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REVIEW

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Circulatory and myocardial effects of endothelin

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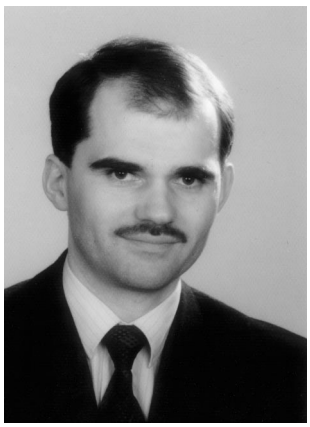

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Abstract The endothelin peptide family consists of the 21 amino acid isoforms endothelin-1, endothelin-2, endothelin-3, and sarafotoxin (a snake venom). Endothelin-1 has been isolated from the supernatant of endothelial cells and has subsequently been shown to be the most potent vasoconstrictor known to date and to be positively inotropic. This review summarizes some of the current literature pertaining to circulatory and myocardial effects of endothelins. Exogenously adminstered endothelin-1 has been demonstrated to increase peripheral resistance and blood pressure in a dose-dependent manner. However, during the first minutes of intravenous administration endothelins also decrease peripheral resistance and blood pressure, presumably due to the release of vasodilatory compounds such as nitric oxide, prostacyclin, and atrial natriuretic peptide. Endothelins appear to be involved in the pathogenesis of salt-dependent and renovascular animal models of experimental hypertension. Although endothelins appear to contribute to basal vascular tone, the role of endothelins in the pathophysiology of human hypertension remains unclear. In addition, a role has been suggested for endothelins in specific vascular lesions and inflammatory conditions (e.g., restenosis after coronary angioplasty, atherosclerotic coronary lesions, acute myocardial infarction, and vasculitis, glomerulonephritis). Endothelins are positively inotropic peptides in cardiac myocyte and papillary muscle preparations. They have also been demonstrated to induce hypertrophy of cardiac myocyte and may play an important role in ventricular processes that lead to chronic cardiac failure. The pathophysiological relevance of the endothelin system in human disease states is elucidated using selective (ET_A) and nonselective ($ET_{A/B}$) inhibitors of the endothelin receptors.

Key words Endothelin · Circulatory effects · Hypertension · Myocardial effects · Inotropy

Endothelin peptide family

Since the discovery of endothelium-dependent relaxation of vascular smooth muscle the vascular endothelium has

increasingly been recognized as an important functional unit involved in the regulation of vascular smooth muscle tone [1]. Relaxation results from release of a labile endothelium-derived relaxing factor which is probably identical to nitric oxide (reviewed in [2, 3]). In addition to endothelium-derived relaxing factor, endothelium-derived vasoconstricting factors with a characteristically slow onset and long duration of action have also been demonstrated [4, 5]. In 1988 Yanagisawa et al. [6] isolated a vasoconstrictive factor from the supernatant of cultured porcine endothelial cells and determined its amino acid sequence. It had 21 amino acid residues with free amino- and carboxy-termini and 4 cysteine residues which formed two disulfide bonds (positions 1–15 and 3–11) with a molecular weight of 2492, which they named endothelin (subsequently, endothelin-1). Endothelin causes vasoconstriction of porcine right coronary artery segments, with an EC_{50} of 400 pM and a maximum tension comparable to that in KCl-induced contraction [6]. Sarafotoxin, isolated from the venom of the burrowing asp *Atractaspis engaddensis*, and also reported in 1988, has a remarkable homology to endothelin isoforms 1–3 [7, 8]. Endothelin is formed by cleaving 164 amino acids from the 203 amino acid preproendothelin [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. Endothelin is now known to be a ubiquitous autacoid that is released from a number of endothelial cell sources as well as from various renal, airway, and endometrial cell lines [9]. Endothelin gene transcription can be regulated in endothelial cells at the mRNA level by thrombin, adrenaline, angiotensin II, arginine vasopressin, transforming growth factor β, the calcium ionophores A23187 and ionomycin, phorbol esters, and shear stress; its release can be inhibited by nitric oxide or atrial natriuretic peptide [9]. Endothelins act as "autacoids," i.e., in a autocrine/paracrine manner and not as a circulating hormone, since plasma levels are very low, and endothelial cells preferentially release the peptide in abluminal direction [9]. 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) [10]. Subsequently, three distinct human endothelin-related genes (ET-1, ET-2, ET-3) have been cloned by screening a human genomic DNA library under low-hybridization stringency [11]. For the purpose of the present report endothelin-1 is designated as endothelin unless otherwise stated.

