Endothelin and its Antagonists in Hypertension: Can we Foresee the Future?

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Introduction

Endothelin-receptor antagonists may soon become a new therapeutic class of agents used to treat cardiovascular diseases. Although the first clinical trials are anxiously awaited to position this new family of compounds in the treatment of essential or secondary forms of hypertension, we dispose of an impressive amount of studies in which plasma endothelin levels have been measured, in addition to chronic preclinical studies that provide a general picture of what we can expect from these drugs. The experimental models that do respond to endothelin-receptor antagonists share vascular overexpression of endothelin, which seems directly linked with vascular hypertrophy of resistance arteries. In addition, salt sensitivity may represent an unbalanced condition between relaxing and constrictive properties of the renal endothelium that can respond favorably to endothelin blockade. Thus, African-American hypertensives may well be a responsive target population for the new drugs. In addition to blood pressure control, endothelin may also be involved in the evolution of end-organ damage by its potent vasoactive and vasoproliferative properties. The kidney, heart, large arteries and brain may therefore benefit from these drugs, but it is still unclear if this benefit goes beyond what can be attributed to the reduction of arterial pressure. Moreover, most studies performed so far have looked at prevention of end-organ damage, while very few have addressed the clinically relevant question of regression of lesions already installed by the disease process.

Endothelin in Hypertension

Administration of exogenous ET is hypertensive in rats, dogs, and healthy volunteers [6–8]. As well, patients with hemangioendothelioma (characterized by high circulating...
levels of ET) show an increase in blood pressure [9]. On the other hand, measurement of circulating levels of the peptide in essential hypertension has provided very conflicting results: some studies show increased levels [10-12], while others reported no significant differences [13-15]. In addition to methodologic considerations such a cross-reactivity of the antibody [14], several other factors may help to explain this heterogeneity. Indeed, plasma ET levels increase with age [14,16], but only younger hypertensives may exhibit higher levels of the peptide than age-matched controls, in contrast to older patients [16]. Racial differences may also contribute to the discrepancy, with black hypertensive patients having a near eightfold increase in circulating levels as compared with normotensives [17••]. In the same study, white hypertensive patients had a twofold increase. Interestingly, normotensive subjects of both races had similar circulating ET levels [17••]. This suggests that depending on the sample of hypertensive patients selected (race and age), differences may or may not be found, as only a subset of the hypertensive population may have increased circulating levels of ET. Although severity of hypertension may influence ET levels, a study in borderline hypertension also provided positive results [18]. Furthermore, normotensive offspring of hypertensive parents demonstrate increased ET release in response to mental stress [19•]. Plasma ET levels may also be influenced by concomitant metabolite or end-organ alterations such as type II diabetes [20], renal failure [21], heart failure [22], hyperlipidemia [23], and early or established atherosclerosis [24].

Small studies in renovascular hypertension also provided conflicting results, but the majority of studies reported increased circulating ET levels [25]. Cyclosporin-induced hypertension represents another condition where increased or unchanged plasma ET levels have been reported. However, experimental data suggest that vascular and renal levels [26,27] of the peptide may be increased. Moreover, the report of enhanced renal ET(A)-receptor density [28], and medullar [26] or mesengial cell [27] ET(B)-receptor density during cyclosporin administration reveals even more complexity by suggesting that peptide levels need not be enhanced for ET to play a role. Erythropoietin-induced hypertension is another paradigm in which ET may be involved, as suggested by animal and human studies [21,29]. There seems to be more consistency in preeclampsia where peptide levels are elevated as compared with normotensive pregnancy [30].

Due to the high potency and the preferential release of the peptide towards effector cells, subtle changes in plasma levels can indicate significant local activation. The best example is deoxycorticosterone acetate (DOCA) salt hypertension, in which local vascular concentrations of the peptide are increased, but plasma levels are normal [31]. Contraction of isolated arteries to exogenous ET is generally blunted in arteries from hypertensive animals and in human patients [32••]. Although this could suggest receptor down-regulation due to excess ET, other explanations may also be appropriate. Altogether, this important but rather indirect evidence makes it difficult to incriminate or discharge ET as an important contributing factor in hypertension. The advent of ET-receptor antagonists now provides the specific tool to address that question more convincingly.

**Preclinical observations with endothelin antagonists**

The first ET antagonists developed were rapidly tested in models of hypertension, and it appeared that they were not going to be ubiquitous antihypertensives. Indeed, Nishi-ikibe et al. [33] observed a reduction in arterial pressure in stroke-prone spontaneously hypertensive rats (SHR-SP), but not in spontaneously hypertensive rats (SHR) after acute administration of a selective ET(A)-receptor antagonist. Additional early work by the group at Hoffmann-LaRoche reported an acute antihypertensive efficacy of their lead compound in salt-depleted squirrel monkeys [34]. These initial acute studies led the way to chronic studies with ET(A)-receptor antagonists in several animal models of hypertension with different pathologic features (Table 1) [32]. However, it is still difficult to extract a common feature of responsive or nonresponsive models. Indeed, ET-receptor antagonists are effective in hypertension induced by increasing circulating angiotensin II levels to that found in early 2-kidney/1-clip (2K/1C) hypertensive rats [35•,36]. However, in renovascular models of hypertension (2K/1C and 1K/1C), ET-receptor antagonists are not very effective [37], making elevated circulating angiotensin II levels a poor determinant of antihypertensive efficacy. In low renin models, the results are also relatively different, the antagonists being effective in Dahl salt-sensitive rats fed a high-salt diet [38], but having a modest efficacy in DOCA salt hypertensive rats [39].

Spontaneously hypertensive rats are clearly resistant to the antihypertensive effect of chronic ET-receptor antagonists [40,41]. In sharp contrast, salt-loaded [42] or control [43] SHR-SP do respond to the antagonists, although late treatment of SHR-SP may not be as effective [42]. The discrepancy between SHR and SHR-SP has prompted many to believe that ET-receptor antagonists would be more effective in severe forms of hypertension, but recent data suggest that this is not necessary the case [35,36,44].

In the NG-nitro-L-arginine methyl ester (L-NAME) model mimicking endothelial dysfunction of hypertension, acute in vivo studies suggested that a significant part of the pressor effect of nitric oxide (NO) inhibition was due to ET [45]. In chronic conditions, however, only a delay in the onset of hypertension was noted [46], without significant improvement of final blood pressure by ET-receptor antagonists [46,47].

Therefore, no definitive pattern of efficacy can be drawn at this point, except that models in which ET-receptor antagonists are effective show a generalized vascular overexpression of the peptide, accompanied by hypertrophic remodeling of resistance arteries (Table 1) (Fig. 1).