Endothelin-receptor antagonists: current and future perspectives

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Despite much effort over recent years to design and develop endothelin-receptor antagonists, these compounds are far from becoming new drug entities. This article will review preclinical data on select endothelin-receptor antagonists as well as clinical data on bosentan, the only molecule currently in Phase III clinical trials. Though efficacious, bosentan is less potent than the angiotensin converting enzyme (ACE) inhibitor, enalapril, in patients with hypertension. We will therefore discuss the possible reason(s) for this low potency, the consequences thereof, and a few therapeutic areas where endothelin-receptor antagonists could find better use.

Since its discovery by Yanagisawa *et al.*[1] in 1988, much work has focussed on understanding the effects of endothelin (ET) and its mechanism of action. It is now known that there are at least three ETs, namely ET-1, ET-2 and ET-3, which act on two distinct cell surface receptors, ET_A and ET_B. Using ET-receptor knockout mice, ET converting enzyme inhibitors, anti-ET antibody, and ET_A- and ET_B-receptor antagonists, it has been shown that ETs play an important role during embryonic development and in the regulation of blood pressure under normal physiological conditions in adults. Furthermore, ET is involved in the initiation and maintenance of several pathophysiological conditions such as hypertension, congestive heart failure, renal failure and pulmonary hypertension[2–6].

To exploit the extensive biochemical, physiological and pharmacological information available on ET and ET receptors, researchers have attempted to design and develop ET-receptor antagonists[7]. However, despite first-generation ET-receptor antagonists [such as BQ123 (Ref. 8), bosentan (Ref. 9) and TAK044 (Ref 10)] entering clinical trials by the early-1990s, ET-receptor antagonists have yet to reach the clinic. In fact, BQ123 and TAK044 (Ref. 11) have dropped out of the race to become drug candidates, while bosentan has only recently moved into Phase III clinical trial. This review will attempt to overview a select group of ET-receptor antagonists, starting with BQ123, that have reached Phase II clinical development. The review will also examine available clinical data on bosentan and try to suggest reasons for its slow progress through clinical trials. Finally, a few areas will be proposed where, in our view, an ET-receptor antagonist should be evaluated more vigorously.

ET-receptor antagonists: an overview

BQ123

The first ET-receptor antagonist was available as early as 1991, when Ihara and his group[12] at Banyu Pharmaceutical Co. Ltd (Tokyo, Japan) reported the discovery of the ET_A-receptor selective antagonist BQ123. This molecule was a cyclic pentapeptide containing three D-amino acids (Fig. 1). BQ123 antagonized binding of radiolabelled ET-1 to recombinant human ET_A and ET_B receptors with an IC_{50} of 13 nM and >10 μM, respectively[13], thereby demonstrating >1000-fold greater affinity for ET_A- over ET_B-receptor subtypes. Similar results were seen using isolated porcine coronary arteries, where BQ123 inhibited ET-1-induced contractile responses in a concentration-dependent and competitive manner, producing a pA_2 of 7.4 (Ref. 12). BQ123 also inhibited an ET-1-induced increase in blood pressure in an anaesthetized normotensive rat model[14] and in normotensive human volunteers[8]. However, a major disadvantage of BQ123 is that it is a peptide, preventing it from being administered orally. In addition, BQ123 is not as potent as the ET-receptor

