Endothelin

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IN 1988, YANAGISAWA AND COWORKERS (55) characterized an endothelium-derived vasoconstrictor, a 21-amino acid peptide subsequently called endothelin (ET). ET-1 is derived from a 203-amino acid peptide precursor, preproendothelin, which is cleaved after translation to form proendothelin. In the presence of a converting enzyme located within the endothelial cells, proendothelin, or big ET, is cleaved to produce the 21-amino acid peptide. Various aspects of the ET system have been addressed by recent publications in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology and other journals. Articles include investigations on cardiac (4, 16, 25, 30, 37, 48), vascular (29, 35, 38, 42, 44, 52), renal (1, 56, 8, 9, 13, 19, 26, 39, 43), pulmonary (52), reproductive (28), fetal (11, 12, 29, 52), and neuroendocrine (9, 10, 25, 47, 56) systems. Although much attention has been given to the role of ET in the pathophysiology of cardiovascular and renal disease acting via an ET type A (ETA) receptor, more recent studies indicate an important physiological role for ET in the regulation of sodium balance and arterial pressure, via an ET type B (ETB) receptor.

Increased synthesis of ET has been reported in various diseases associated with cardiovascular abnormalities such as hypertension, diabetes, cardiac hypertrophy, congestive heart failure, and chronic renal failure (1, 3, 7, 9, 20–22, 40, 43–45). ET receptor binding sites have been identified throughout the body, with the greatest numbers of receptors in the kidneys and lungs (22, 45). Although the biochemical and molecular nature of ET has been well characterized, the physiological importance of ET in the regulation of renal and cardiovascular function in normal disease processes remains to be an important area of investigation. ETA receptors are primarily located on vascular smooth muscle cells. These receptors are involved in mediating ET-1 vasoconstriction and cellular proliferation in various disease states (22, 44). ETB receptors are located on multiple cell types in the brain, on vascular endothelial cells, and renal epithelial cells (8, 17, 18, 22, 23, 26, 31, 53). Although the location and the signal transduction pathways for ETB receptors have been well characterized, the physiological role of these receptors has not been fully elucidated. The ETB receptors appear to play a role as clearance receptors, removing ET from the circulation and interstitial spaces (22). A significant role for ETB receptors in the development of enteric neurons and melanocytes has also been established (13). Loss of ETB receptors results in failure of melanocytes and enteric neurons to develop, resulting in abnormal development of the gastrointestinal tract and megacolon (13). Activation of vascular ETB receptors by ET-1 or other ligands results in vasodilation; however, the physiological importance of ETB-mediated vasodilatation is still unclear.

Although ETA receptors play an important role in mediating the vascular abnormalities that occur in certain forms of hypertension (especially salt-sensitive hypertension), these receptors do not appear to influence cardiovascular and renal function under normal physiological conditions. Indeed, several laboratories have reported that chronic ETA receptor blockade has no significant long-term effect on kidney function or arterial pressure regulation in normal rats (1, 2, 7, 20). However, this may not be the case for all species (6).

Recent studies published in this journal have suggested an important interaction between ET and the renin-angiotensin system. Angiotensin II plays an important role in the regulation of arterial pressure during various physiological and pathophysiological conditions. Indeed, several laboratories have also suggested that angiotensin II may exert its physiological actions via interaction with autacoid factors such as ET (1, 3–5). Consistent with this suggestion are results of several recent studies indicating that the renal and hypertensive effects of angiotensin II can be markedly attenuated or completely abolished by ETA receptor antagonists (1, 3–5, 40, 43). The quantitative importance of ET in mediating the chronic hypertensive actions of angiotensin II may depend on the level of dietary sodium intake (3).

Several lines of evidence support a role for angiotensin II as a regulator of ET synthesis. Angiotensin II is a potent stimulator of ET release by cultured endothelial, smooth muscle, and renal mesangial cells (4, 5). Furthermore, angiotensin II stimulates expression of preproendothelin mRNA in cultured cells such as endothelial and vascular smooth muscle. Evidence supporting an effect of angiotensin II on synthesis of ET in vivo is not as abundant. Barton and colleagues (4) recently reported enhanced ET levels in renal tissue, but not myocardial tissue, in rats with chronic angiotensin II hypertension. More recent experiments by Alexander et al. (1) and others (43) have reported angiotensin II-induced expression of preproendothelin RNA or ET protein levels in kidneys. Thus angiotensin II may exert its chronic physiological actions via stimulation of ET and activation of ETA receptors.

ET has also been implicated in regulating vascular function during normal pregnancy. Both renal blood flow and glomerular filtration increases by over 25% during pregnancy. Renal vascular resistance decreases...
significantly during pregnancy. Moreover, the myogenic reactivity of small renal arteries from pregnant rats is significantly reduced (13, 33). Conrad and colleagues (13, 33) recently provided convincing evidence that ET acting through the endothelial ETA receptor and the nitric oxide pathway accounts for the renal vasodilation and reduced myogenic reactivity of small renal vessels during pregnancy in rats. They also recently provided important evidence that this pathway is stimulated during pregnancy by the hormone relaxin (32, 46).

