Abstract

The rapid development of endothelin-receptor antagonists has made the endothelin pathway a new therapeutic target in the treatment of cardiovascular diseases, only ten years after the report of its discovery. While the first clinical trials will help to position this new family of compounds in our therapeutic armament for the treatment of essential or secondary forms of hypertension, several preclinical chronic studies already provide a picture of what we can expect from these drugs. Endothelin-receptor antagonists are not effective in all experimental models of hypertension, but those that respond present hypertrophy of small arteries, secondary to a local overexpression of the peptide. Although angiotensin II seems to represent a stimulus for endothelin overexpression in some models, other, as yet undetermined, stimuli are likely in others. Besides their narrow spectrum of antihypertensive activity, endothelin-receptor antagonists may also protect from complications of hypertension by improving end-organ function in a pressure-independent manner. This seems to be the case for the structure and reactivity of resistance arteries, as well as for renal damage. However, it is not clear at this point if cardiac structure and function are improved beyond the benefits produced by blood pressure reduction. The first results in essential hypertensive subjects suggest some degree of efficacy of endothelin-receptor antagonists. Other clinical trials will help to determine if secondary forms of the disease benefit equally or more from this new class of drugs, and if end-organ damage can be reduced beyond blood-pressure reduction.

Keywords: Endothelin; Endothelin antagonists; Hypertension; Vascular remodeling; Hypertrophy; Heart; Kidney

1. Introduction

Endothelin (ET)-1 is recognized as an important local modulator of vascular function. During the ten years that elapsed since the publication of its discovery, [1] sustained efforts both by the scientific community and the pharmaceutical industry have promoted the ET pathway as a new therapeutic target in cardiovascular diseases. Endothelin, an endothelium-derived 21 amino-acid peptide, is the most potent vasoconstrictor known, working at nanomolar concentrations [2]. It is also a trophic factor and a mitogen, two additional properties that are of interest considering the trend to improve end-organ remodeling in addition to normalize arterial pressure, in the treatment of hypertension. Now that the industrial race is on and several clinical trials are under way to determine the clinical benefits of ET-receptor blockade [3], it seems appropriate to review the data pertaining to the involvement of ET in the hypertensive cardiovascular system. Although the biology of ET is interesting on its own, it is the subject of several good reviews [4–6] and will not be discussed in detail. The development of endothelin antagonists has also been reviewed appropriately in recent articles [6,7]. This short review will present the experimental observations obtained with ET-receptor antagonists in several models of hypertension and in man, focusing on their blood pressure lowering efficacy and their potential to limit hypertension-induced end-organ damage.

2. Antihypertensive efficacy in experimental and essential hypertension

Before the advent of ET-receptor antagonists, several lines of evidence supported the candidacy of ET as a hypertensive factor. Indeed, ET is a powerful vasoconstrictor and, even at preconstricting levels (picomolar con-
centrations), it enhances the response to other vasoconstrictors [8,9]. These observations suggest that subtle changes of its local concentrations could have profound effects on vascular tone. In addition, ET can influence the cardiovascular system more permanently by altering the cardiovascular structure through its mitogenic [10] and trophic [11] effects. Moreover, administration of exogenous ET is hypertensive in rats [12] and dogs [13], and patients with hemangioendothelioma (characterized by high circulating levels of ET) have hypertension [14]. On the other hand, circulating levels of the peptide (although not a good indication of the activity of the system) are normally not elevated in hypertensive patients [15,16], arguing against the involvement of ET in human hypertension. Furthermore, the vascular responses to ET are generally blunted in arteries from hypertensive animals (Table 2) and in patients [17]. These observations represent indirect approaches to determine the role of ET in hypertension and the advent of ET-receptor antagonists provided the tools to address that question more convincingly.

