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Since its discovery in 1988, endothelin-1 (ET-1) has been widely studied in a diverse number of fields, including neurology, cardiology, development, and to a greater extent, nephrology and hypertension.[1,2] Through the activation of its 2 receptors, ET_A and ET_B, ET-1 influences blood pressure by numerous mechanisms, making it an attractive target for treatment of hypertension and other diseases.[3–10] Although antagonists of the ET-1 system are highly effective in experimental models of hypertension and recently have been shown effective in resistant essential hypertension,[7,11,12] their translation to the clinic has been disappointing thus far because of various side effects, including fluid retention/edema and liver toxicity.[13,14] In fact, only 2 ET-1 receptor antagonists have been approved by the Food and Drug Administration for the use in humans, ambrisentan and bosentan, an ET_A antagonist and dual ET_A/ET_B antagonist, respectively. The sole indication thus far approved is for the treatment of pulmonary hypertension.[15] However, several receptor-specific antagonists are available and are going through animal testing and clinical trials. This review will focus on the recent progress of how ET-1 affects blood pressure and the future use of ET-1 receptor antagonists for the treatment of kidney disease and hypertension.[14]

ET Receptors

Either ET_A or ET_B or both receptors are located on almost every cell type throughout the body. ET_A receptors are mostly located on vascular smooth muscle cells, and activation is not only normally prohypertensive through potent vasoconstriction but also have significant effects to increase inflammation, oxidative stress, and increases in proteinuria through direct changes on renal glomerular permeability.[12,16,17] ET_B receptors, however, function quite the opposite, being mostly antihypertensive. Vascular ET_B receptors are mainly located on the endothelium, and activation leads to vasodilation through enhanced nitric oxide production.[18] The highest concentration of ET_B receptors are located on renal collecting duct cells and are important in long-term blood pressure regulation by directly inhibiting sodium uptake.[18] Chronic disruption of the ET_B receptor, either genetically or pharmacologically, results in salt-sensitive hypertension.[18] Because the hypertensive actions of ET_B receptor disruption can be abolished by ET_A receptor antagonism, it is widely believed that ET_B receptors protect against ET_A receptor activation, and a balance between the 2 receptor subtypes is required for the maintenance of blood pressure. For greater details into the known mechanisms of ET receptor activation, especially within the kidney, the authors direct us to a recent review by Kohan et al.[18]

Targeting ET in the Kidney

Depending on which part of the kidney ET-1 is produced (cortex versus medulla), and which receptor is activated, renal ET-1 can have dramatically different effects on blood pressure. For instance, cortical ET-1 causes hypertension by increasing renal vascular resistance and reducing glomerular filtration rate. Furthermore, cortical ET-1 expression is upregulated in a number of hypertensive models.[11,19,20] Even more specifically, glomerular ET_A activation may lead to hypertension by increasing inflammation through enhanced production of monocyte chemoattractant protein-1 and other proinflammatory factors, such as cell adhesion molecules, thereby sequestering macrophages and lymphocytes.[17] These immune cells, in turn, release a number of factors that act within to kidney to cause vasoconstriction and increases in sodium reabsorption, resulting in higher blood pressure. This has been proposed to play a role in the pathophysiology of numerous hypertensive states, including angiotensin II (AngII) hypertension and early life stress.[21–24] Interestingly, ET-1 causes glomerular and vascular inflammation in the absence of hypertension, suggesting that ET-1 antagonists could have even greater beneficial outcomes beyond that of blood pressure reduction.[17] Therefore, cortical ET-1 is prohypertensive by increasing renal vascular resistance, and directly promoting infiltration of inflammatory cells, specifically to the glomerulus.

In contrast to the renal cortex, renal medullary ET-1 reduces blood pressure by directly inhibiting sodium reabsorption on the collecting duct and increasing medullary blood flow through activation of the ET_B receptor. Inner medullary collecting ducts produce the most ET-1 within the kidney (≈10 times more than any other nephron segment). Known mediators of ET-1 effects on tubular and vasa recta function include increased production of nitric oxide and 20-HETE.[18] Under normal circumstances, activation of this system is directly dependent on the level of salt intake.[25] Moreover, at least half of the immunoreactive ET-1 found in urine is derived from the renal collecting duct.[26] Blockade of ET_B receptors, either genetically or pharmacologically, results

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in hypertension that is highly sensitive to salt intake.[18,27] Impairment of this pronatriuretic pathway as evidenced by reductions in medullary ET-1 production in hypertension is observed in the Dahl salt-sensitive rat.[27] These data suggest that alterations in medullary ET_B receptor function could be an important mediator of salt-sensitive hypertension; however, until we understand the specific mechanisms that are responsible for regulating ET_B receptor function, it will be difficult to discern how to overcome salt sensitivity attributed to this pathway.

