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Review

The Causal Relationship between Endothelin-1 and Hypertension: Focusing on Endothelial Dysfunction, Arterial Stiffness, Vascular Remodeling, and Blood Pressure Regulation

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Abstract: Hypertension (HTN) is one of the most prevalent diseases worldwide and is among the most important risk factors for cardiovascular and cerebrovascular complications. It is currently thought to be the result of disturbances in a number of neural, renal, hormonal, and vascular mechanisms regulating blood pressure (BP), so crucial importance is given to the imbalance of a number of vasoactive factors produced by the endothelium. Decreased nitric oxide production and increased production of endothelin-1 (ET-1) in the vascular wall may promote oxidative stress and low-grade inflammation, with the development of endothelial dysfunction (ED) and increased vasoconstrictor activity. Increased ET-1 production can contribute to arterial aging and the development of atherosclerotic changes, which are associated with increased arterial stiffness and manifestation of isolated systolic HTN. In addition, ET-1 is involved in the complex regulation of BP through synergistic interactions with angiotensin II, regulates the production of catecholamines and sympathetic activity, affects renal hemodynamics and water–salt balance, and regulates baroreceptor activity and myocardial contractility. This review focuses on the relationship between ET-1 and HTN and in particular on the key role of ET-1 in the pathogenesis of ED, arterial structural changes, and impaired vascular regulation of BP. The information presented includes basic concepts on the role of ET-1 in the pathogenesis of HTN without going into detailed analyses, which allows it to be used by a wide range of specialists. Also, the main pathological processes and mechanisms are richly illustrated for better understanding.

Keywords: endothelin-1; hypertension; oxidative stress; low-grade inflammation; endothelial dysfunction; arterial stiffness; arterial remodeling; blood pressure regulation

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1. Introduction

Hypertension (HTN) is one of the most prevalent socially significant diseases and is among the most important preventable risk factors for other diseases [1]. The heart, brain, kidneys, and peripheral arteries are often affected, which is a cause of early disability and reduced life expectancy in patients [2]. This necessitates that the prevention and treatment of HTN be among the top priorities of public health worldwide [3].

HTN is a heterogeneous disease with a complex pathogenesis. It is currently thought to be the result of disturbances in a number of neural, renal, hormonal, and vascular mechanisms regulating blood pressure (BP) [4], as crucial importance is given to the imbalance of a number of vasoactive substances, some of which are produced from the vascular endothelium [5]. The endothelium responds to humoral, neural, and especially hemodynamic stimuli, and regulates platelet function, inflammatory responses, growth and migration of vascular smooth muscle cells (VSMCs), and changes in the structure of the vascular extracellular matrix [6,7]. In addition to these functions, it modulates vascular tone by synthesizing and releasing a number of vasoactive factors that may have vasodilatory effects, such as nitric oxide (NO), prostacyclin (PGI_2), and endothelium-derived hyperpolarizing factor, and vasoconstrictor effects, such as thromboxane A_2 and endothelin-1 (ET-1) [8]. In

HTN, the delicate balance between vasodilators and vasoconstrictors is disturbed, leading to endothelial dysfunction (ED) with excessive release of vasoconstrictor substances, such as ET-1 [9,10].

ET-1 was first isolated in 1988 by Yanagisawa and colleagues from the culture supernatant of porcine aortic endothelial cells (ECs). It is composed of 21 amino acids and two intrachain disulfide linkages in the molecule [11]. Shortly after the discovery of ET-1, two other structurally similar isopeptides, named ET-2 and ET-3, were isolated [12]. ET-1 is the predominant isopeptide involved in regulating the cardiovascular system, and vascular ECs are the most abundant source of ET-1. In addition to ECs, ET-1 is expressed in a wide variety of cells including VSMCs, cardiomyocytes, fibroblasts, macrophages, epithelial cells in the lungs and kidneys, neurons, and glial cells [13]. The endothelins (ETs) are produced from their corresponding approximately 200-residue prepropolypeptides that are encoded by three distinct genes. These peptides are converted into inactive 38- or 39-amino acid intermediates called Big ETs (Big ET-1, Big ET-2, and Big ET-3) by furin-like endopeptidase. The Big ETs are then activated via proteolytic cleavage by the ET-converting enzymes (ECEs), ECE-1 and ECE-2 [14] (Figure 1).

