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ENCYSIVE™ PHARMACEUTICALS

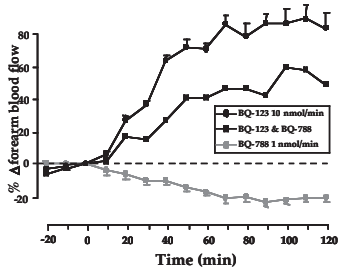
The vascular system is made up of the vessels that carry our blood, oxygen, nutrients, wastes, and the complex biochemical signaling system that regulates most physiologic processes. With the exception of the electrical impulses that characterize nerve and muscle activity, virtually everything that happens in the body does so because of the transit of substances through the vascular system. Nearly all major chronic diseases, including cardiovascular disease, stroke, rheumatoid arthritis, and cancer, depend on cellular and subcellular interactions that occur in the vascular system, and problems in the vascular system can be deadly. This makes it an ideal place to intercept and modify fundamental physiologic processes, whether normal ones, like clotting and inflammation, or abnormal ones, like cancer cell proliferation or atherosclerosis.

Over the last few decades, our knowledge of the mechanisms regulating the vascular system and blood flow has been reshaped by several discoveries. These discoveries have demonstrated that the perivascular autonomic nerves and vascular endothelium release a variety of agents vital for vascular physiology and the blood supply to tissues. The endothelium performs many active functions, such as the secretion and modification of vasoactive substances and the contraction and relaxation of vascular smooth muscle. Among some important agents of endothelial origin are an endothelium-derived relaxing factor (EDRF)/nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin. Further, it has been shown that endothelial dysfunction promotes vascular disease by producing an imbalance between vasodilating/antiproliferative and vasoconstrictive/proliferative elements (*1*).

ET-1 is a peptide produced mainly by vascular endothelial cells. ET-1 has major bearing on the function and structure of the vasculature as it promotes vasoconstriction and cell proliferation through activation of endothelin-A and endothelin-B receptors ($ET_A$and ET_B, respectively) on vascular smooth muscle cells (*2*). Activation of ET_A receptors, which are found in smooth muscle cells and cardiac myocytes, facilitates sustained vasoconstriction and proliferation of vascular smooth muscle cells. In contrast, ET_B receptors, which are localized predominantly on endothelial cells, but are also found on smooth muscle cells, are thought to be primarily involved in the clearance of ET-1, particularly in the vascular beds of the lung and kidney. Additionally, activation of the endothelial cell ET_B receptors stimulates the release of other endothelial mediators, such as NO and prostacyclin, which promote vasodilation and anti-proliferative activity.

As shown in the figure below, selective ET_A blockade induces a vasodilation response in the forearm blood flow model. Selective ET_B blockade induces vasoconstriction. Non-selective ET_A and ET_B blockade attenuates the benefit observed through selective ET_A blockade.

Mixed ET_A/ET_B Blockers: ET_A-Blockade-Induced Vasodilatation is Impaired by ET_B Blockade



Verhaar MC et al. *Circulation* 1998;97:752-756.

Endothelial Dysfunction in Vascular Disease

Endothelial dysfunction plays a role in the development and perpetuation of vascular diseases by creating an imbalance between vasodilating/antiproliferative and vasoconstrcitive/proliferative factors (*1*). Endo-thelial dysfunction can result either from mechanical or biochemical injury to the endothelium, leading to increased ET-1 release and decreased NO activity. Increased ET-1 levels contribute to the pathogenesis of important disorders such as pulmonary arterial hypertension, renal failure, atherosclerosis, and heart failure (*2*).

A blockade of ET-1 activity is thought to prevent its detrimental effects. The most efficient way to antagonize the ET-1 system is the use of ET-1 receptor antagonists that can selectively block ET_A, ET_B, or the nonselective blockade of both ET_A/ET_B

receptors (*3*). ET receptor antagonists have been widely studied in experimental models of cardiovascular disease, and may prove to be effective in the treatment of a variety of diseases where the regulation of vascular constriction is important. Clinical studies have shown that a selective ET_A blockade is linked to improvement in endothelial function. Selective ET_B blockade, on the other hand, prevents ET-1 clearance, resulting in increased ET-1 levels.

Pulmonary Arterial Hypertension (PAH)

The pathological process of PAH involves a complex course of development, including endothelial dysfunction in the pulmonary circulation, resulting in pulmonary vasoconstriction and vascular remodeling (*3*). Although not the only element, increased ET-1 levels and impaired or diminished production of NO appear to play a significant role in the pathophysiology of PAH. The extent of ET-1 elevation correlates with the measurable increase in pulmonary pressure and disease severity. In blinded, placebo-controlled clinical trials, nonselective ET_A and ET_B blockade has shown, among other results, an improvement in symptoms and exercise capacity in PAH patients. Clinical studies have also shown that the use of a nonselective ET_A and ET_B antagonist further aggravates the ET-1 elevations in patients with PAH.

Congestive Heart Failure (CHF)

Studies have indicted that heart failure is commonly associated with high plas-ma concentrations of ET-1, which has accounted for some of the circulatory abnormalities observed in patients with CHF. In patients with CHF, it has been shown that using a selective ET_B blockade fosters vasoconstriction. A nonselective ET_A and ET_B antagonist has been shown to increase ET-1 levels acutely and chronically in patients with CHF. Of note is the fact that these same studies failed to demonstrate clinical benefit in CHF. In contrast, selectively blocking ET_A in patients with CHF has been shown to reduce the elevated levels of ET-1.

Hypertension and Renal Disease

In addition to cardiovascular effects, ET-1 has an impact on normal renal function (*2*). ET-1 encourages vasoconstriction and cell growth in the vasculature and in the kidney (*4*). Accordingly, in experimental models, chronic ET receptor blockade inhibits vascular injury, reduces hypertension associated with other forms of renal and vascular injury and also prolongs survival (*4*). Studies have shown that nonselectively blocking ET_A and ET_B and selectively blocking ET_B increases ET-1 levels in hypertensive patients with chronic renal failure. Studies in L-N^G-nitroarginine methyl ester hypertension suggest that ET-1 is linked to the dysfunction of the L-arginine/NO pathway because ET_A-selective, but not nonselective ET_A and ET_B blockade, improves endothelial function, independent of blood pressure (*4*). Therefore, as shown in studies, by selectively inhibiting ET_A receptors, we can improve the endothelial L-arginine/NO pathway, as is shown by the fact that the simultaneous blockade of ET_B re-ceptors eliminates the favorable effects of an ET_A-selective antagonist on vascular structure (*4*).

Despite enormous efforts by researchers, pharmaceutical companies, and medical device manufacturers, cardiovascular disease continues to be responsible for extensive morbidity, mortality, and healthcare costs. The tools physicians have today are simply inadequate for the task of effectively managing patients with diseases such as pulmonary arterial hypertension, chronic heart failure, hypertension, and stroke. Just to take CHF as an example, nearly five million Americans currently suffer from the disease, with about 400,000 new cases diagnosed each year. Sixty to seventy percent of these patients die within five years. More effective medicines and treatments are urgently needed to improve survival and quality of life for patients, and to reduce significantly the cost of caring for them. **Encysive™ Pharmaceutical**'s **(Bellaire, TX)** expertise in vascular physiology and biochemistry thus positions them to discover a very broad range of novel disease targets. Encysive is committed to discovering, developing, and commercializing small-molecule drugs focused on cardiovascular, vascular, and inflammatory diseases.

For more information concerning Encysive Pharmaceuticals, contact a company representative at ATS, booth #1123, or visit Encysive's Web site at www.encysive.com.

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