Endothelin-receptor Antagonists in Arterial Hypertension: Further Indications?

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Current Hypertension Reports 2007, **9:**59–65
Current Medicine Group LLC ISSN 1522-6417

Endothelin-1 exerts vasoactive, pro-inflammatory, hypertrophic, and profibrotic properties on the heart, kidney, and blood vessels. Hence, endothelin-receptor antagonists hold the potential to reduce blood pressure and to prevent complications of hypertension, atherosclerosis, and diabetes through blood pressure-independent effects on cardiovascular growth, inflammation, and fibrosis. These potentially important effects of endothelin antagonism may contribute to its therapeutic potential in hypertension and other cardiovascular disorders, including chronic renal failure and diabetes. First clinical trial evidence demonstrates a moderate reduction in blood pressure in studies of patients with mild-to-moderate essential hypertension and patients with resistant hypertension. Future large-scale randomized clinical trials will provide more insight into whether the blood-pressure reduction and promising pleiotropic effects observed with several members of this novel class of drugs, which are already established therapy in pulmonary hypertension, will translate into clinical benefit in patients with arterial hypertension.

Introduction

The endothelin (ET) system has been demonstrated to participate pathophysiologically in numerous conditions, including primary pulmonary hypertension, pulmonary fibrosis, arterial hypertension, atherosclerosis, coronary artery disease, heart failure, subarachnoid hemorrhage, diabetes, scleroderma, renal failure, prostate cancer and its metastasis, and others. Of these, the present review addresses only the role of vascular endothelin (specifically ET-1, the main endothelin of vascular origin) and of endothelin-receptor antagonists in hypertension.

Vascular Effect of Endothelin

ET-1 is a 21-amino acid isopeptide that is characterized by sustained and potent vasoconstrictor action [1]. ET-1 is probably the major isoform in the cardiovascular system. The generation of ET-1 by the vascular endothelium is regulated by several factors (Fig. 1). Shear stress downregulates ET-1 generation by the endothelium [2]. Nitric oxide (NO) production, which is stimulated by shear stress, inhibits ET-1 generation [3], and may mediate the effect of shear stress. Epinephrine, thrombin, angiotensin II (Ang II), vasopressin, cytokines, insulin, growth factors, hypoxia, and reactive oxygen species all stimulate ET-1 generation [4••]. Leptin-induced stimulation of ET-1 production [5] may be the mechanism for increased ET-1 in obesity, and could participate in the frequently observed association of hypertension and obesity, as well as in the evolution of the metabolic syndrome toward type 2 diabetes.

ET-1 acts by stimulating endothelin type A (ETA) and endothelin type B (ETB) receptors (Fig. 1). Both ETA and ETB receptors are localized on vascular smooth muscle cells where they induce their vasoconstrictor, proliferative, and hypertrophic action. ETA receptors are the predominant ET vasoconstrictor receptors in arteries [6]. Vasoconstrictor ETB receptors are present in the veins and pulmonary vessels in larger numbers than in arteries, although ETA receptors still predominate over ETB receptors in these vessels [6]. ETB receptors are also localized on endothelial cells and act through the production of NO and prostacyclin to exert a vasodilator effect. It has been reported that coronary arteries have few endothelial vasodilator ETB receptors [7]. As a result, ET-1 acts on coronary vessels mainly as a vasoconstrictor. In other vascular beds, however, ET-1 may function as a vasodilator under physiologic conditions [8]. In fact, the overall vascular effect of ET-1 on vascular tone derives from