Circulatory effects of endothelins

In their initial report in 1988 Yanagisawa et al. [6] demonstrated that endothelin-1 has a vasoconstrictive action and increases blood pressure in rats when given systemically (at a dose of 1 ng i.v.) in vivo. The vasoconstrictive effects of endothelin-1 in, for example, isolated porcine coronary artery rings are elicited at low concentrations of the peptide (EC_{50} of 400 pM), with a characteristically slow onset and a long duration of action [6]. Long-term intravenous administration of endothelin causes sustained hypertension in rats, and endothelins are thought to be involved in experimental models of hypertension that are salt dependent (e.g., deoxycorticosterone acetate salt hypertensive rats) [9]. In an experimental model of renovascular hypertension (one kidney/two clip rats) endothelins are suggested to be involved in the induction, but not maintenance, of hypertension [9, 12]. However endothelin-1 knockout mice have been shown to be mildly hypertensive, and transgenic rats expressing the human endothelin-2 gene under the control of the human endothelin promotor are normotensive [13, 14]. In animals with genetic manipulations of the endothelin gene the unexpected blood pressure responses may be due to counterregulation by other vasoactive systems or developmental defects. Endothelin-1 knockout mice have developmental defects of neural crest-derived craniofacial and cardiovascular structures and additionally impaired development of thyroid and thymus glands and impaired systemic growth [13, 15]. In contrast, transgenic rats expressing the human endothelin-2 gene have no known developmental defects but develop glomerulosclerosis due to a auto-/paracrine action of the peptide [14, 16]. The endothelin-2 gene has recently been shown to cosegregate with blood pressure in an F_2 population derived from a cross of the Dahl salt-sensitive rat and the Lewis rat, and the endothelin-3 gene cosegregates with blood pressure and relative heart weight in inbred Dahl rats [17, 18]. In patients with essential hypertension a moderate association has been demonstrated between a single base insertion in the untranslated region of exon 1 of the ET-1 gene and diastolic blood pressure [19]. Endogenous endothelin-1 has been shown to contribute to basal vascular tone in man and these effects are mediated by both endothelin receptors (ET_A and ET_B) [20, 21]. The endothelin-induced vasodilation (either during the first minutes after administration or at very low doses in some vascular beds) appears to be mediated by ET_B and ET_A receptors and requires an intact capability for the formation of nitric oxide and cyclo-oxygenase products [6, 9, 22, 23]. In humans the number of ET_A receptors predominates over the number of ET_B receptors (90% vs. 10% in renal arteries, 92% vs. 8% in renal veins, 95% vs. 5% in renal arcuate arteries, 85% vs. 13% in epicardial coronary arteries, 100% vs. 0% in intrarenal and intramyocardial resistance arteries and aorta) [24]. The effect of stimulation of ET_B receptors on vasomotion is mediated by both nitric oxide release from endothelial cells (with subsequent indirect vasodilation) and contraction of vascular smooth muscle cells (direct vasoconstriction). Nonselective blockade of ET_A and ET_B receptors may be less efficacious in vivo than predicted from some in vitro data, because potentially beneficial effects of ET_B receptors located on endothelial cells are also blocked [25–27].

The circulatory actions of endothelins are complex since endothelins have been shown both to sensitize vas-

cular smooth muscle cells to vasoconstrictors such as norepinephine, serotonin, and angiotensin II and to stimulate the release of aldosterone, nitric oxide, prostaglandins and atrial natriuretic peptide and inhibit the secretion of renin from isolated juxtaglomerular cells [9]. However the physiological relevance of inhibition of renin secretion from isolated renal juxtaglomerular cells by endothelins is thought to be minor [12, 28].

