Potential Role of Endothelin in Hypertension
Controversy on Endothelin in Hypertension

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The hallmark of hypertension is an increase in peripheral vascular resistance. This increase is considered to be related to an increase in tone of resistance arteries as well as to structural changes (i.e., vascular remodeling) of these blood vessels. Accordingly, hypertension research has focused on identifying the mediator or mediators responsible for this phenomenon. Although several possible candidates have been extensively studied, in particular the renin-angiotensin system and catecholamines, no definite answer has been found. Hence, the search for additional mediators or the mediator causing the increase in peripheral vascular resistance in hypertension continues.

In addition to the increase in peripheral vascular resistance, hypertension is associated with cardiovascular complications such as myocardial infarction and stroke. In both syndromes, severe ischemia to these vital organs is responsible for the clinical syndrome. Again, structural and functional alterations of the supplying circulation are held responsible. In contrast to the increase in peripheral vascular resistance, however, these changes are primarily seen in certain (i.e., coronary and cerebral) vascular beds rather than in the entire circulation.

The question of whether endothelin is involved in hypertension, its complications, or both cannot be solved at this point; however, several aspects can be addressed.

Can Endothelin Induce Hypertension?

When infused intravenously, endothelin causes a rapid and transient vasodilation followed by a profound and long-lasting increase in blood pressure. This increase in blood pressure is dose dependent, occurs at much lower concentrations than with any other vasoconstrictor hormone, and also is remarkably long-lasting. In vitro experiments have demonstrated that this increase in blood pressure is related to profound vasoinhibition of resistance arteries of different vascular beds of the circulation. Although the vasodilator effects of endothelin are related to activation of endothelin B-receptors linked to the formation of prostacyclin and nitric oxide, the vasoconstriction is mediated by endothelin A-receptors on vascular smooth muscle. In addition, evidence is accumulating that endothelin B-receptors (or another type of endothelin receptor) on vascular smooth muscle also contribute to the vasoconstrictor effects of the peptide.

Endothelin not only exerts direct vasoconstrictor effects but also is able to potentiate at threshold and subthreshold concentrations contractile responses to other vasoconstrictor substances such as norepinephrine and serotonin. Hence, even small amounts of locally produced endothelin may act as a regulator of vascular reactivity in the circulation.

Of particular interest in the context of blood pressure regulation is the fact that endothelin (possibly not only by activating endothelin A- but also B-receptors) has profound renal effects (i.e., decrease in renal plasma flow and glomerular filtration rate) in a concentration range at which no generalized alterations in hemodynamics occur. As the kidney plays a crucial role in the chronic hemostasis of pressure-volume regulation, these effects may be extremely important for the development of hypertension.

Can Endothelin Induce Structural Vascular Changes?

Other interesting properties of endothelin are its proliferative effects, which have been demonstrated in vascular smooth muscle cells obtained from various blood vessels as well as in renal cells such as mesangial cells. Hence, the capacity of endothelin to regulate contractile responses as well as proliferation of vascular smooth muscle and its capacity to profoundly affect renal function and proliferation of mesangial cells make it a primary candidate as a mediator of essential hypertension.

Is There a Clinical Model of Endothelin-Dependent Hypertension?

Hemangioendotheliomas are tumors derived from cells of the blood vessel wall and are capable of synthesizing and secreting large amounts of endothelin into the circulation. Indeed, patients with hemangioendothelioma with high circulating levels of endothelin-1 and profound hypertension have been described. These patients, removal of the tumor normalizes both circulating endothelin levels and blood pressure (unless the tumor relapses, metastases occur, or both), indicating that the increased secretion of the peptide is indeed causally involved in the pathogenesis of this rare form of hypertension.
Another potential form of endothelin-dependent hypertension may be cyclosporine-induced hypertension. Indeed, in endothelial cells in culture, cyclosporine A increases endothelin release.26 Endothelin may also be the mediator of the renal vasoconstriction induced by cyclosporine in the rat.25 Furthermore, an endothelin receptor antagonist protects against acute cyclosporine toxicity in the rat renal circulation.26 As cyclosporine appears to increase circulating plasma endothelin levels also in patients (B. Huser, W.E. Haeefeli, M. Wenk, G. Noll, T.F. Lüscher, unpublished observation), these preliminary studies strongly support the notion that the endothelin vasoconstrictor axis may be activated during long-term cyclosporine therapy, particularly in the kidney, and hence may play a role in the development of cyclosporine-induced hypertension and nephrotoxicity.

