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Review

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Role of endothelin in hypertension

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Since the discovery of endothelium-dependent relaxation of vascular smooth muscle [13] vascular endothelium has been recognized as an important functional unit involved in the regulation of vascular smooth-muscle tone. Relaxation results from release of a labile endothelium-derived relaxing factor probably identical to nitric oxide (reviewed in [14, 25]). In addition to endothelium-derived relaxing factor, endothelium-derived vasoconstricting factors, with a characteristically slow onset and long duration of action, have also recently been demonstrated [16, 21, 53, 56]. In 1988 Yanagisawa et al. [76] isolated a vasoconstrictive factor from the supernatant of cultured porcine endothelial cells and determined the amino acid sequence. It had 21 amino acid residues with free amino- and carboxy-termini and four cysteine residues which formed two disulfide bonds (positions 1–15 and 3–11) (Fig. 1) with a molecular weight of 2492 and was named endothelin (subsequently endothelin-1). Endothelin caused vasoconstriction of porcine right coronary artery segments with a concentration of peptide evoking 50% of maximum effect (EC_{50}) of 400 pM and a maximum tension comparable to KCl-induced contraction [76]. Sarafotoxin, the recently described venom of the burrowing asp *Atractaspis engaddensis*, has remarkable homology to endothelin isoforms 1–3 (Fig. 1) [31, 68]. Endothelin is formed by cleaving 164 amino acids from the 203 amino acid prepro-endothelin [by means of specific endopeptidase(s)] resulting in big endothelin (39 amino acids). Big endothelin is subsequently converted to endothelin by means of an endothelin-converting enzyme (Fig. 2).

Endothelin is now known to be a ubiquitous autacoid that is released from a number of endothelial cell sources, including porcine, but also from several renal cell lines, airway epithelial cells, and endometrial cells [36]. Endothelin gene transcription can be modulated in endothelial cells at the mRNA level by thrombin, adrenaline, angiotensin II, arginine vasopressin, transforming growth factor-β (TGF-β), the calcium ionophores A23187 and ionomycin, phorbol esters, and shear stress; its release can be inhibited by nitric oxide or atrial natriuretic factor [42, 44]. The endothelin gene (encoding the 212 amino acid precursor preproendothelin) has been localized to human chromosome 6 and shown to contain five exons (nucleotide sequences encoding the mature 21 amino acid endothelin-1 are contained within the second exon) [5]. Subsequently, three distinct human endothelin-related genes (ET-1, ET-2, ET-3) have been cloned

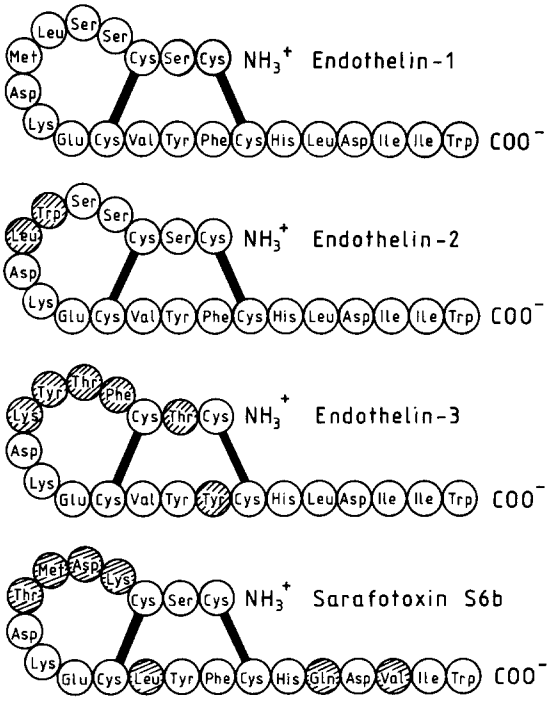

Fig. 1. Amino acid sequences of endothelin-1, endothelin-2, endothelin-3, and sarafotoxin S6b (venom of the burrowing asp *Atractaspis engaddensis*). *Hatched circles*, amino acids where endothelin-2, endothelin-3 und sarafotoxin S6b differ from endothelin-1