Thus, it is no surprise that the first antagonists developed were rapidly tested in models of hypertension. Accordingly, Nishikibe et al. [18] observed a reduction in arterial pressure in stroke-prone spontaneously hypertensive rats (SHR-SP), but not in SHR after acute administration of a selective ET_A-receptor antagonist. The group at Hoffmann-LaRoche also reported an acute antihypertensive efficacy of their compound in salt-depleted squirrel monkeys [19], leading the way to chronic studies with ET-receptor antagonists in several animal models of hypertension with different pathological features (Table 1).

A blood pressure reduction can be observed when hypertension is induced by increasing circulating angiotensin (Ang) II levels to that found in early 2-kidney/1-clip (2K/1C) hypertensive rats [20] with a subcutaneous administration of an initially subpressor dose of the peptide [21]. Endothelin-receptor antagonists are also effective in Dahl salt-sensitive rats fed a high salt diet [23], and demonstrated a modest efficacy in deoxycorticosterone acetate (DOCA)–salt hypertensive rats [24,25]. All three models have vascular overexpression of ET [21,26,27], and this represents a common pathological feature that could explain the antihypertensive efficacy. Ang II has

Table 1

<table>
<thead>
<tr>
<th>Model [reference]</th>
<th>Antagonist</th>
<th>Reduction of Arterial pressure</th>
<th>Vascular CSA</th>
<th>HW/BW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Models with overexpression of ET</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOCA-salt [24]</td>
<td>ET_A/B</td>
<td>22%*</td>
<td>Mesenteric: 77%*</td>
<td>−8%</td>
</tr>
<tr>
<td>DOCA-salt [25]</td>
<td>ET_A/B</td>
<td>14%</td>
<td>n.d.</td>
<td>26%*</td>
</tr>
<tr>
<td>Ang II [22]</td>
<td>ET_A/B</td>
<td>77%*</td>
<td>Mesenteric: &gt;100%*</td>
<td>n.d.</td>
</tr>
<tr>
<td>SHR-SP salt-loaded [37]</td>
<td>ET_A</td>
<td>1%*</td>
<td>Carotid: 50%*</td>
<td>89%*</td>
</tr>
<tr>
<td>SHR-SP [38]</td>
<td>ET_A/B</td>
<td>33%*</td>
<td>Cerebral arterioles: 100%</td>
<td>n.d.</td>
</tr>
<tr>
<td>1K/1C [29]</td>
<td>ET_A/B</td>
<td>9%</td>
<td>Coronary: 20%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal: no change</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mesenteric: 15%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Femoral: 17%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Basilar: no change</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Models without overexpression of ET</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SHR [34]</td>
<td>ET_A/B</td>
<td>0%</td>
<td>Coronary: 35%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Renal: 7%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Mesenteric: 40%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Femoral: no change</td>
<td></td>
</tr>
<tr>
<td>SHR [36]</td>
<td>ET_A/B</td>
<td>0%</td>
<td>Aorta: 4%</td>
<td>0%</td>
</tr>
<tr>
<td>l-NAME [44]</td>
<td>ET_A</td>
<td>0%</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>l-NAME [43]</td>
<td>ET_A/B</td>
<td>15%</td>
<td>Basilar: 22%</td>
<td>n.d.</td>
</tr>
<tr>
<td>2K/1C [29]</td>
<td>ET_A/B</td>
<td>3%</td>
<td>Mesenteric: no change</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

The percentages represent reduction towards control values (100% back to control values) from the values in untreated hypertensive animals with chronic ET-receptor antagonist treatment.

n.d., not determined; no change, the hypertensive model did not exhibit an increase in this parameter, therefore, a reduction could not be calculated.

*The effect was significant (p < 0.05) in the original manuscript.

* Only left ventricular weight was presented.