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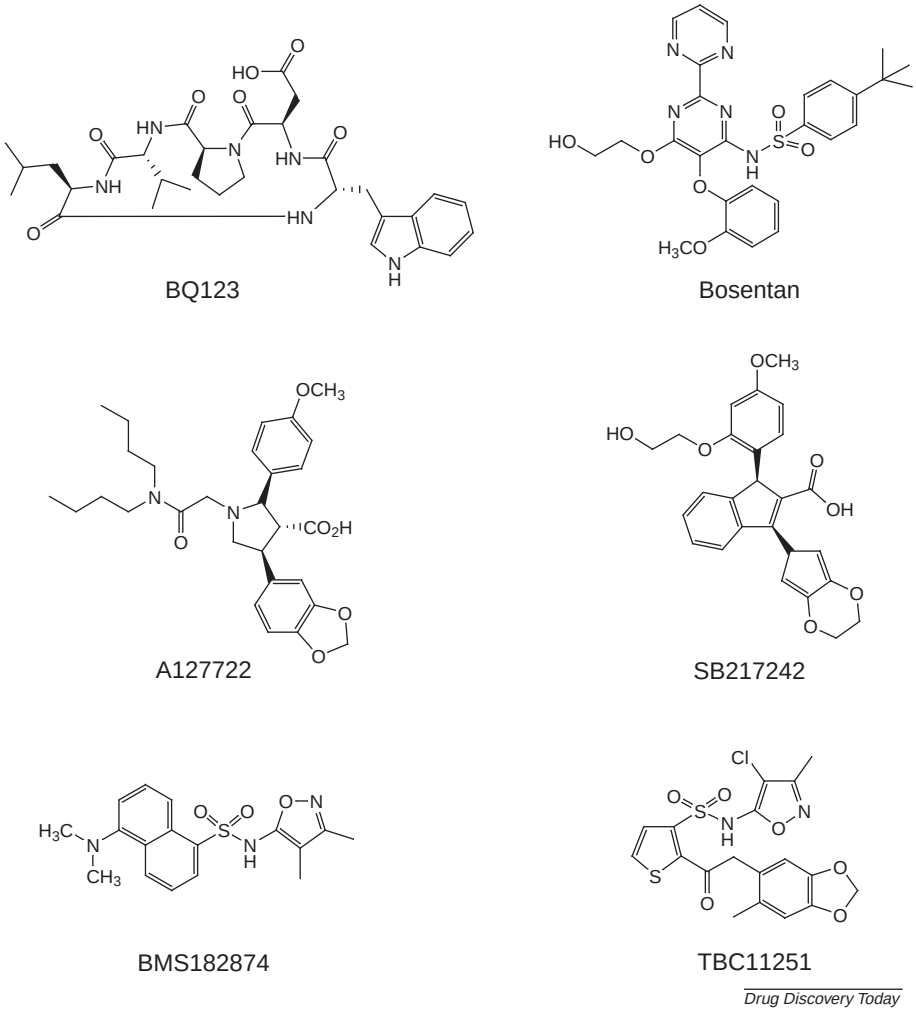

Figure 1. *Chemical structures of six endothelin-receptor antagonists. BQ123 is included as the first endothelin ET_A-receptor antagonist discovered and tested in humans. The other five compounds have reached Phase II stage and beyond in clinical development. Bosentan and SB217242 are mixed endothelin-receptor antagonists, whereas, A127722, BMS182874 and TBC11251 are selective ET_A-receptor antagonists.*

antagonists that were discovered later. Thus, despite being the first ET-receptor antagonist to be tested in humans, development of BQ123 has been discontinued[11].

Bosentan

In 1994, Martine Clozel and group[15] at Hoffman-La-Roche (Basel, Switzerland) reported the discovery of RO37/0203 (bosentan). Unlike BQ123, bosentan is a non-peptidic ET-receptor antagonist (Fig. 1). In receptor radioligand binding assays using recombinant human receptors expressed on Chinese hamster ovary (CHO) cells, bosentan was less discriminatory between ET_A (K_i = 6.5 nM) and ET_B (K_i = 343 nM) receptor subtypes[15], and is therefore known as a mixed ET-receptor antagonist. Bosentan also inhibited the contractile response of isolated rat aorta to ET (pA_2 = 7.2) and isolated rat trachea to sarafotoxin 6C (pA_2 = 6.7), a selective ET_B-receptor agonist. Being a low-MW synthetic compound, bosentan could be administered orally. As a result, it has been tested for efficacy not only to inhibit ET-1-induced pressor responses[15], but also in experimental animal models of, for example, hypertension[16], congestive heart failure[17], cerebral vasospasm[18] and renal failure[19]. Bosentan was ready to enter Phase II clinical trials by 1994. However, it entered Phase III clinical development only recently for hypertension and congestive heart failure[11].

SB217242

After bosentan, the discovery of several other ET-receptor antagonists were reported[20–23]. At SmithKline Beecham Pharmaceuticals (King of Prussia, PA, USA), the ET-receptor antagonist programme involved screening molecules that retained the features of ET-1 that were responsible for receptor binding, and were similar to antagonists of other G protein-coupled receptors. SB217242 (Enrasentan; Fig. 1), an indan carboxylic acid derivative, is a product of such a programme[20]. This compound is a non-peptide mixed ET-receptor antagonist that is more potent than bosentan. SB217242 displaced ET-1 from its binding sites on recombinant human receptors expressed on CHO cells with a K_i of 1.1 nM (ET_A) and 111.0 nM (ET_B)[20]. SB217242 is orally bioavailable (66%) in rats and, following oral administration, can inhibit an ET-1-induced increase in blood pressure in conscious normotensive rats: the antagonistic effect of an orally administered dose (3 mg kg^{-1}) returned to 50% of the peak response in 5 h. No inhibitory effect on the ET-1 response could be seen at 24 h. SB217242 has been tested for efficacy in middle cerebral artery occluded model of cerebral focal ischemia in spontaneously hypertensive rats[24]. Administered orally for 7 days at a dose of 15 mg kg^{-1},

SB217242 reduced both hemispheric infarction and infarct volume by 30%. This compound is now in Phase II clinical development for congestive heart failure and pulmonary hypertension[11].