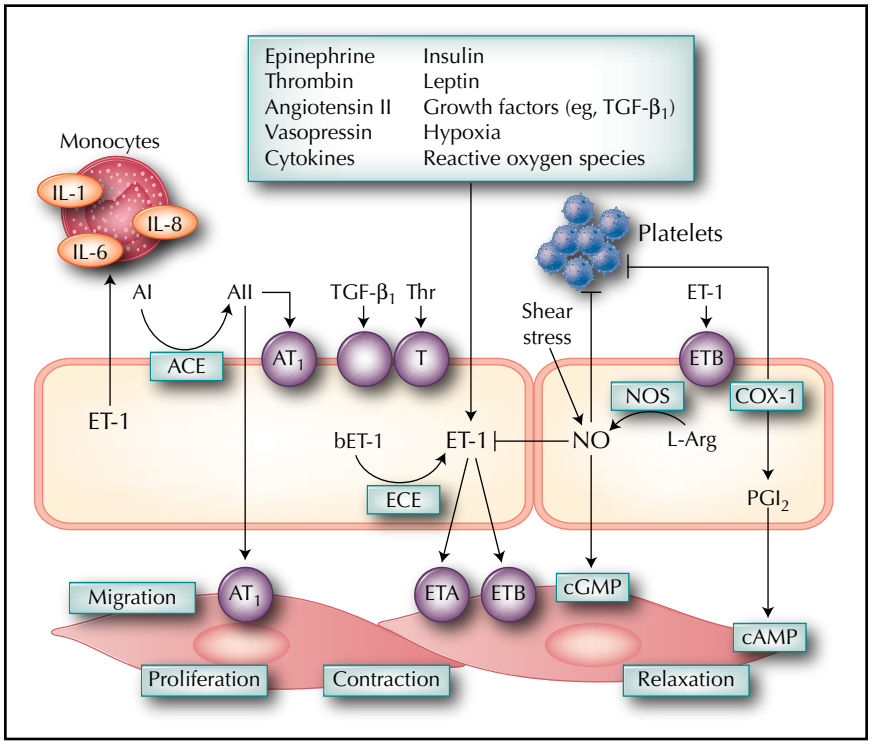

Figure 1. The regulation of endothelin production and its actions on endothelial cells, monocytes, and smooth muscle cells. AI—angiotensin I; AII—angiotensin II; ACE—angiotensin converting enzyme; AT_1—angiotensin receptor; bET-1—big endothelin; cAMP—cyclic adenosine monophosphate; cGMP—cyclic guanosine monophosphate; COX-1—cyclooxygenase; ECE—endothelin-converting enzyme; ET—endothelin; ETA—endothelin receptor A; ETB—endothelin receptor B; IL—interleukin; L-Arg—L-arginine; NO—nitric oxide; PGI_2—prostacyclin; TGF-β_1—transforming growth factor-β_1; Thr—thrombin.

the balance between the direct vasoconstrictor effect via ETA and ETB receptors on smooth muscle cells, and NO- or prostacyclin-induced vasodilation mediated by endothelial ETB receptors [9]. Therefore, although ET-1 is considered a potent vasoconstrictor, this activity can be indirectly attenuated by a parallel vasodilation that is dependent on the expression of endothelial ETB receptors and/or the integrity of ETB-mediated activation of the NO pathway. The balance/imbalance between these two effects (vasoconstriction vs vasodilation) could represent one crucial mechanism explaining why ET-1, which is a physiologic substance, can shift to a pathologic role in cardiovascular disease.

Endothelin and endothelin-receptor antagonists in experimental hypertension

The net contribution of ETA and ETB receptors in blood pressure regulation in humans and experimental animals, including the conscious mouse, remains undefined.

The role of ETA and ETB receptors in the control of basal blood pressure, and the role of ETA receptors in maintenance of hypertension after systemic ETB blockade, was recently studied in mice [10•]. Administration of the selective ETB antagonist A-192621 increased blood pressure, while coadministration of the selective ETA antagonist atrasentan decreased mean arterial pressure to baseline values after 1 day and below baseline after 3 days. In a separate group of mice in which the treatment was reversed, systemic blockade of ETB receptors produced no hypertension in animals pretreated with atrasentan, underscoring the importance of ETA receptors to maintain the hypertension produced by ETB blockade. However, ETA blockade alone produced an immediate and sustained decrease in blood pressure. Thus, these data suggest that ETA and ETB receptors play a physiologically relevant role in the regulation of basal blood pressure.