Abbreviations: SHR = spontaneously hypertensive rat; EC_{50} = concentration of peptide evoking 50% of maximum effect; DOCA = deoxycorticosterone acetate

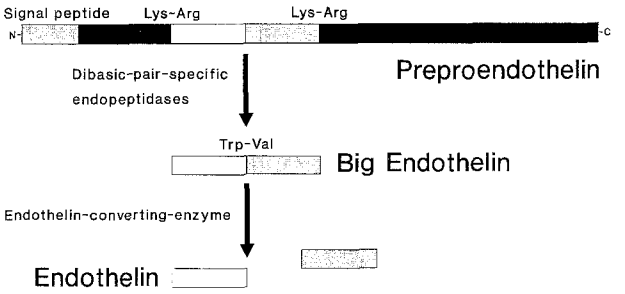

Fig. 2. Biosynthesis of endothelin. Preproendothelin is cleaved by dibasic-amino acid pair-specific endopeptidases to yield big endothelin. Big endothelin is cleaved at Trp-Val by an endothelin-converting enzyme, resulting in endothelin

by screening a human genomic DNA library under low hybridization stringency [26]. For the purpose of the present report endothelin-1 is designated as endothelin if not otherwise stated.

Because endothelin is the most potent vasoconstrictor known in man it has been hypothetized that endothelin may play an important role in hypertension. However, this question remains controversial even 5 years after isolation of the peptide. The present contribution briefly reviews data from in vitro and in vivo animal studies and studies in hypertensive patients in order to characterize the role of endothelin in hypertension.

In vitro studies

The marked vasoconstrictive effect of endothelin was first shown in porcine coronary arteries [76]. The maximum vasoconstrictive effect is comparable to that of high KCl and the EC_{50} of vasoconstriction in porcine coronary arteries is 400 pM [76]. The vasoconstrictive effects of endothelin have been confirmed by a number of laboratories in arterial as well as venous vessels of different vascular beds and species (reviewed in [36, 42, 44]). Dohi et al. [10] have shown in mesenteric resistance arteries of the spontaneously hypertensive rat (SHR) that angiotensin II induced vascular endothelin production augments contractility. Threshold concentrations of endothelin have been shown to sensitize vascular smooth muscle to, for example, norepinephrine and serotonin [10, 67]. In line with these findings, Webb et al. [74] have demonstrated in rabbit aorta that angiotensin II induced contractions can be inhibited with an endothelin receptor antagonist (BQ123).

In addition to the vasoconstrictive effects of endothelin, the peptide has been shown to be positive inotropic in isolated adult rat cardiomyocytes, with an EC_{50} of 50 pM [27, 34]. The positive inotropic effect of endothelin is mediated by sensitizing of cardiac myofilaments for calcium (in part due to endothelin-induced intracellular alkalosis) [27, 34, 36]. Both endothelin-mediated (direct and indirect) vasoconstrictive effects and positive inotropic effects might contribute to hypertension in animals or men.

In vivo studies

Yanagisawa et al. [76] were the first to demonstrate a marked increase in blood pressure after intravenous administration of 1 nmol/kg endothelin in the rat. The sustained and long-lasting increase in blood pressure is preceded by a transient vasodilatation most probably due to stimulation of release of endothelium-derived relaxing facor, atrial natriuretic factor, or prostacyclin [42, 76]. Subsequent studies showed dose-dependent increases in blood pressure as well as a very long duration of action in comparison to angiotensin II (duration of action > 2 h after an intravenous bolus of 2 nmol/kg) [45]. Calcium channel blockers antagonized effectively the chronic phase of increase in blood pressure [45]. Mortensen et al. [49] demonstrated that chronic intravenous administration for 7 days causes a dose-dependent, reversible hypertension in rats. Captopril has been shown to control endothelin-induced hypertension, indicating that stimulation of the renin-angiotensin system may be involved in endothelin-induced hypertension [47]. When dietary sodium intake was manipulated, the same investigators demonstrated the endothelin-infusion model of hypertension to be salt dependent [48]. In prehypertensive Dahl-salt sensitive rats reactivity (isometric contraction of vascular rings, increase in intracellular calcium) to endothelin was enhanced, and in hypertensive Dahl-salt sensitive rats medullary endothelin concentrations were increased in comparsion to salt resistant control animals [18].