Another clinical situation in which endothelin may contribute to increased blood pressure is disseminated intravascular coagulation.27 Indeed, in one patient during two episodes of disseminated intravascular coagulation, blood pressure rose in a parallel fashion with plasma endothelin-1 and big endothelin-1.27 As coagulation products such as thrombin are potent stimulators of endothelin production,3,28,29 the endothelin vasoconstrictor axis may importantly contribute to the clinical course of this syndrome.

Is the Response to Endothelin Altered in Hypertension?

Controversy exists in the literature as to the vascular response to endothelin in hypertension depending on the animal model of hypertension, the duration of hypertension, the experimental conditions used, and the blood vessels studied (for review, see Reference 28). Normal, increased, and depressed vascular responses have been reported. In isolated blood vessels, a marked reduction in the sensitivity of vascular smooth muscle to endothelin has been noted most commonly, particularly in the aorta and isolated mesenteric resistance arteries of spontaneously hypertensive,2 deoxycorticosterone acetate-salt hypertensive,30,31 and renovascular hypertensive (two-kidney, one clip)32 rats. A similar alteration in the sensitivity to endothelin also has been described in subcutaneous resistance arteries obtained from hypertensive humans.33

The depressed responsiveness of hypertensive blood vessels to endothelin may be related to downregulation of endothelin receptors on vascular smooth muscle, e.g., due to increased vascular production of the peptide or due to pressure itself. If the former possibility is correct, downregulation of endothelin receptors may represent a counterregulatory or adaptive mechanism during the development of hypertension protecting the organism from massive endothelin-induced vasoconstriction. Indeed, in mesenteric arteries in the aorta of deoxycorticosterone acetate-salt hypertensive rats, the endothelin content within the endothelium of the blood vessel wall is increased34; however, in young and adult spontaneously hypertensive rats, the vascular endothelin content is reduced relative to Wistar-Kyoto rats.35,36 This indicates that both an increased endothelin production and pressure itself may downregulate the expression of endothelin receptors in vascular smooth muscle. The latter possibility is further reinforced by the fact that antihypertensive therapy indeed restores the paradoxically reduced responsiveness to endothelin in the spontaneously hypertensive rat.35,36,37

The importance of a reduced vascular sensitivity to endothelin in isolated blood vessels for the in vivo situation has to be considered cautiously. Indeed, remodeling of the vascular media occurring in hypertension may, in particular in the resistance and microcirculation, considerably amplify vascular responses and result in an exaggerated active pressure development in intact vascular beds, even in the presence of a reduced sensitivity of the isolated blood vessel wall to endothelin.34 In the perfused, intact mesenteric vascular bed of the spontaneously hypertensive rat, pressure development during endothelin infusion is increased rather than depressed, as suggested by experiments in isolated mesenteric resistance arteries.38

Furthermore, it remains questionable whether these pharmacological experiments studying responses to endothelin at rather high concentrations have any physiological or pathophysiological meaning. Indeed, in most of these experiments, concentrations of the peptide are much higher than those found in plasma under most conditions. Hence, the indirect amplifying effects of endothelin occurring at very low concentrations might be more important. It is therefore of interest that, in contrast to the direct responses to endothelin, the potentiating effects of low and threshold concentrations of endothelin are increased with aging and hypertension,35,36 indicating that this indirect amplifying effect of endothelin may contribute to an increased vascular contractility as pressure rises and the blood vessel wall ages. This aspect may be of particular importance, as the circulating levels of endothelin remain quite low in hypertension (for review, see Reference 28), indicating a low production rate of the peptide in the blood vessel wall.

