Endothelin and endothelin antagonists: Potential role in cardiovascular and renal disease

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Abstract

Endothelin-1 is a recently discovered peptide mainly released from endothelial cells. Hypoxia and ischemia as well as numerous factors such as angiotensin II, thrombin and transforming growth factor β stimulate the formation of the peptide. On the other hand, the synthesis of endothelin is inhibited by nitric oxide and atrial natriuretic peptide via the formation of cyclic guanosine monophosphate. Released from endothelial cells endothelin-1 mediates transient vasodilation followed by a profound and long-lasting vasoconstriction. Endothelin is also a mitogen for smooth muscle proliferation. Endothelins exert their biological effects via activation of specific receptors. Two different receptors have been cloned from mammalian tissues (ET₁ and ET₂ receptors). On vascular smooth muscle cells, both receptors mediate contractions. Endothelial cells only express ET₁ receptors linked to the formation of nitric oxide and/or prostacyclin formation. Increased plasma concentrations of endothelin-1 have been described in a variety of diseases such as pulmonary hypertension, arteriosclerosis, renal failure, acute coronary syndromes, heart failure, migraine and vascular diseases.

Recently an increasing number of endothelin receptor antagonists have been synthesized, which have been shown to inhibit endothelin-mediated vasoconstriction. Clinical studies are now ongoing to elucidate the pathophysiologic role of endothelin and the potential benefit of the blockade of the system in different disease states. (Mol Cell Biochem 157: 259–267, 1996)

Key words: endothelium, endothelin, endothelin receptor antagonist

Introduction

In spite of marked progress in the understanding of human disease, the search for new mediators continues as several disease states remain poorly understood. In particular, in many forms of cardiovascular and renal disease, effective and cause-oriented forms of therapy are not available. The discovery of new pathogenetic mechanisms often leads to the development of new drugs with previously unknown properties which may offer new treatment modalities. Endothelin is a potent biological mediator which occurs in three isoforms, i.e., endothelin-1, -2 and -3 (Fig. 1) [1–3]. The main vascular effects of endothelin are transient vasodilation and profound and long-lasting vasoconstriction [4]. Endothelin also is a mitogen and stimulates proliferation of vascular smooth muscle and glomerular mesangial cells [5–7].

Important sources of the isoforms of the peptide are endothelial cells (endothelin-1), neurons, renal cells and non-contractile vascular smooth muscle cells. Stimuli for the release of endothelins include hypoxia (Fig. 2) [8] and ischemia [9] as well as angiotensin II, vasopressin, transforming growth factor β, insulin, thrombin (Fig. 3) and interleukin-1 beta. Nephrotoxic drugs such as radiocontrast agents, cyclosporin, amphotericin B and OKT-3 also can induce the production of the peptide [1, 3, 10–24]. On the other hand, nitric oxide and atrial natriuretic peptide inhibit endothelin production via a cyclic GMP-dependent mechanism [1, 3, 13, 22]. In addition, smooth muscle cells appear to release an inhibitory factor which limits the production of the peptide. This may explain why intact tissues such as the blood vessel wall produce markedly less endothelin than isolated cells in culture. In vivo in humans, endothelin plasma levels are very low [23]. However, in different disease states, elevated endothelin plasma levels have been described (see below, Fig. 4).

Endothelins exert their biological effects via activation of specific receptors. These membrane bound receptors have seven transmembrane domains and are coupled to G-proteins; 3 types of endothelin receptors have been cloned, i.e., ET₁.
ET\textsubscript{B} in mammalian tissues and an ET\textsubscript{C} receptors from amphibian tissue [25]. Endothelin-1, the primary product of endothelial cells, preferentially activates ET\textsubscript{A}-receptors. ET\textsubscript{B}-receptors exert no isoform specificity and are equally activated by all endothelin isoforms, while the ET\textsubscript{C}-receptor preferentially binds endothelin-3 [26]. ET\textsubscript{A}-receptors on vascular smooth muscle cause vasoconstriction and mediate proliferation, although ET\textsubscript{B} receptors contribute to these effects. Endothelial cells express only ET\textsubscript{B}-receptors linked to nitric oxide and prostacyclin formation. The endothelin receptors on renal cells have only partially been characterized. However, the ET\textsubscript{A}-receptors seem to be expressed mainly in the glomerulus, the vasa recta bundle and the arcuate artery, while the ET\textsubscript{B}-receptor predominates in the initial and terminal inner medullary collecting duct and also in the glomerulus [27].

In the kidney, endothelin reduces renal blood flow and glomerular filtration rate [12, 24, 28–30]; this is mainly due to vasoconstriction of both efferent and afferent arterioles. Systemic infusion of endothelin-1 in humans in vivo leads to blood pressure increase, sodium retention and reduction in urine flow [29, 30]. Although in vitro endothelin inhibits renin release [28, 31] in the intact organism renin plasma levels do not change or increase (due to renal vasoconstriction) after infusion of endothelin-1 [30]. Endothelin stimulates release of aldosteron, vasopressin and atrial natriuretic peptide under experimental conditions [11, 12]. However, in vivo in humans, it does not influence the plasma levels of these hormones [29]. The role of the mitogenic properties of endothelin [5–7] in the kidney are still unclear, but it could be involved in proliferative glomerular diseases.

Recently, an increasing number of endothelin receptor antagonists have been synthetized [32–36]. Certain of these molecules inhibit ET\textsubscript{A} receptors only, while others interfere with both ET\textsubscript{A} and ET\textsubscript{B} receptors. As both ET\textsubscript{A} and ET\textsubscript{B} receptors are expressed on vascular smooth muscle also in the human [37–39], combined antagonists more effectively inter-