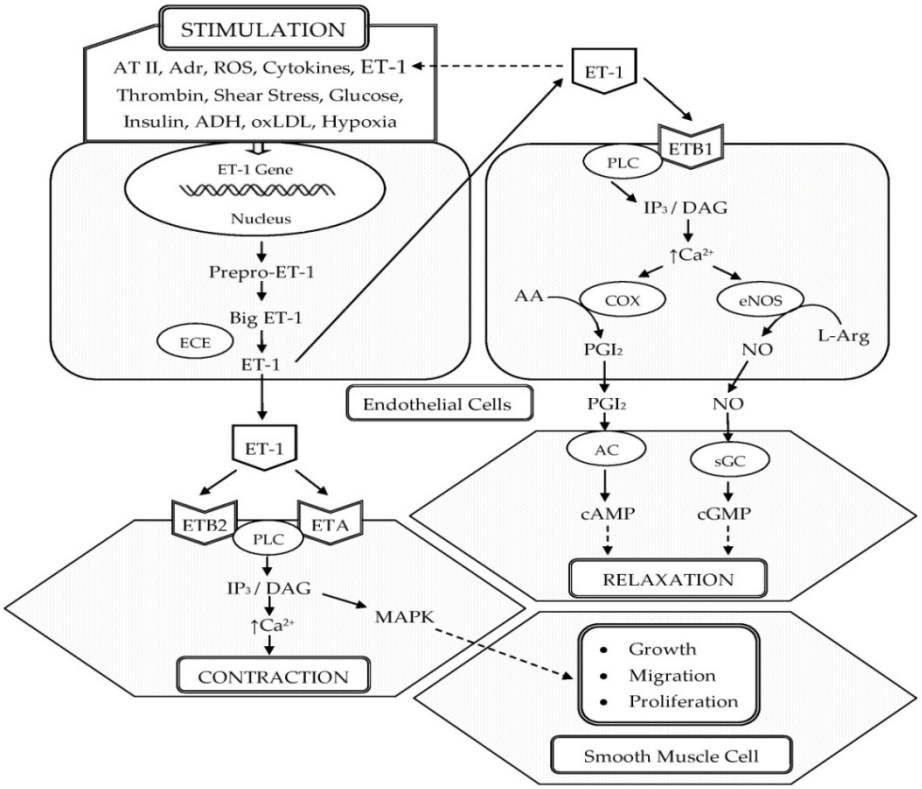

Figure 1. Schematic representation of the biosynthesis and vascular effects of ET-1 in endothelial and smooth muscle cells. ET-1 is generated by ECs in response to different stimuli. ET-1 mediates vasoconstriction by activating ETA and ETB2 receptors on VSMCs. Vasodilation by ET-1 is mediated through the activation of ETB1 on ECs, which increases the production of NO and PGI_2. In addition, ET-1 is a potent mitogen that simulates the growth, proliferation, and migration of VSMCs. Abbreviations: ET-1, endothelin-1; AT II, angiotensin II; Adr, adrenaline; ROS, reactive oxygen species; ADH, antidiuretic hormone; oxLDL, oxidized low-density lipoproteins; ECE, endothelin-converting enzyme; ETA, endothelin receptor subtype A; ETB1, endothelin receptor subtype B1; ETB2 endothelin receptor subtype B2; PLC, phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; Ca^{2+}, calcium ions; COX, cyclooxygenase; AA, arachidonic acid; PGI_2, prostacyclin; eNOS, endothelial nitric oxide synthase; L-Arg, L-arginine; NO, nitric oxide; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; MAPK, mitogen-activated protein kinase; ↑, increased.

In the vasculature, ET-1 acts on ETA and ETB (ETB1 and ETB2) receptors located on the VSMCs and ECs to induce vascular contraction or vasodilation [15]. Vasoconstrictive action of ET-1 is mainly mediated through ETA. ET-1–ETA interaction on VSMCs increases intracellular calcium, leading to the phosphorylation and activation of myosin light chain, which causes vasoconstriction [16,17]. In pathophysiological conditions, the expression of ETB2 on VSMCs is increased and ET-1–ETB2 interaction also promotes vasoconstriction [16]. ET-1 induces long-lasting vasoconstriction resulting from the slow dissociation rate from ET receptors [18]. In 40% of adults, a genetically prohypertensive phenotype is present or is the result of partially epigenetically mediated environmental effects. This is related to the predominance of vasoconstrictor actions of ET-1 mediated by ETA and ETB2 in VSMC, which is due to the hypertensive effect of increased endothelial expression of the ET-1 gene (*EDN1*) [19]. However, vasodilation by ET-1 is mediated through ETB1 on ECs, which increases the production of NO and PGI_2 [17] (Figure 1).