* No normotensive group was included in the study.
been recognized as a stimulus for ET production in vitro [8, 28], and we recently confirmed that this occurs in vivo in the vasculature as well [21]. Since renin angiotensin system (RAS) activity is blunted in DOCA-salt hypertensive rats, and most likely in Dahl rats fed a high salt diet, other factors may also trigger the exaggerated production of ET. Besides Ang II, no other candidates have been put forward, but, based on in vitro cell culture experiments, the list of putative candidates includes hypoxia, thrombin, TGF-β, IGF, interleukin-1, catecholamines, cortisol and vasopressin, to name a few [2, 4].

Chronic administration of an ET-receptor antagonist is unable to lower arterial pressure in renovascular models of hypertension [29]. In the 1K/1C model, there is hypertrophy and significant overexpression of ET in small arteries [30]. However, the lack of responsiveness to ET-receptor antagonists is surprising, especially if one considers that treatment was initiated at the same time as the clip was installed on the remaining kidney [29]. As suggested by the authors, the increases in local ET production may be too modest for a marked pathophysiological involvement [29]. In 2K/1C hypertensive rats, vascular hypertrophy and small artery ET expression are not really enhanced [30], explaining the lack of responsiveness to the antagonists [29]. Interestingly, ET overexpression in small arteries was inversely related to plasma renin activity measurements, suggesting that models of low RAS activity may have greater endothelial ET expression [30]. It must be pointed out, however, that plasma renin activity and even plasma Ang II levels may not reflect the activity of the local vascular RAS. Accordingly, Larivière recently showed, in a remnant kidney model of hypertension (with low circulating Ang II levels) submitted to different pharmacological interventions, that vascular concentrations of ET were directly related to Ang II concentrations in the same tissues, but inversely related to plasma Ang II levels (Larivière 1998, personal communication). These results support a strong local relationship between Ang II and ET at the tissue level. Furthermore, many reports also suggest a dissociation between the circulating and local RAS activity in renovascular hypertension [31, 32], and heterogeneity between tissues in the same animals [33]. Simultaneous evaluation of tissue concentrations of Ang II and ET may therefore represent a desirable approach to verify the interaction between the two peptides.

Li and Schiffrin [34] reported that ET is not overexpressed in the vessel wall of SHR, making the peptide an unlikely participant in the pathophysiological process in this genetic model. Accordingly, SHR are clearly resistant to the antihypertensive effect of ET-receptor antagonists [34–36]. In sharp contrast, salt-loaded [37] or control [38] SHR-SP have increased circulating levels of ET [18], probably coming from increased endothelial production, and do respond to the antagonists.

In the L-NAME model, acute in vivo studies suggested that a significant part of the pressor effect of NO inhibition was due to ET [39–41]. These acute studies confirmed the functional inhibition of ET by NO that was previously demonstrated in vitro [42]. However, at least two chronic studies in rats failed to confirm any significant long-term involvement of ET in L-NAME-induced hypertension [43, 44]. Furthermore, the levels of the peptide in the vessel wall of small arteries do not seem to be enhanced in animals with chronic NO deprivation [44, 45], in line with the lack of antihypertensive responsiveness.

Judging from the preclinical data published so far, the selectivity of the antagonist does not appear to be critical, considering that both ET₄₃-selective and non-selective ETᵥ₋₄-receptor antagonists are effective in Ang II [22, 46], SHR-SP [37, 38] and DOCA-salt hypertension [24, 35], and ineffective in SHR [34, 35], 1K/1C [29, 35] and L-NAME [43, 44] models.

It also appears quite clear that ET-receptor antagonists are not ubiquitous antihypertensives, as more classical therapeutic agents appear to be. No definitive pattern of efficacy can be drawn at this point, except that models in which ET-receptor antagonists are effective show a vascular overexpression of the peptide (Table 1). Although initial results indicated that ET was involved only in severe forms of hypertension, the results in the low-dose Ang II model, which has a moderate increase in blood pressure, suggest otherwise [21, 22, 46]. The local interplay between Ang II and ET may therefore represent a significant determinant of responsiveness to ET-receptor antagonists, and it is of interest that captopril reduced plasma ET levels in hypertensive but not in normotensive subjects [47]. Salt-sensitivity and salt loading also seem to be of importance and may represent another trigger for ET overexpression, considering the results obtained in DOCA-salt and salt-loaded Dahl salt-sensitive rats (Table 1).

