Potential Role of Endothelin in Hypertension

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The hallmark of hypertension is an increase in peripheral vascular resistance.1 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.2-4 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 vasoconstriction of resistance arteries of different vascular beds of the circulation.5,6 Although the vasodilator effects of endothelin are related to activation of endothelin B-receptors7,8 linked to the formation of prosta-
cyclin and nitric oxide,5,9 the vasoconstriction is mediated by endothelin A-receptors on vascular smooth muscle.10 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.11-14

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.15-19 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.6 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.20-22 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.23 Indeed, patients with hemangioendothelioma with high circulating levels of endothelin-1 and profound hypertension have been described.23 In 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.23

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Supported by grants from the Swiss National Research Foundation (No. 32-32541.91), the Helmut Horten Foundation, and the Stanley Thomas Johnson Foundation.

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Another potential form of endothelin-dependent hypertension may be cyclosporine-induced hypertension. Indeed, in endothelial cells in culture, cyclosporine A increases endothelin release. Endothelin may also be the mediator of the renal vasoconstriction induced by cyclosporine in the rat. Furthermore, an endothelin receptor antagonist protects against acute cyclosporine toxicity in the rat renal circulation. As cyclosporine appears to increase circulating plasma endothelin levels also in patients (B. Huser, W.E. HaeFeli, 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. 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. As coagulation products such as thrombin are potent stimulators of endothelin production, a reduced sensitivity of vascular smooth muscle to endothelin also is reduced in isolated mesenteric arteries. 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, deoxycorticosterone acetate–salt hypertensive, and renovascular hypertensive (two-kidney, one clip) rats. A similar alteration in the sensitivity to endothelin also has been described in subcutaneous resistance arteries obtained from hypertensive humans.

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 increased; however, in young and adult spontaneously hypertensive rats, the vascular endothelin content is reduced relative to Wistar-Kyoto rats. 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.

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. 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.

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, 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. 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.

The vasodilator effects of endothelin are mediated by endothelin-derived nitric oxide and prostanoids. This endothelin-dependent inhibition of the contractile effects of endothelin also is reduced in isolated hypertensive resistance arteries, indicating that the formation of prostacyclin and nitric oxide (via endothelial endothelin B-receptors) 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. This is in contrast to other peripheral arteries studied under in vitro conditions (see above) and could...
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vascular smooth muscle) compared with the luminal
contrace, it remains possible that certain forms of hypertension
rat39 (see above), such an alteration would clearly be
capable of mediating long-term increases in arterial
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 atheroscle-
rosis, 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,46 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 endo-
thelial cells and another derived from the neurohy-
rophyphysis.41 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.29 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,42 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 contrac-
tility, 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 indi-
rect evidence such as a decreased responsiveness of
vascular smooth muscle to the peptide may well reflect
an increased local vascular production, at least in cer-
tain forms of hypertension. The fact that the indirect
potentiating effects of endothelin are increased in hy-
pertension further indicates that only very little over-
production 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 Guyton42 and
Kon and Badr64 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.24,26,43
However, as judged from the spontaneously hyperten-
sive rat, the production of endothelin in the renal
medulla is reduced rather than increased.44

Does Inhibition of Endothelin Production Reduce
Blood Pressure?

Endothelin is formed from its precursor molecule big
endothelin via endothelin converting enzyme.2,3,28,45
Although no specific inhibitors are available, phospho-
ramidone (a metalloprotease) has been shown to
effectively reduce endothelin production in vitro.45–47
When infused in vivo into the spontaneously hyperten-
sive rat, phosphoramidone appears to lower blood
pressure.48 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 antago-
nists for endothelin A- and B-receptors,12–14,49–60 re-
search 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-1.59,61

Only very preliminary data on the effects of endothe-
lin 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 signifi-
cantly lowers blood pressure in stroke-prone spontane-
ously hypertensive rats but not in normal spontaneously
hypertensive rats.62 This study would indicate that en-
dothenlin may be particularly important in malignant
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-acting 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 animals2-4 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 of limited use in clinical situations. In the setting of hypertension, the effects of endothelin antagonists are limited by its removal in the pulmonary circulation and by the release of prostanoids and endothelin-derived relaxing factor. Proc Natl Acad Sci U S A 1988;85:797-800


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Key Words • gene amplification • blood pressure • hypertension, mineralocorticoid • endothelins • renal circulation • rats, inbred SHR • rats, inbred WKY
Potential role of endothelin in hypertension. Controversy on endothelin in hypertension.
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_Hypertension._ 1993;21:752-757
doi: 10.1161/01.HYP.21.6.752

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/21/6_Pt_1/752.citation

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