A127722

The most potent and selective ET_A-receptor antagonist (A127722) was produced by the programme of Terry Opgenorth[21] initiated at Abbott Laboratories (Abbott Park, IL, USA). In A127722 (Fig. 1), the indan ring of SB217242 has been replaced with a pyrrolidine ring. This molecule inhibited ET-1 binding to the ET_A receptor with a K_i of 0.069 nM. Affinity for the ET_B receptor was nearly 2000-fold less (K_i = 139 nM). A127722 was orally bioavailable when tested in rats (35.0%), dogs (43.2%) and monkeys (21.7%) and inhibited ET-1-induced pressor response with an ED_{50} of 2 mg kg^{-1} orally. Following oral administration (10 mg kg^{-1}), the antagonistic effect of A127722 on the ET response lasted for up to 8 h, with 50% of the maximum inhibitory effect still persisting at 24 h.

A127722 has been tested in different ET-1-dependent pathophysiological models, namely cerebral ischemia and oedema[25,26] pulmonary hypertension[27], renal failure[28] and neointima formation[29]. However, more interesting is the role of A127722 in prostate cancer for which it is undergoing clinical trials. It has been shown that in nude mice injected with a human amniotic fibroblast cell line, A127722 inhibited new bone formation[30]. In addition, A127722 inhibited ET-1-mediated biochemical responses in the BPH-1 cell line[31] (obtained from a 60-year-old benign prostatic hyperplasia patient and which expressed ET_A-receptor protein). These results suggest that benign prostatic hyperplasia could be a new condition where ET-receptor antagonists might play an important role.

BMS193884

Research at Bristol Myers Squibb (Princeton, NJ, USA) on sulphonamide molecules led to the discovery of a naphthalene sulphonamide derivative, BMS193884 (Fig. 1), also known as BMS182874 (Ref. 22). BMS182874 is a selective ET_A-receptor antagonist (K_i = 48 nM) that is 100% orally bioavailable and can inhibit an ET-1-induced increase in blood pressure in normotensive rats (ED_{50} = 30 μmol kg^{-1}). BMS182874 has prevented myocardial fibrosis and vascular remodelling in a nephrectomised rat model[32]. In addition, in a sheep model of pulmonary hypertension, BMS182874 has shown efficacy in lowering pulmonary artery pressure and preventing development of pulmonary hypertension[33]. BMS182874 is currently in Phase II clinical trials for heart failure[11].

TBC11251

Texas Biotechnology Corporation (San Diego, CA, USA) has synthesized a series of amidothiophenesulphonamides[23]. TBC11251 is a molecule from this series that has an IC_{50} for the human ET_A and ET_B receptors of 1.4 nM and 9800 nM, respectively. This molecule is orally bioavailable (>60%) in the rat and dog with a plasma half-life of 6–7 h. TBC11251, also known as Sitaxsentan, is in Phase II clinical trials for heart failure, bronchial asthma and pulmonary hypertension.

Clinical experience with ET-receptor antagonists

To-date, most ET-receptor antagonists (with the exception of A127722), are being developed for congestive heart failure and hypertension (Table 1). Human data on ET-receptor antagonists is limited. Studies have shown that ET-receptor antagonists such as SB209670 (Ref. 34) and bosentan[9,35] are well tolerated in humans. SB209670 has a

Table 1. Endothelin-receptor antagonists: current status[11]

Compound	Company	Type of endothelin-receptor antagonist	Stage of clinical evaluation	Indication
Bosentan	Hoffman-La-Roche	Mixed	Phase III	Hypertension Heart failure
SB217242 (Enrasentan)	SmithKline Beecham	Mixed	Phase II	Heart failure Pulmonary hypertension
TBC11251 (Sitaxsentan)	Texas Biotech	ET_A	Phase II	Heart failure Asthma Pulmonary hypertension
BMS193884	Bristol-Myers Squibb	ET_A	Phase II	Heart failure
A127722	Abbott	ET_A	Phase II	Prostate cancer
TAK044	Takeda	ET_A	Phase II	Discontinued

plasma half-life of 4–5 h and a linear pharmacokinetic profile when infused at 0.2–1.5 μg kg^{-1} min^{-1} over 8 h. However, SB209670 is no longer being developed. Bosentan, when administered orally as single[9] or multiple doses[35] has shown oral bioavailability of 43–50%, with a plasma half-life of 3–7 h in the single-dose study. On repeated administration, bosentan induces cytochrome P450 3A and increases, at least in part, its own plasma clearance.