The role of ET-1 has been demonstrated in many, but not all, experimental hypertensive models in rats (Table 1). Salt-sensitive models of hypertension, such as the deoxycorticosterone acetate (DOCA)-salt hypertensive rat [11], the DOCA-salt–treated spontaneously hypertensive rat (SHR) [12], and the Dahl salt-sensitive rat [13], are the forms of hypertension in which activation of the endothelin system was initially demonstrated.

In rats infused with angiotensin II, a known stimulant of ET-1 expression, endothelin antagonists lowered blood pressure and reduced cardiac and small artery hypertrophic remodeling [14]. However, in two-kidney one-clip Goldblatt hypertensive rats, a model of renin-(Ang II)–dependent hypertension, the endothelin system is not activated but unselective ET-receptor antagonism reduced blood pressure and improved renal function [15]. In two-kidney one-clip Goldblatt hypertensive rats, and in rats with hypertension induced by a nitric oxide synthase inhibitor, N(omega)nitro-L-arginine methyl ester (L-NAME), ET-1 mRNA was increased selectively in the kidney [16]. Moreover, activation of the ET system was demonstrated in fructose-fed rats, a model of hypertension and insulin resistance [17], and in stroke-prone SHR on a high-salt diet [12].

In contrast, the ET system appears not to be significantly activated in SHR and in a model of malignant hypertension like the SHR rats treated with L-NAME [18]. In chronic L-NAME–induced hypertension no activation

Table 1. Role of endothelin and effect of endothelin-receptor antagonists on blood pressure and target organ damage in many models of experimental hypertension

Experimental model	Activation of ET system	BP*	Organ damage*
SHR	No	No	No
DOCA-salt–treated SHR	Yes	Yes	Yes
Stroke-prone SHR	Yes	Yes	Yes
L-NAME–treated SHR	No	No	Yes
Dahl salt-sensitive rat	Yes	Yes	Yes
Angiotensin II–infused hypertensive rat	Yes	Yes	Yes
Fructose-fed hypertensive rat	Yes	Yes	Yes
1-kidney 1-clip Goldblatt hypertensive rats	?	Yes	?
2-kidney 1-clip Goldblatt hypertensive rats	Local (kidney)	Yes (severe hypertension)	Yes
Chronic L-NAME–induced hypertension	Local (kidney)	No	Yes

* ET-antagonists may reduce BP and target organ damage.
BP—blood pressure; DOCA—deoxycorticosterone acetate; ET—endothelin; L-NAME—N(omega)nitro-L-arginine methyl ester; SHR—spontaneously hypertensive rats.

of the ET system was demonstrated, but administration of an ET-receptor antagonist improved renal function [18].

The role of ET in these experimental models of hypertension is not confined to the vasoconstrictive effect but also contributes to the development of target organ damage. In fact, ET is a potent growth-promoting agent, with known mitogenic and cell hypertrophic actions on smooth muscle; therefore, it may contribute to vascular hypertrophy [4••]. Moreover, ET may contribute to water and sodium retention, renal vasoconstriction, and eventually renal failure [4••].

Administration of combined ETA/ETB or a selective ETA-receptor blocker lowers blood pressure in DOCA-salt hypertensive rats, DOCA-salt–treated SHR, Dahl salt-sensitive rats, and angiotensin II–infused rats [4••]. Treatment with ET-receptor antagonists is associated with regression of hypertrophic arterial remodeling in salt-sensitive hypertension models [11], and amelioration of the renal lesions in rats, which develop malignant hypertension and vascular and glomerular fibrinoid necrosis [19]. In contrast to the beneficial effects of an ET antagonist in hypertensive models with ET-1 overexpression, the hypertensive models without ET-1 overexpression did not exhibit any regression of vascular hypertrophy [18]. Indeed, in SHR chronic ET-antagonism may reduce perivascular fibrosis in the heart and increase the glomerular filtration rate [20].