Sex Differences in ET-1 Signaling

It is well established that sex differences exist in the development of cardiovascular disease and hypertension, in that premenopausal women are less likely to develop hypertension compared with men.[28–30] There is growing evidence that ET-1 may play a role in the differential regulation of blood pressure between men and women. Some of the more compelling data come from very intricate studies by Nakano and Pollock,[31] where it was shown that direct infusion of an ET_B agonist into the renal medulla increases urine flow rate and sodium excretion of male and female rats. Interestingly, the natriuretic response was only present in females when the endogenous ligand, ET-1, was infused. The lack of natriuresis in the males in response to ET-1 was attributed to an ET_A-mediated reduction in medullary blood flow, thereby offsetting any ET_B-mediated tubular effects. Furthermore, female rats also displayed a component of ET_A-dependent natriuresis that was absent in males.[31] Therefore, it seems there is an ET_A-mediated protection against hypertension in female rats that does not exist in males.

A number of laboratories have provided clear evidence that ET-1 plays a role in AngII salt-induced hypertension because ET_A or combined ET_A/ET_B antagonists can block the hypertensive effects of chronic AngII infusion.[32] It is known that female rats are not as susceptible to AngII hypertension, and so it has become increasingly evident that ET-1 may be important in the protection against salt-induced hypertension afforded to female rats.[33] For instance, renal medullary ET_B receptor function is completely lost in AngII hypertensive male rats, whereas still intact in females. This reduced ET_B function is associated with a reduction in ET_B ligand binding in male rats, but not in female rats.[6] Furthermore, blockade of ET_B receptors increases blood pressure to a more significant extent in female AngII hypertensive rats compared with males (unpublished data). Taken together, these data suggest that AngII, either directly or indirectly, reduces ET_B receptor function in male rats; however, ET_B receptor function in female rats is preserved in AngII hypertension, providing a potential mechanism of protection against high blood pressure.

ET in Chronic Kidney Disease

Several lines of evidence suggest that ET-1 is a major factor in the development of chronic kidney disease, and more specifically, contributes to hypertension, proteinuria, and renal inflammation in chronic kidney disease. In fact, ET-1 directly stimulates inflammation both in the vasculature and in the kidney, and this occurs in the absence of hypertension.[7,17,34] Recently, it was shown that an ET_A receptor-specific

antagonist reduces blood pressure and proteinuria in patients with chronic kidney disease.[34] These reductions were in addition to the normal treatments already being administered, including angiotensin receptor blockers and converting enzyme inhibitors. Therefore, although the initial insult in the development of chronic kidney disease may be multifactorial and complex, ET-1 seems to play an important role in the development and progression of the disease. Thus, treatment with ET_A receptor antagonists may prove to be beneficial in cases where standard treatments are not sufficient, especially when blood pressure reduction is needed.

More recent data suggest that selective ET_A antagonism improves outcomes in diabetic nephropathy. The ASCEND (A Study of Cardiovascular Events iN Diabetes) study shows significant reductions in proteinuria among patients with diabetic nephropathy given the ET_A antagonist, avosentan; however, this study was cut short because of fluid retention among the treatment group. Although this was disappointing, it must be pointed out that the doses used in this trial were very high relative to the known dose–response effect on fluid retention observed in prior phase 2 trials and the lack of a dose–response effect on proteinuria.[35] In fact, a much lower dose of atrasentan, another selective ET_A antagonist, reduces albuminuria, but with far less peripheral edema than the ASCEND trial.[18] These studies highlight not only the importance of the ET_A receptor in mediating kidney disease in diabetes mellitus but also the great potential that these drugs may have in treating renal disease associated with glomerular injury and proteinuria.

ET in the Pathogenesis of Preeclampsia

Preeclampsia is a disease of pregnancy in which the mother becomes hypertensive in the third trimester of gestation. It is thought to be caused by abnormal remodeling of uterine spiral arteries, leading to placental insufficiency and the release of factors, such as soluble fms-like tyrosine kinase-1 and tumor necrosis factor-α, from the placenta into the blood stream that result in overproduction of ET-1 by the vascular endothelium and the renal cortex.[11,36–39] In fact, a very well-established model of preeclampsia in the rat, in which clamps are placed on the ovarian arteries and the descending aorta to reduce blood flow to the placenta, is characterized by hypertension that is abolished by ET_A receptor antagonism.[37,40] Furthermore, soluble fms-like tyrosine kinase-1 and tumor necrosis factor-α infusion into pregnant rats result in hypertension that is also mediated by ET_A receptor activation.[19,20] Although ET_A receptor antagonists seem promising for the treatment of pregnancy-induced hypertension, there is the potential problem of teratogenicity. ET_A receptor knockout mice have severe developmental defects that are lethal and so it is unlikely that any pharmaceutical company would want to or be able to test this idea.[18] Whether drugs can be developed that do not cross the placenta is not well established.