Interestingly, in mesenteric resistance arteries of the spontaneously hypertensive rat, angiotensin II increases preproendothelin messenger ribonucleic acid (mRNA) and via the production of endothelin indirectly augments contractile responses to norepinephrine in an endothelium-dependent manner.18 These experiments suggest that the endothelin pressor axis may not be similarly activated in all forms of hypertension, but its activity may depend on the circulating and/or local vascular levels of angiotensin II and other vasopressor hormones that induce preproendothelin mRNA such as arginine vasopressin and epinephrine.2,3,28

The vasodilator effects of endothelin are mediated by endothelium-derived nitric oxide and prostacyclin.5,9 This endothelium-dependent inhibition of the contractile effects of endothelin also is reduced in isolated hypertensive resistance arteries,3 indicating that the formation of prostacyclin and nitric oxide (via endothelial endothelin B-receptors9) and in turn the endothelium-dependent protection against endothelin-induced contraction, is depressed in hypertension as well.

For long-term regulation of blood pressure, alterations of the renovascular and renal responses to endothelin are of great importance. Interestingly, the response to endothelin appears to be increased in renal arteries obtained from the spontaneously hypertensive rat.29 This is in contrast to other peripheral arteries studied under in vitro conditions (see above) and could
indicate an augmented sensitivity of the hypertensive renal circulation to this potent vasoconstrictor peptide.

It remains to be determined whether these differences might be due to different upregulation and downregulation of endothelin B- and A-receptors in the renal circulation of the spontaneously hypertensive rat or whether this is related to other mechanisms. No data are available so far as to the renal effects of endothelin in human essential hypertension. If the response were increased, as it is in large conduit arteries of the renovascular bed of the spontaneously hypertensive rat (see above), such an alteration would clearly be capable of mediating long-term increases in arterial blood pressure.

In summary, the vascular response to endothelin clearly is altered in hypertension at the level of both the endothelium and vascular smooth muscle, although this alteration does not appear to be uniform within the circulation. The renal effects have not been extensively studied yet in hypertension, but alterations of this vascular bed may be very important for the long-term regulation of blood pressure.

Is Endothelin Production Increased in Hypertension?

As judged from the circulating levels of endothelin in human essential and rat experimental hypertension, endothelin production is not increased in this disease, unless renal failure, vascular disease such as atherosclerosis, or both are present (for review, see Reference 28). It is unclear at this point why certain groups have observed increased levels of endothelin in hypertensive patients. Although methodological problems cannot be excluded (in particular, cross-reactivity of certain of the antibodies used to measure endothelin-1 with isoforms and/or precursors of endothelin or with other peptides), it remains possible that certain forms of hypertension are associated with increased endothelin production (see above), whereas others are not.

Circulating endothelin levels, however, do not reflect the local vascular production of the peptide. Indeed, endothelin most likely acts in a paracrine fashion, regulating predominantly vascular smooth muscle cells nearby. As endothelial cells in culture appear to release twice as much endothelin in the abluminal (i.e., toward vascular smooth muscle) compared with the luminal direction, the circulating levels of the peptide may be well within the normal range even in the presence of an increased local vascular production of endothelin.

It recently has been suggested that two endothelin vasopressor systems may exist—one derived from endothelial cells and another derived from the neurohypophysis. Indeed, in the blood vessel wall, endothelin is primarily released by endothelial cells (which form exclusively endothelin-1), and this vascular production of the peptide requires de novo protein synthesis rather than release of endothelin from intracellular stores. In isolated vascular tissue, this process takes 2–4 hours. In contrast, in vivo, rapid changes of endothelin occur, which parallel those seen with vasopressin, suggesting that changes in endothelin secretion during change in posture and exercise may be related to release of the peptide from the neurohypophysis. These preliminary data indicate that the vascular endothelin system is more involved in long-term changes of vascular contractility, whereas neurogenic endothelin is involved in short-term adaptations of the cardiovascular system.

Hence, in summary, there is no proof yet for an overproduction of endothelin in hypertension, but indirect evidence such as a decreased responsiveness of vascular smooth muscle to the peptide may well reflect an increased local vascular production, at least in certain forms of hypertension. The fact that the indirect potentiating effects of endothelin are increased in hypertension further indicates that only very little overproduction would be required to upregulate vascular contractility, a hallmark of hypertensive blood vessels.

Is a Generalized Defect of the Endothelin-Vasoconstrictor System Required to Induce Hypertension?

Although peripheral vascular resistance is increased in hypertension, vasoconstriction is more important in some vascular beds than in others to maintain increased blood pressure. In particular, Hall and Guyton and Kon and Badr have suggested that the renovascular bed may be of primary importance in this context (see above).