ET is also involved in regulating vascular function during the pregnancy disorder preeclampsia. Preeclampsia is associated with hypertension, proteinuria, and endothelial dysfunction (21). Because endothelial damage is a known stimulus for ET synthesis, increases in the production of ET and activation of ETA receptors may participate in the pathophysiology of preeclampsia (21). Plasma concentration of ET has been measured in a number of studies involving normal pregnant women and women with preeclampsia. Most investigators have found higher ET plasma concentrations of approximately two- to threefold in women with preeclampsia. Typically, plasma levels of ET are highest during the latter stage of the disease, suggesting that ET may not be involved in the initiation of preeclampsia, but rather in the progression of disease into a malignant phase. Although the elevation in plasma levels of ET during preeclampsia is only two- or threefold above normal, previous studies have reported that this level of plasma ET can have significant long-term effects on systemic hemodynamics and arterial pressure regulation (54). Thus long-term elevations in plasma levels of ET comparable to those measured in women with preeclampsia could play a role in mediating the reductions in renal function and elevations in arterial pressure observed in women with preeclampsia.

Although most studies have reported no significant changes in circulating levels of ET during moderate forms of preeclampsia, a role for ET as a paracrine or autocrine agent in preeclampsia remains worthy of consideration (21). Alexander et al. (2) recently examined the role of ET in mediating the hypertension in response to chronic reductions in uterine perfusion pressure in conscious, chronically instrumented pregnant rats. Using an RNase protection assay, they found that renal expression of preproendothelin was significantly elevated in both the medulla and the cortex of the pregnant rats with chronic reductions in uterine perfusion pressure compared with control pregnant rats. Moreover, they reported that chronic administration of the selective ETA receptor antagonist markedly attenuated the increase in mean arterial pressure in pregnant rats with chronic reductions in uterine perfusion pressure. In sharp contrast to the response in reduced uterine perfusion pressure rats, ETA receptor blockade had no significant effect on blood pressure in the normal pregnant animal (2). These findings suggest that ET plays a major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure in pregnant rats. Despite this important finding, the mechanism linking enhanced renal production of ET to chronic reductions in uterine pressure in pregnant rats or in preeclamptic women is unknown. One potential mechanism for enhanced ET production is via transcriptional regulation of the ET-1 gene by tumor necrosis factor (TNF)-α (21). TNF-α is elevated in preeclamptic women and has been implicated in the disease process (21). Another potential stimulus for ET production during preeclampsia is activation of the angiotensin type 1 receptor. As noted above, studies from various laboratories have found that angiotensin II, via the angiotensin type 1 receptor, is a potent stimulator for ET production. More importantly, ET plays a critical role in mediating the long-term renal and hypertensive action of angiotensin II in rats (55). Thus the role of factors such as TNF-α and angiotensin type 1 receptor activation in mediating the increased synthesis of ET in preeclampsia remains to be determined.

There is growing evidence to suggest that ET-1, acting through the ETB receptors, is involved in the regulation of sodium balance under normal physiological conditions. The kidney is an important site of ET-1 production, and ETB receptors are expressed at important renal sites of ET synthesis, particularly in the renal medulla (8, 9, 17, 22–24, 31, 49, 51, 53). Some of the first studies using synthetic ET-1 demonstrated that nonpressor doses of ET-1 produced significant natriuresis and diuresis (22, 45). It is now known that ETB receptors are located in various parts of the nephron, including the proximal tubule, medullary thick ascending limb, collecting tubule, and the inner medullary collecting duct (8, 17, 18, 22–24). The highest concentration of ETB receptors appears to be on the inner medullary collecting duct in the renal medulla. Activation of ETB receptors has been reported to inhibit sodium and water reabsorption along various parts of the nephron. Taken together, these data indicate that ET-1, via ETB receptors, may influence the renal handling of sodium and water.

For the renal ET system to be an important control system for the regulation of sodium balance, the production of renal ET should change in response to variations in sodium intake. Moreover, blockade of ETB receptors should result in a salt-sensitive form of hypertension. Although there are ample data showing that ET-1 can influence sodium reabsorption, there is a paucity of data in the literature examining the relationship between sodium intake and renal production of ET-1. A recent study by Pollock and Pollock (39), however, has shown a positive correlation between sodium intake and renal excretion of ET. The most convincing evidence for a role of the renal ET in controlling sodium excretion and arterial pressure during chronic changes in sodium intake are the results of studies by Gariepy et al. (14), Pollock and Pollock (39), and Ohuchi et al. (34). Gariepy and colleagues demonstrated that rats deficient in ETB receptor expression display salt-sensitive hypertension. Likewise, Pollock and Pollock reported that chronic pharmacological...
blockade of the ETα receptor in rats resulted in hypertension that was very sensitive to dietary sodium intake. Moreover, Ohuchi et al. reported elevation in blood pressure by genetic and pharmacological disruption of the ETα receptor in mice. Although these studies support an important role for the renal ET system in controlling sodium excretion, additional experiments are necessary to not only define the link between sodium intake and renal ET synthesis, but also to understand the tubular and hemodynamic mechanisms whereby ETα receptor activation regulates renal sodium handling.

REFERENCES


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