A marked increase in the gene expression of ET-1, ET-3, endothelin-converting enzyme 1, ET_A, and ET_B receptors has been demonstrated in rat carotid arteries after balloon angioplasty, suggesting an active role of the endothelin system in neointima formation [29]. Increased levels of endothelin immunoreactivity have been demonstrated in atherosclerotic coronary lesions of patients with acute coronary syndromes [30].

On the other hand, the release of endothelin from aortic endothelial cells by cytokines (e.g., tumor necrosis factor α and interleukin 1β) suggests that endothelins likely play a role in a number of vascular pathologies and inflammatory conditions (e.g., glomerulonephritis, vasculitis [31]).

The clinical implications of these findings in experimental animals and of studies in humans suggests the use of endothelin receptor antagonists or inhibitors of the endothelin-converting enzyme for the treatment of hypertension (e.g., salt-dependent forms, renovascular hypertension), for coronary artery disease (acute coronary syndromes, restenosis after coronary angioplasty), and for vasculitis.

Myocardial effects of endothelins

Ishikawa et al. [32] were the first to demonstrate a positive inotropic effect of endothelin-1 in isolated guinea pig left atria, with a slow onset, long-lasting mode of action, and an EC_{50} of about 1 nM. Endothelin-1 has subsequently been demonstrated to be a positive inotropic compound in a multitude of cardiac preparations, including isolated ventricular cardiomyocytes in vitro [33]. In isolated adult rat ventricular cardiomyocytes endothelin-1 has been demonstrated to be positively inotropic, with a low EC_{50} of about 50 pM. This inotropic effect is mediated by sensitizing cardiac myocytes to intracellular calcium $[Ca^{2+}]_i$, due in part to intracellular alkalinization induced by stimulation of the sodium-proton exchanger, and involves the stimulation of a pertussis toxin sensitive G protein and subsequent activation of phospholipase C [34, 35]. In human myocardium in vitro endothelin has been shown to exert a positve inotropic effect via sensitiziation of cardiac myofilaments to calcium and activation of the sodium proton exchanger [36, 37]. In contrast to the results obtained in vitro, clearly suggesting a positive inotropic effect of endothelins, the studies in vivo in rats, dogs, and cats yield contradictory results with regard to cardiac inotropy [9, 33]. Most studies show cardiac output to decrease with an increase in total peripheral resistance following an initial and short-lived increase in cardiac output [9, 33]. Neubauer et al. [38] demonstrated a parallel decrease in coronary flow and cardiac performance in an isolated perfused rat heart after administration of endothelin, indicating a secondary (ischemic) negative inotropic effect of endothelin. A recent study using open-chest rats demonstrated that despite a marked increase in peripheral resistance after administration of endothelin, isovolumic LVSP (peak LVSP) and the corresponding dp/dt_{max} (peak dp/dt_{max}) values were unchanged [39]. Inhibition of coronary constriction by adenosine unmasked a positive inotropic effect of endothelin-1 in anesthetized rats [40]. In addition, a positive inotropic effect was also demonstrated when employing the ET_B receptor agonist IRL 1620 since this compound has less vasoconstrictory potency than endothelin-1 [40, 41]. In addition to the inotropic effects of endothelins, positive chronotropic and indirect (via myocardial ischemia) and direct (QT prolongation) proarrhythmic effects have been demonstrated [42, 43]. A highly selective ET_A receptor antagonist LU 127043 has been shown to completely prevent the ET-1 induced sudden (ischemic) death [44]. In line with this finding Kojima et al. [45] demonstrated that the nonselective endothelin receptor antagonist TAK-044 reduces infarct size in rats, rabbits, and dogs when administered either before or after induction of acute myocardial infarction. Coronary vasoconstriction induced by cytokine-stimulated release of endothelin-1 in hemorhagic shock can be prevented by the nonselective endothelin receptor antagonist SB 209670 [46]. Endothelins also seem to be involved in cardiac hypertrophy and may play a role in cardiac failure [33, 36, 47, 48]. In rats in vivo cardiac endothelin-1 gene expression is increased in animals with pressure overload but not in animals with volume overload [49]. In deoxycorticosterone acetate salt hypertensive rats the development of cardiac hypertrophy is significantly attenuated by administration of an ET_A receptor antagonist [50].

