ELSEVIER

editorial

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Trapping endothelin-1 to hunt down cardiovascular disease?

In a recent article in this journal Jain et al. discuss the potential of endothelin-1 (ET-1) traps in the treatment of diabetes, endothelial dysfunction, and atherosclerosis [1]. Indeed, ET-1 is a promising target for cardiovascular disease [2].

ET-1 exerts its pro-inflammatory, vasoconstrictive, and proliferative capabilities via endothelin receptors A and B (Fig. 1). The ET-1 production and secretion are controlled at the transcriptional level. Transcriptional factors, including hypoxia-inducible factor-1 and nuclear factor-kB, associated with atherogenesis and diabetes, regulate ET-1 expression. In healthy adult individuals, ET-1 is primarily secreted in an autocrine and paracrine manner in endothelial cells. In disease states associated with endothelial dysfunction, such as atherosclerosis, diabetes, and pulmonary hypertension, smooth muscle cells, cardiac myocytes, and leukocytes produce ET-1 [2].

Elevated ET-1serum concentrations were reported in distinct cardiovascular diseases and diabetes, but also in cancer, eclampsia, and neurological disorders [3]. Increased ET-1 levels are associated with the induction of inflammation, both oxidative and endoplasmatic stress, as well as vasoconstriction [4]. Besides an increase in ET-1 plasma and tissue concentration, an upregulation of ET receptor expression in diseases such as diabetes further aggravates pathological pathways mediated by ET-1.

Patients with diabetes mellitus evidence high rates of micro- and macrovascular disease, which lead to high morbidity and mortality. Several factors contribute to the endothelial dysfunction in diabetes: Nitric oxide (NO) bioavailability is reduced, oxidative stress increased, and chronic hyperglycemia leads to more pronounced glycosylation. ET-1 plasma levels were shown to be elevated in diabetes. ET-1 was proposed to contribute to out-of-proportion vasoconstriction and endothelial dysfunction in diabetes. Furthermore, ET-1 plasma concentration correlates with chronic hyperglycemia and microvascular dysfunction. Of note, ET-1 may contribute to the insulin resistance observed in diabetes. Besides elevated ET-1 levels, both ET-1 receptors are upregulated in experimental diabetes models. ET-1 blockade might, therefore, constitute an interesting target in diabetes and diabetic endothelial dysfunction and atherosclerosis [2].

In atherosclerosis, ET-1 expression is increased. As described above, in atherosclerosis, cells other than endothelial cells, such as smooth muscle cells and leukocytes, secret relevant amounts of ET-1. Endothelial ET-1 expression upregulation was shown to speed up the formation of atherosclerotic lesions in a murine

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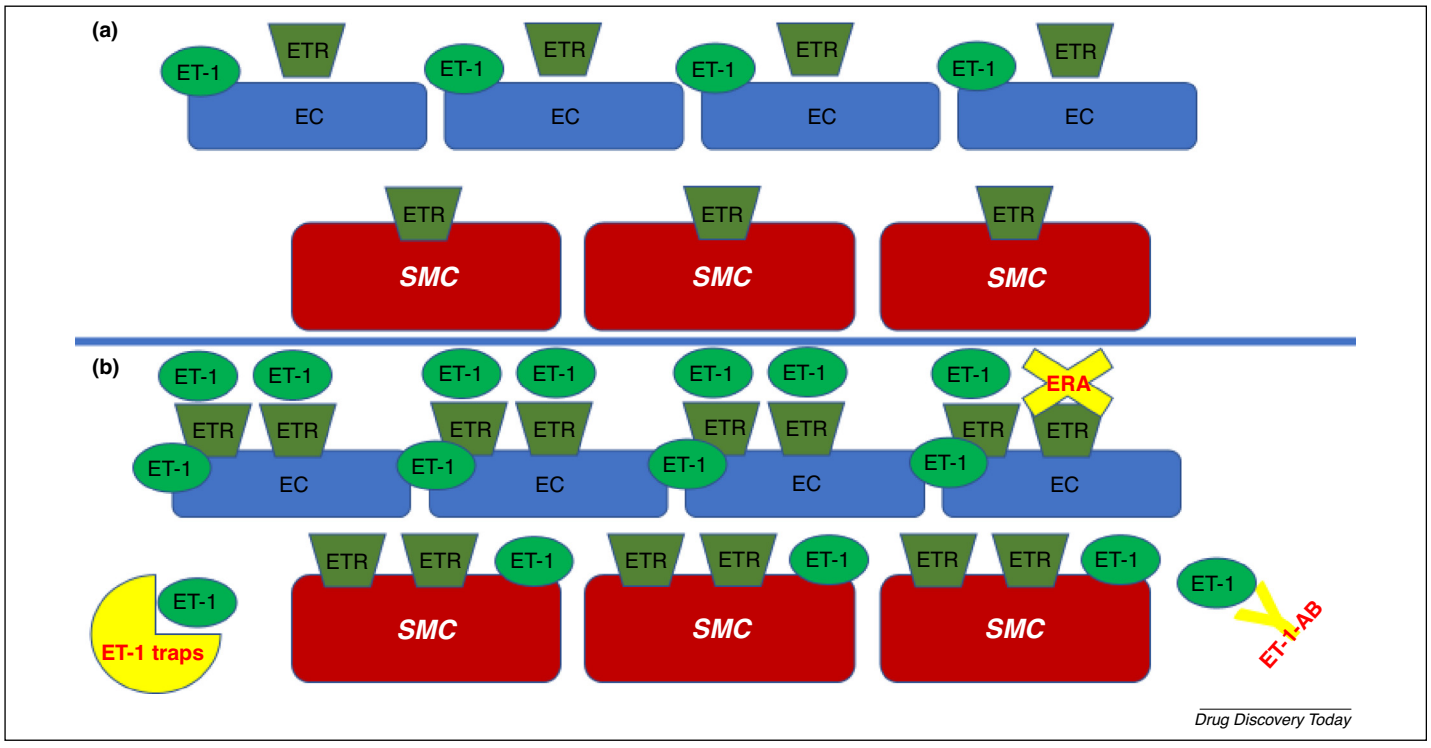

