Invited Controversy

Is Endothelin Involved in the Pathogenesis of Hypertension?

Paul M. Vanhoutte

Endothelins are a family of potent vasoconstrictor peptides released by endothelial cells. The production of endothelin-1 (ET-1) can be stimulated by aggregating platelets and angiotensin II. It is inhibited by increases in intracellular concentration of cyclic GMP. ET-1 causes biphasic changes in arterial blood pressure and of peripheral resistance in several vascular beds: an initial transient decrease (due to release of nitric oxide, prostacyclin, or both from the endothelium) followed by a sustained increase (mainly due to direct activation of vascular smooth muscle). The vasoconstriction induced by the peptide is inhibited by increases in cyclic GMP. Few studies, except in pregnant women with preeclampsia or eclampsia, indicate that the circulating levels of the peptide are augmented in hypertension. Likewise, the information available on changes in responsiveness to endothelins in blood vessels from hypertensive animals is controversial. Until the effect of selective antagonists on the production or action of the peptide can be determined in hypertensive patients, caution must be exerted when implying a role for endothelin in the pathophysiology of hypertension.

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The endothelium can release both dilator (endothelium-derived relaxing factor [EDRF, most likely nitric oxide], endothelium-derived hyperpolarizing factor, prostacyclin) and constrictor (superoxide anion, thromboxane A₂, endoperoxides) substances, which help to control the tone of the underlying smooth muscle (see References 1-4). Isolated arteries taken from animals with experimentally induced or genetic hypertension exhibit reduced endothelium-dependent relaxations (see References 2 and 3). Depending on the animal model of the disease, this reduction has been attributed either to a reduced release or action of EDRF (e.g., see Reference 5) or to an exaggerated production of endothelium-derived endoperoxides (e.g., see References 6 and 7). Endothelial cells in culture release vasoconstrictor peptides, which have been identified as endothelins. Intact blood vessels also produce endothelin (e.g., Reference 11), and circulating levels of the peptide have been detected in a number of species, including humans (e.g., References 12-16; see also “Levels of Endothelin” below). Because endothelin is the most potent endogenous vasoconstrictor substance known (see References 17-20), it is tempting to assume that it may play a role in the pathophysiology of hypertension (see Reference 21). The present essay reviews the information available so far, which does not seem to permit that conclusion yet, at least in mild-to-moderate forms of the disease.

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Background Information

Of the three members of the endothelin family, endothelin-1 (ET-1) and endothelin-3 (ET-3) circulate in the blood and thus are potentially important as homeostatic hormones. The production of ET-1 by endothelial (and other) cells is well characterized and involves the final transformation of big endothelin by endothelin converting enzyme (see References 17 and 20). The production of ET-1 can be augmented by a number of physiological and pathological stimuli. Among these, the more important potentially for hypertension include aggregating platelets, angiotensin II, vasopressin, catecholamines, and the ouabainlike factor. Judging from experiments with isolated blood vessels, the release of ET-1 increases with age. The relatively slow rate of production of ET-1 suggests that if the peptide plays a physiological role, it is more likely to do so in mid- or long-term regulation rather than by contributing to moment-to-moment changes in vascular tone. When the production of cyclic guanosine monophosphate (GMP) is stimulated in endothelial cells, the cyclic nucleotide exerts a braking effect on the secretion of ET-1. Thus, both endothelin-derived nitric oxide (EDRF) and atrial natriuretic peptides inhibit the production of the vasoconstrictor peptide.

When ET-1 is injected into intact animals, the first response usually is a transient decrease in peripheral resistance leading to a decrease in blood pressure. Likewise, in perfused blood vessels, the first response to lower concentrations of ET-1 often is dilatation. This depressor effect of lower concentrations of ET-1 can be attributed to the release of vasodilator prostanoids, in particular, prostacyclin, and of endothelin-derived nitric oxide.
The depressor response to ET-1 is followed by a sustained and long-lasting increase in blood pressure, which is explained best by the direct constrictor effect of the peptide on vascular smooth muscle (see References 2, 10, 17, and 20). The activation of vascular smooth muscle by ET-1 involves an endothelin-A receptor, which is linked to the phosphatidylinositol metabolism, voltage-operated calcium channels, or both to increase the cytosolic concentration of the activator ion. Because nitric oxide is a potent inhibitor of the contractions evoked by ET-1, the presence of the endothelium curtails the vasoconstrictor response to the peptide; the curtailment involves both the basal and stimulated release of endothelin-derived nitric oxide. By contrast, the presence of small amounts of other vasoconstrictor substances (e.g., norepinephrine, serotonin, ouabain-like factor) amplifies the vasoconstrictor response to ET-1 and vice versa.

ET-1 can activate a number of cells other than those in the blood vessel wall (see References 17–19). Hence, it is conceivable that the changes in peripheral resistance during ET-1 evoked in this animal model, at least in part, be due to more indirect ways of inducing constriction of the resistance vessels. These include activation of specific areas of the central nervous system, resulting in an increase in sympathetic tone (e.g., see References 49 and 50) or enhanced release of vasconstrictor hormones (e.g., adrenal catecholamines and vasopressin).

ET-1 may promote the proliferation of vascular smooth muscle cells and fibroblasts. If this were to occur in the intact organism, it may contribute to chronic morphological adjustments in vascular diameter.

Endothelins and Hypertension

To imply a role for endothelin in the pathophysiology of hypertension, one would have to demonstrate that the levels of the peptide are augmented (because of either an increased production or a delayed degradation) or that the vasoconstrictor responses that it evokes are potentiated (because of either a diminished production of vasoconstrictor mediators, an augmented responsiveness of vascular smooth muscle, or an amplified proliferative effect). To make the involvement of endothelin in the hypertensive process credible would require the demonstration that reasonably selective antagonists of the production or the actions of the peptide lower arterial blood pressure in hypertensive animals and humans.