Obviously, the definitive answer to the therapeutic use of ET-receptor antagonists will come from clinical trials. So far, one study in essential hypertensive patients, compared the antihypertensive efficacy of a non-selective ET-receptor antagonist with that of an angiotensin-converting enzyme (ACE) inhibitor and placebo [48]. With an appropriate dosage (500 mg daily or more), four weeks of treatment with the antagonist proved to be as effective as 20 mg of enalapril. However, 500 mg already produced the maximal efficacy and further increments in dosage (up to 2000 mg daily) did not bring diastolic pressure to normotensive values. Indeed, pretreatment diastolic pressure in the treated groups varied between 101 to 107 mmHg and the antagonist produced a maximal reduction of 6 mmHg, well above normotension. Nevertheless, these results do suggest a role of ET in essential hypertension.

This seems to contradict what has been suggested from preclinical studies in which vascular hypertrophy and local overexpression of ET predicted the antihypertensive efficacy (Table 1). It is indeed interesting to note that small arteries of mild essential hypertensives are characterized by eutrophic remodeling [49] without overexpression of
the peptide [50]. This apparent discrepancy between rat models and man is further emphasized by the reduction of arterial pressure in normal subjects after the acute administration of an ET-receptor antagonist [51], an effect that is seldom seen in normotensive animals. In addition, the first clinical trials in patients with congestive heart failure reported a pressure reduction of 10–15 mmHg, making hypotension a major side effect [3,52]. Future studies will help to determine if ET exerts a more significant control of blood pressure in man than in animal models.

3. Protection of end-organs

In addition to lower arterial pressure, new antihypertensive agents are developed to protect target organs from the deleterious effect of chronic pressure elevation. These may include tissue hypertrophy, capillary rarefaction and perfusion restrictions, all leading to a progressive loss of function of vital organs. Although increased vascular tone may be involved in these processes, more permanent changes are brought by remodeling of the vasculature. Accordingly, besides being a potent vasoconstrictor, ET has been shown to be mitogenic [10] and trophic [11,53] on cultured cell systems derived from cardiovascular tissues. It is not clear which effect predominates in vivo, but a study in serum-free primary cultures suggests that ET is a trophic factor, with poor mitogenic activity [11]. Thus, ET has the potential to be involved in hypertrophy, although it may also modify cell number by inhibiting apoptosis, as suggested by some recent reports [54,55].

3.1. Remodeling of resistance arteries

When submitted to a sustained increase in pressure, small arteries (<300 μm) adapt their structure to normalize wall stress, by increasing the media thickness-to-lumen diameter ratio (M/L) [49]. A nomenclature for all possibilities to obtain such an increased ratio has been put forward by several investigators [56]. The term eutrophic inward remodeling has been coined for a change in M/L without an actual change in tissue content (or cross-sectional area, CSA). This necessarily implies that the content of the vessel wall is rearranged (with or without cellular turnover) around a smaller lumen diameter. This type of remodeling seems to occur in several models of hypertension [49], including the L-NAME model (Fig. 1) [57], and in essential hypertension [49]. Hypertrophic remodeling (outward or not) represents another process in which the lumen diameter is not necessarily modified, but the surface area of the vessel wall (CSA) is clearly enhanced, again in an effort to normalize wall stress by increasing M/L. This process is found in Ang II-induced hypertension (Fig. 1) [21,58], in some secondary forms of human hypertension [59] as well as in severe human hypertension [50]. The initial influences that determine the type of remodeling (eutrophic vs. hypertrophic) are not known, but ET overexpression may participate at some point (see below).

