, with two disulfide bonds between amino acids 1 and 15, and 3 and 11. There are three endothelin isomers: endothelin 1 (ET-1), endothelin 2 (ET-2) and endothelin 3 (ET-3) coded by three independent genes. Their chemical structure and potency for smooth muscle contracting effect are different (2). ET-1, ET-2 and ET-3 act by binding to receptors. There are two main types of receptors for endothelins and they are referred to as A and B type receptors.

ET is formed by cleaving 164 amino acids from 203 amino acids of pre-pro-endothelin, which results in formation of big endothelin. Big endothelin is subsequently converted to endothelin by endothelin converting enzyme. Endothelin -1 (ET-1) can bind to ETA receptors found on adjacent vascular smooth muscle cells. The ETA receptor is coupled with a G-protein. This coupling between ET-1, ETA receptor and G-protein leads to the formation of inositol triphosphate (IP<sub>3</sub>). Formation of IP<sub>3</sub> leads to calcium



**Figure 1.** Mechanism of smooth muscle contraction induced by ET-1 (25)

mobilization and smooth muscle contraction (Figure 1.). ET-1 is produced mainly by endothelial cells and vascular smooth muscle cells. Sertoli cells, mesangium, hepatocytes, neuron and astrocytes in central nervous system (CNS) also produce ET-1 but to a lesser extent. ET-2 is predominantly produced within intestine and kidney. The highest levels of ET-3 are found in brain, and it is believed that ET-3 is involved in regulation of neuronal function (3).

Different factors can stimulate or inhibit production of endothelin by endothelial cells. These factors are summarized in Table 1.

In humans and animals, levels of ET-1, ET-2, ET-3 and big endothelin in blood range from 0,3 to 3 pg/ml. Concentrations of endothelin in body fluids, especially in urine, saliva, milk, cerebrospinal fluid are several times higher than the concentration in plasma (4).

The half-life time of endothelin in plasma is very short. It is estimated that about 90 % of circulating endothelin is eliminated by pulmonary uptake, and the remaining portion mainly through kidneys and very small quantity through liver (3,4).

### *Physiological effects of endothelin on:*

#### **Blood vessels**

One of the main effects of endothelin is a marked and sustained vasoconstriction. This vasoconstriction is caused by the modulation of dihydropyridine channel function by endothelin as well as by an increase of intracellular calcium level. This increase in calcium level in sarcoplasm

**Table 1.** Stimulating or inhibitory factors of endothelin production

Stimulating factors	Inhibitory factors
Lipids: low density lipoproteins (LDL), high density lipoproteins (HDL)	Cyclic guanosine monophosphate (cGMP)
Stress	Nitric Oxide (NO)
Cytokines: IL-1, IL-6	Atrial natriuretic peptide (ANP)
Mechanical stimulation of endothelium	Bradykinin
Thrombin	Prostacyclin
Calcium ions	
Epinephrine, vasopressin	
Angiotensin II, erythropoietin	
Growth factors: epidermal, fibroblastic, insulin-like, growth-transforming factor	

leads to the contraction of smooth muscle cells (4). Vasoconstricting actions of endothelin are dependent not only on its concentration, but also on the condition of the vascular endothelium. If the endothelium is intact, stimulation of the sympathetic system increases smooth muscle contractility caused by endothelin. If the endothelium is damaged, vasoconstricting effect of endothelin is even more marked because it overlaps the effects of serotonin. Endothelin also affects blood flow in various regions of circulation. In mesenteric and cerebral circulation it reduces blood flow but in pulmonary vessels it causes an increase in blood flow (5).

Numerous studies have shown that endothelin causes an increase of arterial blood pressure in a dose-dependent manner.

### Heart

Studies have shown that endothelin has positive inotropic and chronotropic effect on isolated left atrium of guinea pig's heart (1,4). It is believed that this effect is mediated by protein G and phospholipase C. ET-1 is also a potent growth factor for cardiomyocytes.

### Kidney

Endothelin has a strong influence on kidney function. ET-1 decreases renal blood flow and glomerular filtration and increases vascular resistance (6). Studies in vitro have shown that ET-1 reduces the production of renin in isolated juxtaglomerular cells (7,8). It also reduces excretion of sodium and potassium in urine.

### Lungs

ET-1 has also effects on lungs. When stimulated by ET-1 pulmonary fibroblasts produce collagen, and at the same time stimulation by ET-1 results in increased mucous secretion and contraction of bronchial smooth muscle (9).

Other tissues and functions

Numerous studies carried out with purpose to elucidate effects of endothelin in the human body have shown that this compound affects conductivity of parasympathetic ganglia and nerves, regulates the function of myofibroblasts in the process of wound healing, increases the expression of protooncogenes, exerts a mitogenic effect and increases human renal interstitial fibroblasts proliferation (3,4).

### Endothelin and diseases

During the past decade research on endothelin has become very extensive as the increase or decrease of blood endothelin was observed in patients with certain diseases.