BQ123 (Ref. 8), TAK044 (Refs 10,36), TBC11251 (Ref. 11) and Bosentan[37–41] have been tested for efficacy in humans. Although BQ123 and TAK044 exhibited efficacy in early human trials following intravenous administration, neither agent is being considered for development[11]. A preliminary study on the efficacy of TBC11251 reported that, following intravenous administration, TBC11251 reduced pulmonary arterial pressure (15%) and pulmonary vascular resistance by (39%) in patients with congestive heart failure[11].

Bosentan in coronary artery disease

In a small study, Wenzel *et al.*[41] administered bosentan (200 mg) intravenously to 28 patients with stable coronary artery disease. Bosentan increased the diameter of nonstenotic coronary arteries, decreased systolic blood pressure and increased heart rate. In the same study, glyceryl trinitrate, when administered concurrently with bosentan, did not dilate coronary arteries any further, compared with the control group, where glyceryl trinitrate increased coronary artery diameter significantly. These results suggest that bosentan is as effective as glyceryl trinitrate in dilating coronary arteries.

Bosentan in hypertension

Bosentan was tested for efficacy in 293 moderately hypertensive (diastolic blood pressure 95–115 mm Hg) subjects. Four different doses of bosentan were tested (100 mg, 500 mg and 1000 mg once-a-day, and 1000 mg twice-a-day)[40], with 49–50 subjects in each group. Bosentan inhibited systolic blood pressure in a dose-dependent manner but had no effect on diastolic blood pressure. Only the 500 mg once-a-day and 1000 mg twice-a-day doses showed a statistically significant reduction in diastolic blood pressure (5.7 mm Hg) compared with the control group. In the same study, enalapril, an angiotensin converting enzyme (ACE) inhibitor, produced a 5.7 mm Hg reduction in diastolic blood pressure at 20 mg kg^{-1}.

Bosentan in congestive heart failure

Bosentan was also tested for efficacy in two acute[37,38] and two 14-day studies[38,39] in New York Heart Association (NYHA) type III congestive heart failure patients. In the first study[37], patients were taking a combination of a diuretic, digoxin and an ACE inhibitor and had an ejection fraction of <30%. One group of 12 patients received 100 mg bosentan administered by intravenous infusion, followed 1 h later by a second intravenous infusion of 200 mg for the next hour, while the second group of patients received placebo. Compared with the placebo group, bosentan reduced systemic blood pressure, pulmonary blood pressure, systemic peripheral resistance and pulmonary vascular resistance, with no detectable change in heart rate.

In the second study[38], patients with a similar degree of congestive heart failure as described in the first study (left ventricular ejection fraction <30% and pulmonary capillary wedge pressure >15 mm Hg) were administered intravenous bosentan (300 mg). Bosentan was well tolerated by these patients and improved haemodynamic parameters.

Short-term studies involved oral administration of bosentan 500 mg twice-a-day[38] or 1 g twice-a-day[39] or placebo to 36 subjects with severe congestive heart failure (NYHA, type III, with ejection fraction <30%). These patients were on triple therapy as already described. Oral administration of bosentan improved systemic and pulmonary haemodynamics in 12 h and a further reduction in systemic and pulmonary blood pressure and vascular resistance was observed after 2 weeks.

Concerns with bosentan

Safety and efficacy studies of bosentan have demonstrated that bosentan is orally bioavailable, well tolerated and effective when tested in hypertensive and heart failure patients. However, potency remains the major concern, and the high doses used in the studies described could increase the propensity for non-specific adverse effects. This suggestion is supported by data that shows bosentan increasing plasma levels of liver enzymes in a dose-related manner[11]. In fact, this could be one of the reasons why the Phase III trial for bosentan was suspended for some time, and this molecule is now being developed by a different company under license from the parent company[11]. We also feel that unless bosentan, and for that matter ET-receptor antagonists in general, can demonstrate efficacy at a much lower dose, these agents could lose their competitive edge compared with more established agents such as ACE inhibitors.