If one looks at small arteries in a hypertensive context, circumferential wall stress is generally normal, due to the increased M/L, as discussed above. When blood pressure is brought to lower levels, M/L will again change to normalize wall stress, so that there always exist a strong relationship between M/L and arterial pressure at, least in animals (Fig. 1). However, there is a clear dissociation between CSA changes and those of blood pressure and M/L (Fig. 1). As an example, two weeks of Ang II or L-NAME treatments produced similar increases in pressure with similar M/L of basilar arteries. However, CSA increased

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Fig. 1. Relative changes, from control values, of systolic blood pressure (SBP), vascular media width/lumen diameter ratio (M/L) and vascular cross-sectional area (CSA) of basilar arteries in rats treated with L-NAME, angiotensin II (Ang II), Ang II plus an ET₁-receptor antagonist, LU135252 (LU), and L-NAME plus an ET₃-receptor antagonist, Bosentan (Bos). The numbers in parentheses represent the number of weeks of L-NAME treatment. These data are taken from the author’s work and demonstrate a close relationship between changes of SBP and M/L ratio [correlation coefficient (r)=0.985], and a dissociation between variations of SBP and vascular CSA (r=0.354) at the level of basilar arteries. Qualitatively similar results were obtained for mesenteric resistance arteries.
only in the Ang II group, indicating an increased amount of material in the vessel wall (Fig. 1). Thus, vascular hypertrophic remodeling has a pressure-independent component. This was already suggested some years ago when normalization of blood pressure in Ang II-treated rats by hydralazine failed to normalize CSA [58]. We recently demonstrated that ET-receptor blockade prevented totally Ang II-induced hypertrophic remodeling, without normalizing arterial pressure (Fig. 1 Table 1), suggesting that endogenous ET is responsible for increased vascular CSA, independently of arterial pressure [21].

Even more striking are the results found in Dahl salt-sensitive animals fed a high sodium diet. In the same animals, basilar arteries showed characteristic signs of eutrophic remodeling (increased M/L ratio without increased CSA), while mesenteric resistance arteries had increased CSA (Fig. 2). Chronic administration of an ETα-receptor antagonist normalized the CSA of mesenteric arteries, without altering that of cerebral arteries. The reduction of the M/L ratio followed changes in arterial pressure. These observation again confirm the involvement of ET in hypertrophic but not in eutrophic, remodeling, a conclusion shared by Chillon et al. [38] who studied cerebral arterioles in SHR-SP. In fact, all models studied so far in which increased tissue ET levels have been reported also show some degree of vascular hypertrophy. Interestingly, ET-receptor antagonists are able to lower arterial pressure significantly in these models, except in 1K/1C animals displaying a modest increase in vascular ET levels (Table 1).

3.2. Vascular reactivity and endothelial function

As an unusually potent vasoconstrictor, ET could be involved in blood pressure elevation by direct vasoconstriction, especially if vascular tissues were more sensitive to its action. In contrast, however, most forms of experimental hypertension, such as SHR, l-NAME [57,60], DOCA-salt [61] and Ang II [46], as well as essential hypertensive subjects [17], show a reduced maximum contraction to ET. This may not be true for all vascular beds, and the renal circulation may represent a notable exception, considering its long-term role in pressure regulation and its high sensitivity to the vasoconstrictor effect of ET [62]. Indeed, in the SHR, the vasoconstrictor responses to ET are maintained [63] or even increased [64]. Furthermore, in human hypertensive subjects, the renal vascular effects of exogenous ET administration are not blunted [65].

Some of the published effects of chronic treatments with ET-receptor antagonists on vascular reactivity are summarized in Table 2. Most of the pathological changes that were observed in the untreated hypertensive animals were improved by these antagonists. It is the case for those that respond to the antihypertensive and hypotrophic effects of the antagonists [23,24,27], but also for l-NAME-treated rats, which are resistant [43]. Thus, this effect does not seem to be pressure-dependent or even secondary to improvement of vascular structure. Of special interest is the amelioration of ET-1-induced contractions by receptor antagonists in most models (Table 2), despite ET overexpression (and possible receptor down-regulation) in some models only. The reason for the normalization of vascular function in terms of responsiveness to vasoconstrictors remains elusive.