Moreover, the selective ETA-receptor antagonist LU-135252 improved endothelial dysfunction in the aorta and renal artery and attenuated the blood pressure increase in salt-sensitive Dahl rats on a high-salt diet [21].

Endothelin and endothelin-receptor antagonists in human arterial hypertension

Immunoreactive ET plasma levels, which poorly reflect ET-1 tissue production, are not elevated in essential hypertension [22], except in African Americans [23] and patients with salt-sensitive hypertension [24•]. Hirai et al. [25] studied immunoreactive ET in plasma in 1492 subjects, and showed by multiple stepwise regression analysis that age, creatinine levels, and smoking were significantly correlated to plasma ET, whereas no relation was demonstrated between plasma ET and blood pressure (BP).

Available evidence concerning the response to exogenously administered ET-1 is conflicting. Haynes et al. [26] showed an increased venoconstriction in response to ET-1 in essential hypertension, whereas Schiffrin et al. [27] demonstrated a blunted response to the peptide in subcutaneous small arteries of essential hypertensive patients as compared to normotensive controls.

Aldosterone and endothelin have been shown to have a higher plasma concentration as well as an important role in the target organ damage of salt-sensitive hypertension in both rodents and humans [24•]. Recently, different effects of salt on putative mechanisms of target organ damage in human hypertension have been demonstrated. Indeed, oxidative stress is enhanced in patients in whom aldosterone is not suppressed by salt. Once elicited, oxidative stress can, in turn, produce endothelin release. Therefore, target organ damage in patients with salt-sensitive hypertension could be mediated via inflammatory effects of aldosterone excess and through activation of mitogenic and fibroblast-stimulating actions of both isoprostanes and endothelin by aldosterone-induced oxidative stress [24•].

Available results with ET-receptor antagonists point to a major contribution of NO pathway alteration in supporting a pathologic role for ET-1 in essential hypertension. The selective ETA-receptor antagonist BQ-123, alone or in combination with the selective ETB-receptor antagonist BQ-788, did not significantly modify basal vascular tone in healthy subjects [28]. Cardillo et al. [29] tested the effect of ETA and ETB blockade in patients

with essential hypertension; BQ-123 caused a slight vasodilation (forearm blood flow increased 33% above baseline), and the combination of BQ-123 with BQ-788 produced a greater vasodilating response (forearm blood flow increased 63% above baseline). Of particular interest are the results with BQ-788 infused alone, as the selective ETB-receptor antagonist caused vasoconstriction in healthy subjects and vasodilation in patients with essential hypertension [29]. Together, these findings indicate that under physiologic conditions with normal NO bioavailability, the vasoconstrictor activity of ET-1 is masked by ETB-mediated NO-related vasodilation. On the other hand, the ETB antagonist BQ-788 induced vasoconstriction on forearm resistance arteries in normotensive subjects [30,31]. Moreover, forearm blood flow responses to BQ-123 in normotensive subjects were similar in white and black subjects, whereas in hypertensive patients the vasodilator effect of ETA-receptor blockade was significantly higher in blacks than in whites [32]. ET-1 induced a significant vasoconstriction without differences between white and black patients. Together, these data suggested that in hypertensive blacks there is increased ETA-dependent tone that participates in vasoconstriction and contributes to blood pressure elevation.