Finally, if ET-receptor antagonists are to compete or replace ACE inhibitors in the therapy of congestive heart failure, an issue that yet remains unanswered is whether ET-receptor blockade can regress ventricular hypertrophy in patients with congestive heart failure. ACE inhibitors have proven themselves in numerous large clinical trials (>90,000 patients) to reduce overall mortality and cause regression of hypertrophy[42]. By contrast, the clinical efficacy

data on bosentan are very limited both in terms of patient numbers and the scope of the drug as a first-line therapeutic agent. Bosentan and related agents still have a long way to go before they can establish themselves as first-line therapy, and not as secondary option for ACE inhibitor-unresponsive subjects in the management of congestive heart failure.

In receptor binding studies, bosentan exhibited a reasonably high affinity towards recombinant human ET_A (K_i = 6.5 nM) and ET_B (K_i = 343 nM) receptors and inhibited contractile responses to ET-1 and sarafotoxin 6C (a selective ET_B-receptor agonist), with pA_2 values of 7.2 and 6.0, respectively[15]. With such a high affinity, why did bosentan need such a high dose in human subjects with hypertension and congestive heart failure? One possibility is the concept of pure versus mixed receptor antagonists. It has been variously reported that ET exerts its vasodilatory effect through endothelial ET_B receptors[4]. It is possible that in clinical studies, bosentan required a high dose to be effective because it antagonises the vasodilator effect of ET mediated through ET_B receptors. However, this does not explain why the ET_A-receptor-selective antagonist, Q123, albeit with tenfold less affinity for the receptor than bosentan, was not successful in clinical trials.

An alternative suggestion for complex cardiovascular complications (such as hypertension and congestive heart failure), where multiple factors contribute towards ET synthesis and release (Fig. 2), is that a much more potent ET-receptor antagonist is required than bosentan. With regard to this possibility, it is worth mentioning that while affinity (K_i) of ET-1 for human ET_A receptors is 100 pM, the ET-receptor antagonists currently being tested for congestive heart failure and hypertension recognize ET_A receptors with much lower affinity (K_i for ET_A receptors: BMS182874 = 48 nM; bosentan = 6.5 nM; SB217242 = 1.1 nM; TBC11251 = 0.43 nM). Furthermore, the most potent compound (A127722, K_i = 0.069 nM) is not currently scheduled for testing in humans against hypertension and congestive heart failure. However, clinical trials of TBC11251 [a compound that has exhibited tenfold higher affinity (K_i = 0.43 nM) compared with bosentan towards the ET_A receptor[23]] and SB217242 (a mixed antagonist) could provide some explanations.

Potential therapeutic areas for ET-receptor antagonists

This section will describe four select areas where, in our view, an ET-receptor antagonist could be more successful than existing endothelin-receptor antagonists, both in terms of efficacy and commercial viability. This assessment is based on the role of the endothelium and/or ET-1 in the pathophysiology, availability of therapeutic alternatives, and efficacy data for ET-receptor antagonists in experimental animals as well as in the clinic.

Metastatic prostate carcinoma

Prostate cancer is one of the most common cancers among men in the United States. According to a published report[43], 180,000 new cases of prostate cancer were reported in 1999, of which 10–20% might lead to metastasis. While primary tumours can be treated using radiation and/or surgery, androgen deprivation therapy remains the mainstay of pharmacotherapy for metastatizing prostate cancer.