FIGURE 1

(a) In healthy individuals, endothelin-1 (ET-1) is primarily secreted by endothelial cells (EC). Both EC and other cells including smooth muscle cells (SMC) and leukocytes express the endothelin-1 receptors A and B (ETR). **(b)** In diseases including diabetes and atherosclerosis, ET-1 expression and secretion by endothelial cells (EC) is increased. Further, other cells such as smooth muscle cells (SMC) secret ET-1. The endothelin-1 receptor (ETR) expression is increased. Possible therapeutic interventions include endothelin receptor antagonists (ERA) blocking ETR, antibodies (ET-1-AB) against ET-1 as well as ET-1 traps.

model of atherosclerosis (ref). Besides ET-1, both its receptors A and B were shown to be upregulated in human atherosclerosis. ET-1 was shown to increase the uptake of oxidized LDL in endothelial cells, which is known to greatly contribute to the progression of atherosclerotic lesions.

In early clinical studies, several agents aiming at reducing ET-1 mediated effects were evaluated in diabetes, endothelial dysfunction, and atherosclerosis (Fig. 1). In patients with type 2 diabetes, treatment with the ET-1 antagonist bosentan, blocking both ET-1 receptors A and B, improved endothelial vasodilatation [5]. Further, ET-1 receptor blockade increased coronary blood flow in patients with coronary artery disease [2]. Even long-term treatment with ET-1 receptor A antagonist for six months in patients with early atherosclerosis was shown to improve endothelial function at a microcirculatory level and to be safe [6]. However, treatment with bosentan did not improve the recruitment of endothelial progenitor cells known to improve re-endothelialization, nor reduced levels of endothelial cell microparticles associated with endothelial activation and apoptosis [7,8]. Of note, in patients with pulmonary hypertension, treatment with endothelin receptor antagonists is well established.

However, with ET-1 antagonists, several safety and efficacy issues remain. First, it is unclear how the human body responds to ET-1 blockage in the long-term, as ET-1 plays an important role in normal physiological pathways, and treatment with a blunt antagonist might have unknown adverse outcomes. For bosentan, liver toxicity is a known side-effect. Second, for ET-1 antagonists, usually, a daily dosage is necessary. Third, the differential role of ET-1 receptor A versus B blockade is complex as at least receptor B is thought to change its properties in diseases. The treatment with antibodies is expensive and parental administration could further limit its use. Therefore, Jain et al. recently developed ET-1 traps and evaluated ET-1 traps in a murine model of type 1 diabetes [9,10]. ET-1 traps are an antibody-based, Fc-fused construct binding and sequestering ET-1 (Fig. 1) [10]. Treatment with a subcutaneous ET-1 trap three times a week reduced collagen 4α1, but also left ventricular function and renal function back to non-diabetic levels [9]. The affinity of ET-1 traps for ET-1 is in the picomolar range, which could allow for low dosages and longer dosage intervals. Further, the isoelectric point close to the human physiologic pH could enable optimal tissue penetration of ET-1 traps.

Therefore, treatment with ET-1 traps could attenuate the vasoconstrictor, pro-inflammatory, proliferative effects of ET-1 in a comfortable, safe, and effective manner. Further research on ET-1 traps in endothelial dysfunction in diabetes and atherosclerosis is warranted.

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