Endothelin antagonists and endothelial function

ET-receptor antagonists improve endothelial dysfunction, a cardiovascular surrogate endpoint, well known to characterize patients with arterial hypertension [22]. In fact, in the forearm of patients with both hypertension [30] and atherosclerosis [33], ETA/ETB blockade potentiated the response to acetylcholine, an endothelium-dependent vasodilator, without affecting the endothelium-independent vasodilation to sodium nitroprusside. In patients with essential hypertension, the nonselective ET-receptor antagonist TAK-044 caused greater forearm vasodilatation compared with normotensive controls [34], and the nonselective antagonist bosentan resulted in greater forearm vasodilatation than the selective ETA-receptor blocker BQ-123 [35]. Moreover, in healthy subjects mental stress-induced impairment of endothelial function could be partially reversed by infusion of BQ-123 [36].

Endothelin antagonists and angiotensin II

Human subjects infused with stepwise increasing intravenous doses of Ang II exhibited decreased renal plasma flow and glomerular filtration rate, and increased blood pressure and renal vascular resistance, which were unaffected by the co-administration of the selective ETA-receptor antagonist BQ-123 [37]. In contrast, Montanari et al. [38] infused humans with Ang II and the ETA blocker BQ 123, and observed significantly less blood pressure increase than with Ang II alone. Renal blood flow and glomerular filtration rate also changed to a significantly lesser extent than with Ang II alone. These results suggest that ET-1 contributes via ETA receptors to angiotensin II-induced systemic and renal vasoconstriction in healthy humans, which adds to the controversy on whether part of the actions of Ang II are indeed mediated by ET-1 [39].

Blood pressure reduction in clinical studies with endothelin-receptor antagonists

The combined ETA/ETB antagonist bosentan (500 mg to 2000 mg/day for 4 weeks) lowered office systolic BP by 10.3 mm Hg, office diastolic BP by 5.7 mm Hg, and 24-hour systolic BP by 11.0 mm Hg (with 2000 mg) in patients with mild-to-moderate essential hypertension. This reduction was comparable to that observed with the angiotensin-converting enzyme (ACE) inhibitor enalapril (20 mg/day) [40]. A potent but short-lasting effect on blood pressure was described in a small pilot study (31 patients) investigating the ETA-receptor antagonist sitaxsentan in moderate essential hypertension [41].

In a multicenter randomized, double-blind, parallel-group, dose-response study, 392 patients with moderate hypertension were treated with darusentan (10, 30, or 100 mg) or placebo for 6 weeks. The selective ETA antagonist darusentan reduced systolic BP by 6.0 (10 mg/day) to 11.3 mm Hg (100 mg/day) and diastolic BP by 3.7 (10 mg/day) to 8.3 mm Hg (100 mg/day) [42]. Elevation of liver enzymes, a side effect found with bosentan, was not encountered with darusentan in this study. Recently, first results of a phase 2b randomized, double-blind, placebo-controlled clinical trial with darusentan (DAR-201) in 115 patients with resistant hypertension demonstrated that 300 mg (at week 10) of darusentan provided statistically significant placebo-corrected reductions in systolic blood pressure by 11.6 mm Hg [43]. Further trials in resistant hypertension with darusentan are temporarily under way.

Several trials with ET-receptor antagonists in chronic heart failure have been performed, but not all have been published yet. Although all trials so far did not show a benefit of the treatment, promising data about blood pressure reduction come from such heart failure trials. Acute effects of the selective ETA antagonist darusentan have been investigated in 95 patients with stable chronic heart failure where mean arterial blood pressure was reduced between 5% (1 mg) and 10% (300 mg) [44]. In the Endothelin A-Receptor Antagonist Trial in Heart Failure (EARTH), even low doses of darusentan (10 and 25 mg) reduced blood pressure significantly by 6 and 5 mm Hg (systolic) and 4 mm Hg (diastolic) [45••]. It is of note that this effect was achieved on top of an established heart failure therapy, including ACE inhibitors (> 93% of patients), diuretics (> 88% of patients), and beta-blockers (> 69% of patients). In the Heart Failure ETA-Receptor Blockade Trial (HEAT) blood pressure decreased by 5 to 10 mm Hg after 3 weeks [46]. However, this reduction did not reach statistical significance.