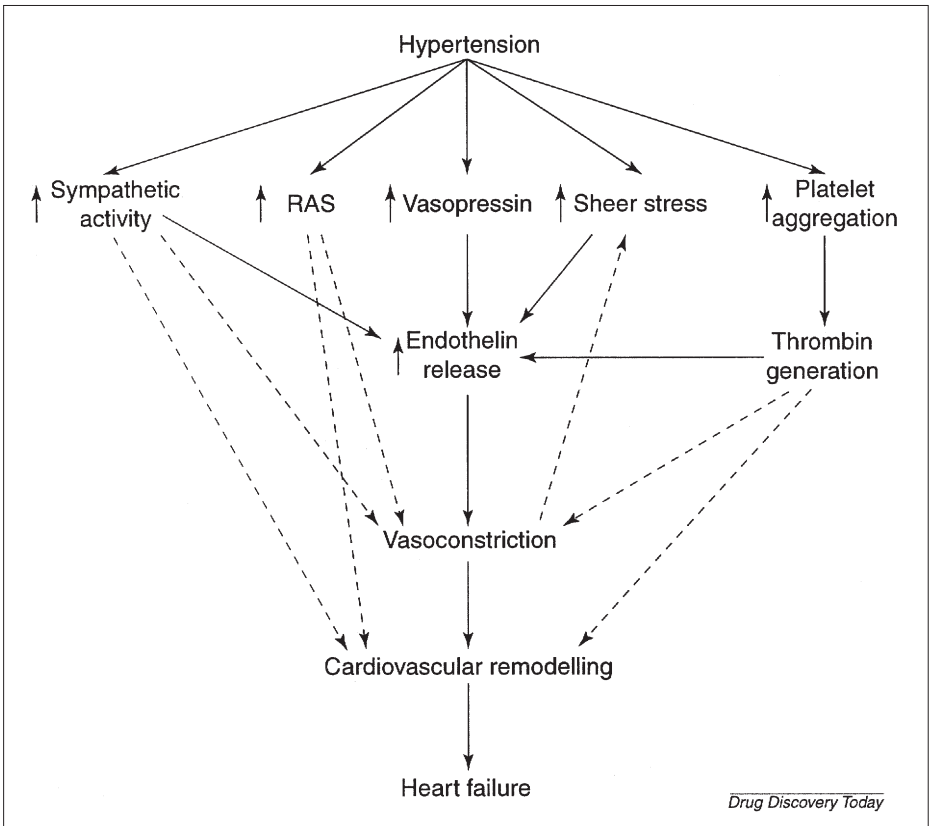

Figure 2. *Endothelin 1 (ET-1) in hypertension and heart failure. A wide array of factors/pathways are activated in hypertension. Any or all of these factors can independently lead to vasoconstriction and vascular remodelling. These factors can also promote gene expression, synthesis and release of ET-1, contributing to vasoconstriction, cardiovascular remodelling and, ultimately, heart failure[64]. Abbreviation: RAS, renin–angiotensin system.*

Although this method is well accepted by patients and the circulating hormone levels reduce to castration levels, prostate cancer becomes refractory to hormone deprivation therapy with time, forcing patients to undergo bilateral orchiectomy. However, even after castration, prostate cancer often recurs.

One of the unique features of prostate cancer is its tendency to metastasize to the skeleton and promote new bone formation. A role for ETs and their receptors is emerging in the pathophysiology of metastatic prostate cancer. One hypothesis that is being actively pursued is the role of the ET_B receptor and its ligand as part of a tumour suppressor mechanism in the prostate that somehow becomes down-regulated in patients with prostate carcinoma[44]. However, more direct evidence exists for a role of ET-1 and ET_A receptors in the process of new bone formation in metastatic prostate cancer.

Studies[30,45] have shown that *in vitro*, all prostate cancer cell lines tested express ET-1, and exogenous ET-1 selectively promotes the growth of cancer cells. Furthermore, ET-1 acts synergistically with other growth factors and increases expression of osteopontin, osteocalcin and alkaline phosphatase activity (an index of new bone formation). In a study using primary prostate tumour and metastatic tissue obtained from several different organs of five patients who died of metastatic prostate cancer, Nelson *et al.*[44] reported the presence of immunoreactive ET-1 in 14/14 sections from the prostate and 14/16 sections from metastasis sites. Moreover, when autoradiography was performed on prostate tissue, ET_A-receptor signal density was very high in the prostate stroma, while ET_B-receptor signal was very low. To establish the role of ET-1 in new bone formation, these workers injected athymic mice with a human amniotic fibroblast cell line stably transfected with ET-1 cDNA (Ref. 30). The authors reported osteoblastic growth in mice that was significantly reduced in the presence of the ET_A-receptor antagonist, A127722. A127722 is currently undergoing Phase II clinical trials for prostate cancer and, if successful, an uncharted therapeutic area for ET-receptor antagonists might be created.

Pulmonary hypertension

Primarily a disease of the damaged pulmonary endothelium, pulmonary hypertension is characterized by increases in pulmonary artery pressure, pulmonary vascular resistance, pulmonary oedema, and pulmonary vascular and right ventricular remodelling[46].