Plasma endothelin levels were surprisingly lower in SHR and stroke-prone SHR in comparison to normotensive control rats, whereas deoxycorticosterone acetate (DOCA) salt sensitive rats had normal plasma endothelin levels [66]. Since the vascular reactivity for endothelin was increased in DOCA-salt sensitive rats, endothelin might play a role in sodium overload hypertension [66], possibly due to a decrease in plasma endothelin clearance [77]. Overall, there have been conflicting reports with regard to vascular sensitivity in different vascular beds and different strains of rats [42, 43].

In addition, there is good evidence that endothelin plays a role in central cardiovascular func-

tion. Increases in cerebrospinal endothelin levels are associated with pronounced hypertension and, on the other hand, phenylephrine-induced increase in blood pressure has been shown to cause a decrease in cerebrospinal endothelin levels [50]. Very recent studies have investigated the effect of endothelin receptor A antagonists on blood pressure. Bazil et al. [3] demonstrated that the endothelin receptor A antagonist BQ123 inhibits the pressor response of endothelin-1 but not that of endothelin-3. Administration of BQ123 produced a mild antihypertensive effect in low- to normal-renin (DOCA-salt sensitive and SHR) but not in high-renin (two-kidney, one-clip, and aortic ligated rats) models of hypertension [3]. Nishikibe et al. [52] demonstrated antihypertensive efficacy of BQ123 in stroke-prone SHR, a model of malignant hypertension, but not in normotensive controls or SHR. The results of Bazil et al. [3] and those of Batra et al. [2] suggest that not only endothelin receptor A but also endothelin receptor B is involved in vasoconstrictive responses of endothelin. Pollock et al. [54] reported the interesting observation that BQ123 completely inhibits the pressor response of endothelin in Sprague-Dawley rats but is unable to affect the renal vasoconstrictor effects (decreases in glomerular filtration rate, renal plasma flow, increases in renal vascular resistance). Endothelin had inconsistent effects on cardiac output in intact animals: transient increase in cardiac output and sustained decrease in cardiac output in most reports in conscious or anesthetized rats, dogs, and cats [17, 22, 24, 30, 35, 38, 40, 46, 55, 73]. Cardiac output in the intact animal is influenced by many different factors, including endothelin-induced increases in peripheral resistance, direct positive inotropic effects, hormonal effects of endothelin, and most importantly by constriction of the coronary arteries with subsequent ischemia. Neubauer et al. [51] demonstrated a parallel decrease of coronary flow and cardiac performance after administration of endothelin, using an isolated perfused rat heart. Despite a decrease in cardiac output and a marked increase of peripheral resistance isovolumic dp/dt_{max} was slightly increased in anesthetized rats [35]. The effects of intravenous endothelin are not necessarily representative of the effects of endothelin in situ, where an autocrine/paracrine mode of action is predominant. Therefore a dysregulation of local endothelin secretion might nevertheless, by means of its direct positive inotropic effects, contribute to hypertension.

Another important mechanism for endothelin-induced blood pressure regulation may be the well-known renal effects of endothelin: dose-dependent decreases in glomerular filtration rate, decreases in renal plasma flow, and increases in filtration fraction in the anesthetized rat and anesthetized dog and in the isolated perfused rat kidney, whereas the fractional excretion of sodium remains either unaffected or is moderately increased depending on the dose of endothelin and the animal model employed [1, 28, 33, 41, 65]. Natriuresis induced by low doses of endothelin [20, 28] may be counterregulatory to the vasoconstrictive effects of endothelin.