In particular, in ischemia-induced renal failure of the rat and in cyclosporine nephrotoxicity, the production of or response to endothelin or both are altered. However, as judged from the spontaneously hypertensive rat, the production of endothelin in the renal medulla is reduced rather than increased.

Does Inhibition of Endothelin Production Reduce Blood Pressure?

Endothelin is formed from its precursor molecule big endothelin via endothelin converting enzyme. Although no specific inhibitors are available, phosphoramidone (a metalloprotease) has been shown to effectively reduce endothelin production in vitro. When infused in vivo into the spontaneously hypertensive rat, phosphoramidone appears to lower blood pressure. Although nonspecific effects cannot be excluded, these data at first would be compatible with the notion that endothelin contributes to the increased peripheral vascular resistance in hypertension.

Do Endothelin Antagonists Prevent or Reverse Hypertension?

With the development of specific endothelin antagonists in experimental hypertension, research tools to better address this question have become available. Endothelin antagonists may be effective in lowering blood pressure in established hypertension, the prehypertensive phase, or both when blood pressure starts to rise. Indeed, particularly in young rats, a supersensitivity of small blood vessels to endothelin can be noted. Selective endothelin A-receptor antagonists such as BQ-123 or FR139317 inhibit pressure responses to endothelin-1. Only very preliminary data on the effects of endothelin A-antagonists in experimental hypertension have been presented so far, and they do not allow a firm conclusion yet; however, it appears that BQ-123 significantly lowers blood pressure in stroke-prone spontaneously hypertensive rats but not in normal spontaneously hypertensive rats. This study would indicate that endothelin may be particularly important in malignant hypertension.
forms of hypertension as a mediator of both the increase in blood pressure and possibly also the complications thereof (see below). Also of interest in this context is the fact that the effects of cyclosporine A in the renal circulation appear to be preventable by the endothelin A-receptor antagonist BQ-123. 26 Although these antagonists may provide an approach to delineating the role of the endothelin A-receptors in the maintenance of high blood pressure in various models of experimental and human hypertension, it remains possible that endothelin A- and B-receptors are differentially regulated in different forms of hypertension as well as in different vascular beds across the circulation. Hence, this situation requires careful studies looking at the effects of systemic and local application of endothelin A- and B-antagonists as well as combined endothelin A- and B-antagonists and their effect on blood pressure and organ perfusion.

It is a common paradigm of hypertension research that the role of a regulatory system in the genesis of hypertension is revealed by the effects of an acute blockade of the system. However, considering the long-lasting effects of endothelin and the tight binding to its receptor, it remains possible that acute infusions of specific endothelin receptor antagonists do not provide appropriate answers in this context. Indeed, the pressure effects of endothelin in the human forearm in vivo as well as in experimental animals 2-4 persist for prolonged periods of time even after the infusion of the peptide has been stopped, demonstrating the tight binding of endothelin to its receptor. Hence, long-term therapy with receptor antagonists may be required to achieve a blood pressure-lowering effect. This concern is reinforced further by the relatively high concentrations of currently available endothelin antagonists required to fully inhibit the effects of the peptide in isolated blood vessels.

Furthermore, when the effects of endothelin antagonists in hypertension are being analyzed, it should be kept in mind that the endothelin pressor system may be very important for the development of hypertension at an early stage but may lose its importance in established hypertension. It is of interest in this context that resistance arteries of young animals are extremely sensitive to the vasoconstrictor effects of endothelin. 6

**Does Endothelin Contribute to Hypertensive Vascular Disease and Its Complications?**

Hypertension is associated with several forms of cardiovascular disease, such as angina pectoris, myocardial infarction, peripheral vascular disease, and cerebral vascular disease including transischemic attacks and stroke. Under most conditions, ischemia of vital organ tissue is responsible for the observed clinical symptoms. The underlying causes of ischemia are usually proliferative changes of the blood vessel wall, platelet disposition, and activation of the coagulation cascade as well as increased vasoconstrictor responses. Endothelin as a vasoconstrictor could contribute to ischemia and, through its proliferative effects, 20-22 could contribute to or facilitate the development of atherosclerotic plaques and renal failure. On the other hand, the peptide does not affect platelet function except through an indirect endothelium-dependent inhibitory effect (i.e., stimulation of prostacyclin and nitric oxide). Obviously, vaso-


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