It is well established that the endothelium plays an important role in maintaining the patency of blood vessels by releasing vasodilator substances and preventing blood cells from adhering to the blood vessels[47]. As shown in Fig. 3, in pulmonary hypertension patients, several factors might contribute towards endothelial damage and compromise its vasodilatory and antiaggregatory properties. Of the various factors listed, it is well documented that hypoxia, shear stress and catecholamines can induce ET-1 gene expression, mRNA transcription, translation, processing and release[48]. In addition, activation of the coagulation cascade could stimulate thrombin generation and platelet aggregation, factors that can also contribute towards ET release along with other growth promoting factors like platelet-derived growth factor[49]. ET, along with growth factors and inflammatory mediators, can contribute towards vasoconstriction as well as vascular remodelling.

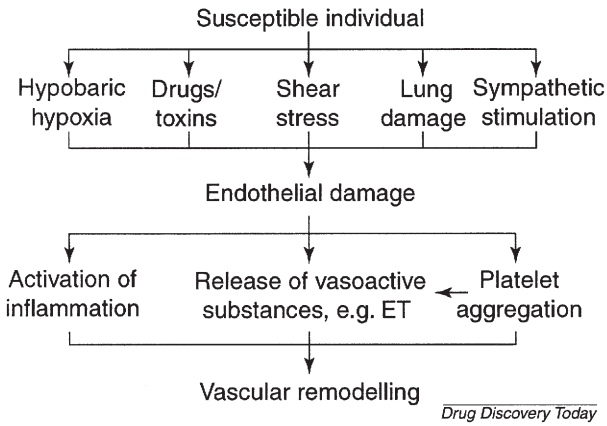

Figure 3. *Involvement of the endothelium in pulmonary hypertension. In susceptible individuals, several factors contribute to pulmonary endothelial damage. Damaged endothelium promotes platelet aggregation, release of vasoactive substances such as endothelin 1 (ET-1) and activation of inflammatory processes. Together, these mediators enhance vascular contractility and promote vascular remodelling leading to pulmonary hypertension[46].*

Much experimental data exists to show the involvement of ET-1 in pulmonary hypertension[3] and a beneficial role of ET-receptor antagonists have been shown in animal models of pulmonary hypertension. For example, SB209670 (Ref. 50), BMS182874 (Ref. 33) and A127722 (Ref. 27) have exhibited beneficial effects in dog, sheep and rat models of pulmonary hypertension, respectively. A127722 is effective when given before, during and following onset of pulmonary hypertension in rats. Similar results have been demonstrated in humans: plasma and tissue ET-1 levels were elevated in the pulmonary circulation of subjects with pulmonary hypertension[47], and two ET-receptor antagonists [namely bosentan[37,38] and TBC11251 (Ref. 11)] lowered pulmonary artery pressure and pulmonary vascular resistance in subjects with congestive heart failure. In fact, the inhibitory effect

of bosentan on pulmonary haemodynamics was superior to its effect on systemic blood pressure and vascular resistance.

It must be remembered that, at the present time, there exists only limited therapeutic options for patients with pulmonary hypertension[46]. Although intravenous prostacyclin is highly effective, it is an expensive (approximately $50,000 per patient per year) and inconvenient proposition, as an intravenous catheter will be a permanent companion of the subject for their remaining living days. Vasodilator therapy involving high doses of calcium channel blockers such as nifedipine (120–240 mg day^{-1}) have shown efficacy in only 25% of patients. In such a scenario, an orally active ET-receptor antagonist would come as a welcome relief.

Cyclosporin-induced renal failure

Renal failure is a condition where kidneys fail to remove water, electrolytes and waste from the body. There can be several causes for renal failure, such as poor blood flow to the kidneys as a result of decreased cardiac output, decreased intravascular volume and redistribution of vascular fluid volume. Alternatively, tubular necrosis or a physical obstruction to urine flow can also precipitate renal failure. At the present time, the therapy for renal failure includes correction of fluid and electrolyte imbalance, treatment of the underlying pathophysiology and, in extreme cases, haemodialysis.

Current evidence suggests that ETs might play a role in the pathophysiology of renal failure. Poor flow through the renal artery activates the renin–angiotensin system leading to generation of angiotensin II that, together with an accompanying hypoxia, can switch on expression of the ET-1 gene[48]. The ET-1 thus generated might contribute towards vasoconstriction and renal failure. In rat and dog models of renal failure, ET levels are elevated[51] and ET-receptor antagonists have demonstrated efficacy in improving creatinine clearance (an index of renal function), and in decreasing plasma creatinine levels[52,53]. However, it should be remembered that there is a significant difference between the rat and the dog models. While both selective ET_A- and mixed ET-receptor antagonists were effective in the rat model[52,54], only the mixed antagonists exhibit efficacy in the dog model[53]. Recent discontinuation of TAK044 from the Phase II trial of acute renal failure[11] raises several questions. Firstly, is the human urinary system closer to the rat or the dog? Secondly, was TAK044 tested in an appropriate experimental model of renal failure? Finally, does the sheer abruptness of clinical renal failure render administration of ET-1-receptor antagonists meaningless?