Judging from the above results, endothelin may play a role in hypertension (via its vasoconstrictive, positive inotropic effects, stimulation of aldosterone secretion, and affecting central cardiovascular function), and in the development of some forms of acute renal failure [33, 61]. At present, endothelin seems to contribute most to salt-sensitive forms of hypertension.

Human studies

Forearm blood flow is diminished in a dose-dependent manner with a long duration of action (in comparison to angiotensin II) after intra-arterial administration [8, 29], demonstrating that endothelin is a vasoconstrictor in man. Vierhapper et al. [71] demonstrated that exogenous endothelin causes hypertension in man. Yokokawa et al. [78] demonstrated that patients with malignant hemangioendothelioma are hypertensive and have elevated plasma endothelin levels. After surgery both blood pressure and plasma endothelin levels normalized. However, in one patient with recurrent disease both plasma endothelin levels and blood pressure increased again. Likewise, plasma endothelin levels are markedly elevated in women with preeclampsia/eclampsia and in patients with severe hypertension [11, 58, 69, 75]. In addition, endothelin may be involved in cyclosporine A induced hypertension since it has been shown that cyclosporine releases endothelin from human endothelial cells [7]. In rats treated chronically with cyclosporine an increased urinary excretion of endothelin has been shown [4]. A cyclosporine-induced increase in plasma endothelin levels in hypertensive cardiac transplant patients has been suggested [19], but the role of endothelin in cyclosporine-treated hypertensive patients has clearly to be investigated in further and more detailed studies. The endothelin receptor A antagonist BQ123 has been shown to be protective in cyclosporine-induced nephrotoxicity possibly by blocking the cyclosporine-induced vasoconstriction of the afferent arteriole [12, 37]. Finally, a role of endothelin in the erythropoietin-induced hyper-

tension of, for example, dialysis patients has been put forward [6].

Measurement of plasma endothelin levels in essential and secondary hypertension showed controversial results (normal or elevated concentrations) [9, 32, 57, 59, 60, 62, 70]. These differences may be due to different assays or patient samples. Lerman et al. [39] have shown that plasma endothelin levels are correlated with atherosclerosis, probably explaining part of the difference between different groups of hypertensive patients. In general, the validity of plasma endothelin levels as a marker of action is questionable since endothelin is thought to act predominantly in an autocrine/paracrine fashion. Supporting this assumption, Wagner et al. [72] have recently demonstrated a markedly higher endothelin release in abluminal direction in cultured human endothelial cells.

In addition to its cardiovascular effects (e.g. vasoconstriction/positive inotropy), its well-known (co-)mitogenic/atherogenic effects may be of importance as causative factor or with regard to progression of the disease [36]. Specifically, endothelin has been shown to promote proliferation of smooth-muscle cells, mesangial cells, and cardiomyocytes [23, 63, 64] – implicating a possible role of endothelin in the formation of atherosclerotic plaques as well as in cardiac growth and hypertrophy. Interestingly a role of endothelin in primary pulmonary hypertension has recently been suggested [15].

Conclusions

The demonstrated in vitro, in vivo, and human data are supportive of but in no way prove a role of endothelin in hypertension. Inhibitors of endothelin-converting enzyme and/or endothelin receptor antagonists are expected to contribute to the ultimate solution of this important question, especially when results become available during long-term treatment with these drugs. Short-term studies may not allow conclusions with regard to the role of endothelin in hypertension because of the known prolonged action of the peptide. Therefore the potential of endothelin receptor antagonists and/or endothelin-converting enzyme inhibitors as antihypertensive agents in human hypertension must be elucidated in further studies in experimental animals and in man.

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