Endothelium-derived vasorelaxation may represent a significant aspect of end-organ protection by endothelin antagonists. In that respect, selective ETα-receptor antagonists may prove to be more protective than ETβ-receptor antagonists, which block ETβ-receptor-mediated NO and

Fig. 2. Relative changes, from control values, of systolic blood pressure (SBP), vascular media width/lumen diameter ratio (M/L) and vascular cross-sectional area (CSA) in mesenteric resistance arteries (MA) and basilar arteries (BA) of control Dahl salt-sensitive rats fed a high salt diet (CII), and similar rats treated with an ETα-receptor antagonist, LU135252 (LU). The results suggest an involvement of ET in vascular hypertrophy (increased CSA), but not in eutrophic remodeling (increased M/L without increased CSA). Indeed, eutrophic remodeling responds in relation to the blood pressure reduction with ET-receptor blockade. See text for additional details. Adapted from [23].
Table 2
Effect of chronic ET-receptor blockade on hypertension-induced changes in vascular reactivity

<table>
<thead>
<tr>
<th>Model [reference]</th>
<th>Vessel type</th>
<th>Antagonist</th>
<th>Relaxation</th>
<th>Contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOCA-salt [24]</td>
<td>Mesenteric</td>
<td>Untreated</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;↓</td>
<td>Ang II↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ET&lt;sub&gt;endo&lt;/sub&gt;↑</td>
<td>NE↑</td>
</tr>
<tr>
<td>l-NAME [43]</td>
<td>Mesenteric/basilar</td>
<td>Untreated</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;↓</td>
<td>Ang II↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ET&lt;sub&gt;endo&lt;/sub&gt;↑</td>
<td>NE↑</td>
</tr>
<tr>
<td>l-NAME [43]</td>
<td>Aorta</td>
<td>Untreated</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;↓</td>
<td>Ang II↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ET&lt;sub&gt;endo&lt;/sub&gt;↑</td>
<td>NE↑</td>
</tr>
<tr>
<td>l-NAME [67]</td>
<td>Aorta</td>
<td>Untreated</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;↑</td>
<td>Ang II↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ET&lt;sub&gt;endo&lt;/sub&gt;↑</td>
<td>NE↑</td>
</tr>
<tr>
<td>Dahl-SS [23]</td>
<td>Mesenteric</td>
<td>Untreated</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;↑</td>
<td>Ang II↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ET&lt;sub&gt;endo&lt;/sub&gt;↑</td>
<td>NE↑</td>
</tr>
<tr>
<td>Dahl-SS [27]</td>
<td>Aorta</td>
<td>Untreated</td>
<td>ET&lt;sub&gt;A&lt;/sub&gt;↑</td>
<td>Ang II↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ET&lt;sub&gt;endo&lt;/sub&gt;↑</td>
<td>NE↑</td>
</tr>
</tbody>
</table>

The arrows depict the changes observed in untreated hypertensive rats compared to normotensive controls, and in rats treated chronically with an ET-receptor antagonist compared to untreated hypertensive rats. Thus, arrows in opposite directions between the two situations denote an improvement.

Ach, acetylcholine; SNP, sodium nitroprusside; Ang II, angiotensin II; ET-1, endothelin-1; NE, norepinephrin; 5-HT, serotonin; ‡, increase; †, decrease; ↔, no change.

prostacyclin release [66]. This is especially true if one considers the enhanced levels of ET that are normally observed with the chronic administration of selective or non-selective ET-receptor antagonists [46,52]. So far, however, very few direct comparisons of both types of antagonists have been made with respect to endothelium-dependent relaxation. We recently obtained results showing a pressure-independent improvement of endothelium-dependent vasorelaxation with an ET<sub>A</sub>-receptor antagonist in l-NAME-induced hypertension [67], while our previous study with a non-selective antagonist showed no improvement of the relaxations in the same model (Table 2) [43]. In DOCA-salt hypertensive rats, the use of a non-selective antagonist did not improve the endothelial function [24]. In contrast, an ET<sub>A</sub>-receptor antagonist improved endothelial function both in the aorta [27] and mesenteric resistance arteries [23] of Dahl salt-sensitive rats (Table 2). However, no direct comparison was made with the other type of antagonist in these two models.