An important reason for the unexciting results of the previously conducted clinical trials may be the populations of hypertensive patients investigated. In essential hyper-

tensive patients, as well as in animal models of essential hypertension (eg, SHR), the pathophysiologic role of ET may be limited. Salt-sensitive hypertensive patients often have low plasma renin activity, and their plasma endothelin responds in an exaggerated fashion, with an increase after sodium depletion together with enhanced plasma catecholamines [47]. This suggests a relationship between the sympathetic system, sodium sensitivity, and the reactivity of the endothelin system that may contribute to blood pressure elevation in these subjects. Thus, in human hypertension, results seem to agree with the activation of the endothelin system found in experimental models of severe and salt-sensitive hypertension. Chronic renal failure, erythropoietin and cyclosporine administration–induced pheochromocytoma, pregnancy-induced hypertension, and resistant hypertension are other forms of hypertension in which ET may play a crucial role. Therefore, with the exclusion of pregnancy-induced hypertension (because of the teratogenic effect of the endothelin-antagonists), these specific forms of human arterial hypertension may be successfully treated with endothelin-receptor antagonists.

Resistant Hypertension and Endothelin-receptor Antagonists

The term *resistant hypertension* is used for the persistence of blood pressure above target levels (140/90 mm Hg) despite treatment with three or more antihypertensive drugs, including a diuretic, at full doses. The prevalence of such a condition remains unclear in the overall population of hypertensive patients. Most data are derived from the generally higher risk population enrolled in large clinical trials. One example would be the high-risk patients enrolled in the massive Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [48] and Losartan Intervention for Endpoint Reduction (LIFE) study [49], where 30% to 50% of the patients required three or more drugs but remained above target blood pressure levels. Approximations of the prevalence can be derived from analyses of multiple smaller studies [50•].

In general practice the prevalence is around 5%; in nephrology clinics treating highly selected patients with underlying chronic renal disease, the prevalence is 50% or higher. The presence of resistance to therapy is usually accompanied by extensive target organ damage, in particular, arterial wall thickening, left ventricular hypertrophy, and nephrosclerosis. Each of these, in turn, may reduce the blood pressure responsiveness to traditional antihypertensive therapy with ACE inhibitors, diuretics, calcium channel blockers, or beta-blockers. Therefore, novel pharmacologic treatment options, such as ET-receptor antagonists, have to be evaluated.

Although the above trial results of blood pressure reduction in selected patients sound promising, it remains unclear whether ET-receptor antagonists will become part of the therapeutic armamentarium in resistant hypertension and associated target organ damage. Potential drawbacks are the effect on liver enzymes, which might be a class effect; the potential worsening of chronic heart failure; and the duration of action because most of these drugs require more than once-a-day dosing. The last would compete unfavorably with other antihypertensive drugs, which are once-a-day agents.

Conclusions

The use of selective ET-receptor antagonists helps to reveal the physiologic roles of ET and the pathophysiologic interactions of this peptide in patients with cardiovascular risk factors and diseases. In experimental models of hypertension, ET-receptor antagonists reduce blood pressure and prevent target organ damage in many, but not all, models. In uncomplicated hypertension in men, blood pressure is reduced and endothelial dysfunction is reversed, but these drugs have shown only mild effects without superiority over established antihypertensive drugs, such as ACE inhibitors. However, available data suggest a role for selective ETA-receptor antagonism in resistant hypertension as an add-on therapy to ACE inhibitors/angiotensin receptor antagonists, diuretics, calcium-channel blockers, and/or beta-blockers.

Randomized controlled trials in hypertensive patients with forms of hypertension in which ET plays a crucial role, such as hypertension in kidney disease or resistant hypertension, have to demonstrate beneficial effects of ET-receptor antagonism added to established therapy. In particular, the impact on target organ damage (renal function, diastolic function, left ventricular hypertrophy, and atherosclerotic lesions) should be addressed in these trials.

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Interesting review about resistant hypertension.