Potential clinical implications of the above findings are blockade of the endothelin system during acute myocardial infarction, in order to prevent cardiac hypertrophy, and in the treatment of chronic cardiac failure.

Future prospects

The development of a variety of compounds selective for ET_A and ET_B receptors with either agonistic or antagonistic properties will facilitate experimental and clinical research dealing with the role of endothelins in physiology and pathophysiology/disease [51, 52]. An overview of some of the most common endothelin receptor antagonists and agonists is given in Table 1. In addition, IRL 1620 and BQ 3020 have been used as ET_B receptor agonists, PD 142893, SB 209670, and TAK-044 as mixed $ET_{A/B}$ receptor antagonists, LU 127043 as ET_A receptor antagonist, and IRL 1038 as ET_B receptor antagonist; however, IRL 1038 has recently been shown to have highly variable affinities between batches (therefore IRL 1038 should no

Table 1 Binding characteristics (affinities, in nM) of endothelin receptor agonists and antagonists (adapted from [52])

	ET_A receptor		ET_B receptor		
	K_i	IC_{50}	K_i	IC_{50}	
Endothelin-1	0.6–3.5	0.2–0.3	0.1–1.0	0.1–1.6	
Endothelin-3	83–900	5–150	0.1–2.0	0.1–1.6	
Sarafotoxin S6c	2800	1300	0.3	0.1–0.3	ET_B agonist
[$Ala^{1,3,11,15}$]ET-1		398		0.3	ET_B agonist
BQ 123	17–25	13–63	11 100–31 000	>10 000–100 000	ET_A antagonist
FR 139317	1	6–13	7300	>20 000–100 000	ET_A antagonist
BMS 182874	63	1600	55000	>10000	ET_A antagonist
BQ 788		1300		1.2	ET_B antagonist
Bosentan	6.5		343		$ET_{A/B}$ antagonist
Ro 462005		200–360		160–530	$ET_{A/B}$ antagonist
SB 209670	0.4	2.0	15	32	$ET_{A/B}$ antagonist

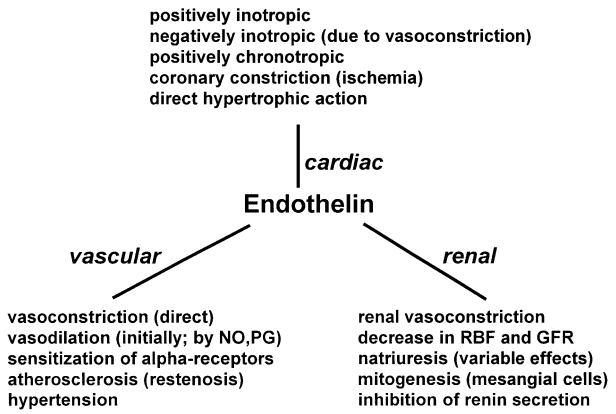

Fig. 1 Major circulatory, myocardial, and renal effects of endothelin. *PG*, Prostaglandins; *GFR*, glomerular filtration rate; *RBF*, renal blood flow

longer be used). Figure 1 gives a summary of major circulatory, myocardial, and renal effects of endothelins. As illustrated in this figure and in the evidence presented above, endothelins may be involved in acute and chronic renal failure, including the hepatorenal syndrome, cyclosporine nephrotoxicity, and glomerulonephritis, in (salt-sensitive) hypertension and renal hypertension, in coronary ischemia including myocardial infarction, in restenosis, and cardiac failure. The broad availability of the above receptor antagonists will allow the role of the endothelin system to be defined in human disease and will clarify whether blockade of ET_A receptors or of both ET_A and ET_B receptors should be preferred.

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