3.3. Left ventricular hypertrophy and cardiac function

The in vivo trophic effect of ET seems to be confirmed by the ability of ET-receptor antagonists to prevent cardiac hypertrophy in Ang II-induced hypertension (Table 1) [22]. A major role for ET has also been suggested in NE-induced cardiac hypertrophy, where a transient ET overexpression was documented [68]. However, the results obtained in the DOCA-salt model are less striking. Indeed, one study failed to show prevention of cardiac hypertrophy [24], while another one, using the same antagonist, reported a reduction in left ventricular area and thickness, without significant reduction in left ventricular weight [25]. It is remarkable, however, that perivascular and subendocardial fibrosis were significantly improved by chronic ET-receptor antagonism in these animals [25]. Accordingly, overexpression of ET seems to be limited to endothelial cells of coronary vessels and the endocardium, and not in the myocardium [69]. In the SHR, a model resistant to ET-receptor antagonists in terms of pressure reduction, Karam et al. [36] could observe a small reduction in left ventricular area/body weight ratio (7%, p<0.05), but no overt improvement of heart weight/body weight or left ventricular weight/body weight ratios. In SHR-SP, the reduction in blood pressure was accompanied by reduced cardiac hypertrophy [37]. Overall, the information available would suggest that, although ET may have a focal role in cardiac fibrosis, hemodynamic factors, such as arterial pressure per se, may prove to be more essential in cardiac hypertrophy.

Another significant finding is that the maximal coronary blood flow was not improved by chronic ET-receptor antagonism in SHR and DOCA-salt hypertensive rats [25,36]. In the DOCA-salt model, this seems to contradict the improvement of vascular structure [24]. It must be pointed out, however, that hypertrophic remodeling (increased CSA without reduction in lumen diameter), such as seen in this model, may not limit blood flow in maximally dilated arteries, but it may allow the vessels to contract in an exaggerated fashion in response to agonists in more physiological conditions [70].

A recent study reported a deleterious involvement of ET (and benefits from ET-receptor antagonism) in cardiac remodeling following myocardial infarction. Indeed, after eight weeks of treatment (but not after the first week) with an ET-receptor antagonist, there were significant reductions in left ventricular dilatation and improvements of heart performance [71]. This observation, together with the earlier report of acute effectiveness of ET-receptor antagonists in human chronic heart failure [52], suggests a beneficial role of ET-receptor antagonists in the long-term cardiac complications of hypertension.
3.4. Renal function

Renal effects of ET may also include cellular proliferation and vasoconstriction [72]. Interestingly, the renal vasculature is highly sensitive to the vasoconstrictor action of ET that takes place both at the pre- and postglomerular level [72]. Indeed, supressor doses of the peptide have a marked effect on renal hemodynamics in man [73,74]. In addition to its hemodynamic effects, ET also inhibits medullary sodium and water reabsorption in certain conditions, such as ischemia [75]. However, the physiological significance of these observations seems to be limited in animals, since ET-receptor antagonists do not have a marked effect on normal kidney function [72]. The receptor subtypes involved in these different actions of ET may also vary between species, and extrapolations should be made with caution [72]. In SHR, blood pressure is not affected by ET-receptor antagonists, but a non-selective ET-receptor antagonist was more effective than a calcium channel blocker or an ACE inhibitor at improving creatinine clearance [36]. Similarly, ET-receptor antagonists were able to improve renal vascular injuries (inflammatory and proliferative) in the L-NAME model, without altering the state of hypertension [76]. In Dahl salt-sensitive animals, local administration of an ET-receptor antagonist, which did not show any systemic effect, improved renal hemodynamics and excretory functions [77]. Overall, there may be beneficial effects of ET-receptor blockade in limiting hypertension-induced kidney damage, despite poor efficacy to lower arterial pressure.