Levels of Endothelin

There is little information on the release and disposition of endothelin in hypertensive animals. The mesenteric artery of the spontaneously hypertensive rat (SHR) releases more of the peptide spontaneously than that of its normotensive control animal (Wistar-Kyoto [WKY] rat) of the same age; in both rat strains, the release of endothelin augments with age. Ouabain causes a greater release of endothelin in prehypertensive salt-sensitive Dahl rats than in normotensive controls. The clearance of the peptide is delayed in deoxycorticosterone hypertensive rats. The circulating levels of the peptides are not augmented in rats with various types of the disease unless malignant hypertension is evoked.

In essential hypertensive humans, certain studies indicate that the circulating levels of endothelin are augmented modestly, to say the least, judging from the data reported (e.g., see References 62–65). However, an equally convincing number of studies failed to uncover augmented levels of the peptides in patients with moderate hypertension (e.g., see References 66–70). In the studies in which ET levels were augmented between circulating levels of endothelin and arterial blood pressure, rather inconclusive results were obtained. It should be stressed that if endothelial cells were to release the peptide or peptides preferentially toward the media, circulating levels of endothelins may not reflect accurately their local modulatory role, especially when the small distribution space between the endothelium and the underlying vascular smooth muscle is considered.

Although the circulating levels of endothelin are normal, or only marginally augmented, in most patients with moderate or established hypertension, this is not the case in malignant forms of the disease. Tumors secreting the peptide may cause hypertension, which subsides after removal of the tumor. Patients with severe hypertension and end-organ complications have higher plasma endothelin levels than mild hypertensive patients and normotensive subjects. Likewise, in pregnant women with preeclampsia or eclampsia, augmented plasma levels of endothelins have been reported repeatedly (e.g., see References 74 and 75).

Responsiveness to Endothelin

The depressor and vasodilator effects of ET-1 are present in the deoxycorticosterone acetate hypertensive rat and in the SHR and, if anything, are more pronounced in the spontaneously hypertensive strain than in normotensive controls. The release of atrial natriuretic peptides evoked by endothelin is larger in atra from SHR than WKY rats, although this probably does not contribute to the depressor effect of endothelin in the hypertensive strain. Judging from the endothelin-dependent relaxations that they cause in the aorta of the SHR compared with the WKY rat, the ability to release EDRF in response to ET-1 and ET-3 is certainly not curtailed in the SHR. A greater release of EDRF would help to explain why removal of the endothelium causes a greater potentiation of the contractile response to endothelin in the aorta of the SHR than that of the WKY rat, although this phenomenon is not observed in all types of spontaneous hypertension. If lower concentrations of endothelin inhibit peripheral adrenergic neurotransmission, the effect tends to be less pronounced in SHR than in WKY arteries.

The changes in pressor responsiveness to endothelin with hypertension are controversial. Thus, in the SHR, the increase in blood pressure and the peripheral vasoconstriction evoked by the peptide are reported to be similar, reduced, or marginally augmented. The reported changes in responsiveness of isolated blood vessels to the vasoconstrictor effects of endothelin are equally inconclusive. In the aorta of the adult SHR (compared with that of the WKY rat), the sensitivity to the peptide is enhanced, normal, or reduced.
could be explained by previous exposure to increased levels of endogenous endothelin leading to sustained receptor occupancy, receptor downregulation, or tachyphylaxis. In other blood vessels of the SHR, the reactivity to endothelin appears to be augmented, although this may be indirectly due to structural adaptations. In the mesenteric artery of the rat, endothelin augments the constrictor response to norepinephrine but not less so in the SHR than in the WKY rat. In two-kidney, one clip hypertensive rats, larger arteries exhibit a normal responsiveness to endothelin, whereas that of mesenteric microvessels is augmented. In the deoxycorticosterone acetate hypertensive rat, the responsiveness of the aorta to endothelin is augmented, and the activation of the phosphatidylinositol pathway accomplished by the peptide in mesenteric arteries is enhanced compared with normotensive controls. In arteries of the salt-sensitive Dahl rat, endothelin evokes larger contractions and augmented Ca²⁺ signals before but not after the induction of hypertension with a salt-containing diet.

Although ET-1, and to a lesser extent ET-3, can stimulate mitogenesis in vascular smooth muscle of the SHR, there is no evidence that this effect is more pronounced in the hypertensive strain than in normotensive rats.

Effect of Antagonists

Phosphoramidon, a nonselective antagonist of the conversion of big endothelin into endothelin, lowers blood pressure in the SHR. By contrast, anti-endothelin γ-globulins do not affect arterial blood pressure in the SHR.

Conclusion

Although the chronic infusion of ET-1 (and of larger amounts of ET-3) can cause sustained increases in arterial blood pressure, there are few indications that an augmented production of, or an increased sensitivity to, endothelins contributes to the pathogenesis of most forms of hypertension. Notable exceptions are tumors secreting the peptide and fulminant increases in blood pressure associated with eclampsia. Even in the latter case, it is unknown whether the augmented levels of endothelin explain, at least in part, the peripheral vasoconstriction or should be considered as an epiphenomenon resulting from end-organ damage. Obviously, until the effect of reasonably selective antagonists of the conversion or the vasoconstrictor action of the endothelins can be tested in hypertensive animals and humans, caution must be exerted when attempting to implicate them in the pathophysiology of hypertension (or of any vascular disease). Such caution does not take away from the fact that the discovery of the endothelins and the unraveling of their effects, has been, and still is, an extraordinary scientific adventure.

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