What is the Future of ET-1 Antagonists for the Treatment of Hypertension?

Although it is well established that ET-1 plays an important role in blood pressure control and alterations in this system can lead to hypertensive consequences, there are still no approved ET-1 antagonists for the treatment of arterial

hypertension. Several fairly large clinical trials demonstrated that both ET_A selective and combined ET_A and ET_B antagonists reduce blood pressure in patients with resistant essential hypertension.[13,41] However, further development of these drugs for use in resistant hypertension has been thwarted for several potential reasons that are not all scientific. The ET_A antagonist, darusentan, produced a significant reduction in 24-hour blood pressure in hypertension subjects already being treated with at least 3 other antihypertensive medications, yet for reasons unclear, the primary end point of clinic blood pressure was not significantly different from placebo on the final day of the trial. This led to the decision of the company developing the compound, Gilead, to discontinue further development. This decision was particularly disappointing also because of the additional benefits observed in hypertensive patients, including reduced glycemia, improved lipid metabolism, and reductions in proteinuria.[13,41]

As previously mentioned, another important factor that seems to have contributed to reduced enthusiasm for developing ET blockers for the treatment of hypertension is edema. Fluid retention is a serious side effect that has been observed with all the various antagonists, but this was a particularly significant problem in patients with diabetic nephropathy in the ASCEND trial that was terminated early.[35] However, lower doses that maintain efficacy have fewer issues with fluid retention and seem to be manageable by adjusting cotreatment with diuretics.[18]

The delicate balance between the ET_A and ET_B receptors is required for the normal regulation of fluid and water balance (Figure). For instance, as sodium intake is increased, the ET_B receptor becomes increasingly more important in blood pressure control because of its role in reducing renal tubular sodium reabsorption.[18] Although disruption of the balance between receptor subtype activity may ultimately lead to hypertension, that is, loss of ET_B and gain of ET_A receptor activity, knowledge of the distinct function of these receptors is needed when attempting to treat different forms of hypertension. Furthermore, there are a number of factors that shift balance between ET_A and ET_B receptors, including salt intake,[12,42–46] sex,[6,31,47] and AngII, and may contribute to the somewhat confusing results from clinical trials compared with the very clear findings in experimental models.

Finally, one cannot ignore the business aspects of developing new drug therapies. New drugs that may require careful management and cotherapies in the early treatment phase may be difficult to manage when dealing with a chronic disease that is not immediately life-threatening. Both patient and physician compliance can be difficult when focusing on what can be viewed as simple blood pressure management. However, patients with resistant hypertension are on many different medications without blood pressure control and so the effort should be worthwhile. In addition, it is important to note that most of the ET antagonists are nearing the end of their initial patent life. Although a limited degree of exclusivity may be allowable, the earning potential may not be worth the costly investment required for clinical trials. The mistakes of the previous clinical trials are also an obstacle to overcome from a perceptual basis. Companies are reluctant to invest in drugs that have been tainted by a failed trial even when
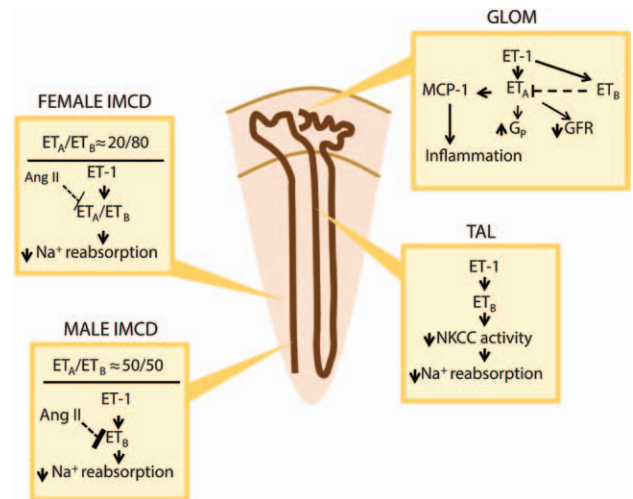

Figure. General schematic showing major actions of endothelin-1 (ET-1) along the nephron. AngII indicates angiotensin II; GFR, glomerular filtration rate; GLOM, glomerulus; GP, glomerular permeability; IMCD, inner medullary collecting duct; MCP-1, monocyte chemoattractant protein-1; NKCC, sodium, potassium, 2-chloride cotransporter; and TAL, thick ascending limb of the loop of Henle.

there are rational scientific explanations. Nonetheless, when one studies the history and considers the scientific specifics, there remains the valid possibility that the ET antagonists are potentially useful, life-prolonging drugs in patients experiencing hypertension.

Disclosures

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