### Blood vessels

In hypertensive patients the levels of ET-1 were significantly higher than in normotensive controls. Also, the level of ET-1 in plasma of hypertensives significantly correlated with mean arterial pressure (10). The involvement of endothelin in etiopathogenesis of hypertension led to a research on possible use of endothelin receptor blockers in the treatment of hypertension. Currently, few endothelin receptor blockers are being tested for the treatment of hypertension. So far, the use of Bosentan (non-specific ET receptor antagonist) leads to a decrease in mean blood pressure in aorta, peripheral vascular blood pressure and reduction of elevated left ventricular end diastolic pressure (11). This drug also reduces pulmonary arterial pressure and is used in the treatment of pulmonary hypertension (12).

Vasoconstricting effects of endothelin have been intensively studied for possible pathogenic roles in diabetic vascular complications. Results of Kakizawa et al. have shown that plasma ET-1 was higher in poorly controlled diabetic patients than in healthy controls. Improved

glycemic control did not affect plasma ET-1 concentration (13). Migdalis et al. have also demonstrated involvement of ET-1 in diabetes and atheromatosis (14).

Key aspect of atherosclerosis is the imbalance of vasoactive factors. Boussette et al. have demonstrated correlation between the expression of endothelin and the underlying atherosclerotic lesion. Endothelin's role in atherosclerosis must stem from its varying physiological activities, including vasoconstriction, mitogenesis, neutrophil adhesion, and platelet aggregation, and hypertrophy, as well as its propensity to induce the formation of reactive oxygen species (15).

Endothelin is also one of causative substances in cerebral vasospasm after subarachnoid hemorrhage (5,16,17).

### Heart

Prolonged exposure to ET-1 can lead to myocardial hypertrophy and cellular damage of cardiac myocytes. The cellular effects of ET, including constriction of vascular smooth muscle, cell proliferation, hypertrophy of cardiac myocytes, and activation of cardiac fibroblasts, are those that are associated with both the clinical manifestations of heart failure and the pathological remodeling of the heart that results in progressive cardiac dysfunction. ET has also been shown to exert effects that may be involved in the pathogenesis of heart failure (18). These include effects on the central and autonomic nervous system, the baroreflex response, and sodium excretion in kidneys. In patients with heart failure, levels of ET in blood are elevated and a rough correlation between circulating ET levels and the severity of heart failure has been observed (18). The cause of this increase remains uncertain. According to Parker et al. the cause of elevated ET-1 concentrations in patients with chronic CHF is increased ET-1 production rather than decreased clearance of ET-1 (19).

Increased blood levels of endothelin were also observed in patients with acute myocardial infarction, in congenital and acquired heart defects, ischemic heart disease and following heart transplantation treated with cyclosporin (20). Results of Ficai et al. have demonstrated that ET-1 has an important role in atrial hypertension (21).

Endothelins are associated with cardiac remodeling. This remodeling can be a direct effect of this hormone or indirect response to a relative ischemia promoted by vasoconstrictor effect. Ramires et al. have demonstrated that

endothelin may have a pivotal role in myocardial fibrosis by direct stimulation of collagen accumulation (22).

### Kidney

Elevated blood concentrations of endothelin were noted in patients with acute and chronic renal failure (6). This increase was even higher in advanced uremia and in patients on dialysis.

Mesangial cells (MCs) play a central role in the physiology and pathophysiology of endothelin-1 (ET-1) in kidneys. MCs release ET-1 in response to a variety of factors. Release of ET-1 can lead to MC hypertrophy, proliferation, contraction, and extracellular matrix accumulation. Excessive stimulation of ET-1 production by MC is likely to be of pathogenic importance in glomerular damage in the setting of diabetes, hypertension, and glomerulonephritis (23).

### Lungs

It is considered that endothelin has effects on ethiopathogenesis of pulmonary hypertension, asthma and fibrinous alveolitis (9,12).

The production of endothelin is increased in pulmonary arterial hypertension. In addition to its potent pulmonary vasoconstricting effects, endothelin in lungs causes hypertrophy, fibrosis and inflammation. Endothelin expression correlates significantly with disease severity and outcome in patients with pulmonary arterial hypertension. These findings suggest that endothelin, through binding to both ETA and ETB receptor subtypes, is a key causative agent in the pathophysiology of pulmonary arterial hypertension (12).

Endothelin-1 is a potent bronchoconstrictor both in vitro and by inhalation in animal models in vivo. The bronchial epithelial cells of asthmatic patients show increased expression of ET-1 and increased sensitivity to ET-1. Plasma levels of ET-1 were reported to be elevated in acute exacerbation of asthma and to correlate with clinical severity of asthma (24). The mechanism of ET-1 activity in human airways still needs to be clarified.

### Conclusion

In all the above-mentioned diseases, the role of endothelin is still not fully understood and therefore, this important compound is still subject to extensive research in biomedical world.

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