Cyclosporin A-induced renal failure is a condition where an ET-receptor antagonist might be better utilized. Cyclosporin A is an immunosuppressant drug that is used to prevent host versus graft rejection in transplantation patients. However, a major side effect of cyclosporin A is nephrotoxicity. It has been reported that nearly 4–8% of transplant patients on cyclosporin A develop renal toxicity leading to end-stage renal failure, eventually requiring renal replacement[55,56]. It is known that cyclosporin A can stimulate expression of ET-1 in cultured cells[48] and, in human kidney tissue from cyclosporin A-treated subjects, an elevated expression of ET-1 was reported[57].

As cyclosporin A-mediated renal damage requires a finite time to appear, timely and well planned intervention using ET-receptor antagonists could offer better protection here than it does in the treatment of acute renal failure. To-date, experimental data has been obtained using an ET_A-receptor antagonist in a rat model of renal failure. However, not only did the study design solely involve acute administration of the drug (i.e. only 10 min) but BQ123 was only effective when administered through the renal artery prior to cyclosporin A administration[58]. More recently, in a double-blind, placebo-controlled crossover study involving ten normal human volunteers, bosentan, when administered with cyclosporin A for 7 days, reduced the cyclosporin A-induced decrease in renal plasma flow by 17% (Ref. 59). This was the first report of its kind involving human subjects and many more such studies are required to establish the beneficial role of ET-receptor antagonists in cyclosporin A-induced renal failure.

Erectile dysfunction

Although little work has been carried out examining the role of ET on the physiology and pathology of penile erection, it appears that the endothelium plays an important role in the process. The corpus cavernosum, the tissue that gets engorged with blood during penile erection, is deemed to be an extension of the systemic circulation[60]. At the molecular level, it has been established that nitric oxide released from nerve terminals as a result of sexual stimulation elevates intracellular cGMP levels by stimulating soluble guanylate cyclase in the endothelial cells lining the corpus cavernosum. This process is considered essential for cavernosal relaxation[61]. Recently, it has been shown that sildenafil, an agent that prevents degradation of cGMP, can induce penile erection in patients suffering from erectile dysfunction[62].

There is no evidence to suggest that ET-receptor antagonists might mimic the pharmacological and clinical effects of sildenafil. At the same time, it cannot be denied that in maintaining patency of blood vessels, nitric oxide and ETs have opposing effects. It has been reported that in nearly 80% of patients with erectile dysfunction, the major problem is poor blood flow to the corpus cavernosum.

Moreover, a sizable number of patients with erectile dysfunction suffer from hypertension, non-insulin-dependent diabetes mellitus or atherosclerotic vascular complications. Evidence from animal and human studies indicate that functioning of the endothelium is altered in these disease conditions[63]. Indeed, erectile dysfunction is variously considered to be a marker of impending cardiovascular complications for which ET-receptor antagonists are undergoing clinical trials.

Summary

In summary, after extensive preclinical studies, several ET-receptor antagonists have reached clinical trials. At the present time, almost all of these molecules are slated to be tested for cardiovascular ailments such as hypertension and congestive heart failure. Bosentan, the only molecule that has reached Phase III clinical trials, has shown efficacy in hypertension and congestive heart failure. However, when compared with more established agents such as enalapril, a major problem with bosentan was its poor potency and associated side effects. Moreover, many more trials involving a large number of subjects are required to demonstrate that in patients with congestive heart failure, ET-receptor antagonists can regress cardiac hypertrophy. Thus, it appears that current ET-receptor antagonists still have a long way to go before they become new drug entities for cardiovascular diseases.

An alternative strategy to advance these molecules could be to look for areas where the role of ET in the disease process is emerging and available therapeutic options are limited. We have discussed four such areas in this article. While one ET-receptor antagonist is being tested for efficacy in metastatic prostate cancer, others have exhibited promise in improving pulmonary haemodynamics in patients with congestive heart failure. Similarly, prevention of cyclosporin A-induced renal failure in organ transplant patients remains a potentially interesting and uncharted territory to test ET-receptor antagonists for efficacy. Finally, erectile dysfunction is an area with accumulating evidence in favour of a dysfunctional endothelium, and where the efficacy of ET-receptor antagonists merits exploration.

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