Convincing evidence exists to show that ET-receptor antagonists can alleviate acute renal failure in animal models (for reviews, see [6,72]). The pathological process most likely involves renal vasoconstriction, leading to ischemic necrosis of renal tubules [78]. ET seems to be a major player in this process, and its antagonists may prove to be therapeutically meaningful. ET-receptor antagonists may also be of therapeutic use in the prevention of the development of chronic renal failure, and this is particularly significant in the context of hypertension. Indeed, ET has the potential to be partly responsible for the glomerular hypertension and hyperfiltration, mesangial cell proliferation and extracellular matrix production that have been observed during the progression of the disease [6]. Accordingly, ET overexpression seems to be limited to preglomerular arteries and to glomeruli in rats with reduced renal mass [79]. In addition, ET gene expression correlates well with the progression of the disease [80], and ET-receptor antagonists protect the kidney in animal models of chronic renal failure [81]. Moreover, in these experimental models, ET-receptor antagonists reduce arterial pressure, suggesting a substantial role of ET in elevation of blood pressure during the disease process [81]. Increased local Ang II generation represents an attractive candidate to trigger the overexpression of ET [79].

From available preclinical observations, the future of ET-receptor antagonists seems promising for kidney protection in the context of hypertension or not. Appropriate studies in man will help to determine the therapeutic role of ET-receptor antagonists in renal disease and in the prevention of hypertension-induced renal damage, and the type of antagonist most helpful in these conditions [72] (see also a review on the subject in this issue).

4. Conclusion and perspectives

During the last few years, the availability of ET-receptor antagonists has generated a lot of information on the pathophysiological role of ET in preclinical models of hypertension. However, it is not clear by which mechanism ET influences blood pressure in most models. Direct vasoconstriction does not appear to be the most likely mechanism, if one considers the general blunted vascular responsiveness in hypertensive animals and in man. Amplification of constriction by other agonists seems more likely, especially if one considers the strong influence of ET on vascular structure, which may also contribute to the enhancement of vascular responsiveness. Although the antagonists may reduce kidney damage and lower arterial pressure in renal failure models, the positive renal effects in hypertensive models were not associated with blood pressure reduction. However, it is possible that improved renal function participates in the pressure reduction in models that are responsive to ET-receptor antagonists.

What seems rather clear, however, is that ET-receptor antagonists are not ubiquitous antihypertensives in animal models. The responsive models have vascular overexpression of the peptide and hypertrophic remodeling of arteries. In contrast, the first results obtained in man seem to suggest a moderate efficacy of the antagonists in essential hypertension, which does not show vascular overexpression of ET. Therefore, the identification of the patient profile responsive to ET-receptor antagonists will be of major interest during the next few years. In addition, the (dis)agreement of the clinical trials with the preclinical results summarized above will provide a critical evaluation of the validity of several of our animal models of hypertension to predict the efficacy of new antihypertensive strategies. Finally, end-organ protection may represent an important asset of ET-receptor antagonists, hopefully leading to a reduction in cardiovascular morbidity and mortality beyond what is currently achieved with available therapies.

Acknowledgements

The author would like to thank the scientific contribution of Thomas F. Lüscher to most of the author’s results presented in this article. In addition, the financial support of the Medical Research Council of Canada, the Heart and
Stroke Foundation of Canada, the 'Fonds pour la Formation de Chercheurs et l’Aide à la Recherche' and Knoll AG (Germany) is also acknowledged. The author is currently a Research Scholar from the ‘Fonds de la Recherche en Santé du Québec’.

References