ET-1 is continuously released from the endothelial constitutive pathway. Low levels of ET-1 promote vasodilatation, whereas higher and pathophysiological concentrations increase BP and total peripheral vascular resistance [13]. In healthy volunteers, low doses of ET-1 infused into the brachial artery cause vasodilatation, consistent with ETB-mediated release of vasodilators, but this was followed by sustained vasoconstriction of the forearm vascular bed at higher doses because the peptide accessed the smooth muscle ETA receptors [20]. Thus, ETB-mediated release of NO and other vasodilators is crucial in acting as a counterregulatory pathway to limit ETA-mediated vasoconstriction. In pathophysiological conditions where there is ED with a loss of vasodilators, the vasoconstrictor and other pathophysiological effects of ET-1, such as cell proliferation, will be potentiated [13]. In patients with essential HTN, the activity of exogenous ET-1 is increased, similar, or decreased compared to normotensive subjects, depending on which vascular district or scheme of administration is considered [21].

2. Data on the Participation of ET-1 in the Development of HTN

Due to its ability to maintain basal vascular tone [22,23] and homeostasis of sodium and water [24,25], it is suggested that ET-1 is involved in some forms of HTN [26], which is supported by various experimental and clinical observations.

2.1. ET-1 in Experimental HTN

The role of ET-1 in HTN was initially observed in models of experimental HTN, and more recently by using genetically modified mouse models in which a component of the endothelin system was either knockdown or overexpressed in certain specific organs or tissues [27]. It should be noted that when ET-1 is overexpressed in the endothelium of transgenic mice, BP is significantly higher than in wild-type mice [28]. Moreover, selective knockout of ET-1 in the collecting duct of the nephron was associated with a higher BP and the development of salt-sensitive HTN [29]. A similar BP phenotype was obtained with the deletion of ETB or both ETA/ETB receptors in collecting duct cells, suggesting the important role of the renal endothelin system in the development of salt-sensitive HTN [30,31]. In non-transgenic animals, elevated ET-1 production was found in salt-sensitive and some other models of experimental HTN, such as deoxycorticosterone (DOCA)-salt HTN, DOCA-salt-treated spontaneously hypertensive rats (SHR), and Dahl salt-sensitive rats, 1-kidney 1 clip (1K1C) Goldblatt hypertensive rats, SHR 2-kidney 1 clip (2K1C) Goldblatt hypertensive rats, angiotensin II-infused rats, and stroke-prone SHR [32]. In the models known to overexpress vascular ET-1, BP significantly decreases upon the administration of selective ETA or mixed ETA/ETB receptor antagonists [33].

2.2. ET-1 in Human HTN

One of the first comparisons of ET-1 concentrations in people with HTN was made between pheochromocytoma patients and healthy controls. Higher levels of ET-1 were observed in patients with pheochromocytoma. In this report, the authors note that HTN

in patients with pheochromocytoma is mainly catecholamine dependent, but may be secondarily ET-1 dependent [34]. These data are supported by previously reported cases in patients with hemangioendothelioma who have significantly elevated ET-1 levels along with HTN [35]. Elevated ET-1 levels and high BP in patients from these studies returned to normal after surgical removal of the tumors [34,35]. In addition, resistant HTN with elevated ET-1 levels has been observed more frequently in patients of African-American descent or those with obesity, in whom the risk of developing cardiovascular and renal diseases is increased [36]. Furthermore, in individuals with normal BP, high plasma ET-1 levels are associated with the development of HTN [37]. The role of ET-1 in the development of the hypertensive process is also supported by data in patients with essential HTN or resistant HTN, which show that when treated with a nonselective ET-receptor antagonist bosentan [38] or with the selective ETA receptor antagonist darusentan [39–41], BP is significantly reduced. These data are also consistent with the meta-analyses, which show that HTN patients have higher plasma concentrations of ET-1 than control subjects [42]. Other authors have reported that the levels of ET-1 are normal in patients with essential HTN, but point out that the local levels of ET-1 in the vascular wall are elevated [36,43,44]. The controversial and not always consistent results regarding ET-1 concentrations in patients with HTN are probably related to two main reasons. The first is that its elimination from the blood is too fast (plasma half-life 1–2 min) [45]. The second is that the secretion of ET-1 by ECs is polarized mainly to the underlying VSMCs, leading to a minimal increase in its circulating levels [46]. Other possible causes of these disparate results are the specificity of the antibodies used in the immunoassay, the degree of cardiovascular damage, dietary salt intake, obesity, diabetes, and race [24]. All of the above findings support the hypothesis that ET-1 may have an important pathogenetic role in the development of HTN (Table 1).

Table 1. Studies on the contribution of ET-1 to the hypertensive phenotype in humans.

Study	Results	Significance
Saito, 1990 [47]	Patients with essential HTN showed a significant elevation in the plasma ET-1 level compared with age-matched control subjects.	$p < 0.01$
Shichiri, 1990 [48]	Patients with essential HTN had significantly higher plasma ET-1 levels than normal subjects.	$p < 0.025$
Oishi, 1994 [34]	In patients with pheochromocytoma, the hypertensive group had higher ET-1 than the normotensive group. Elevated plasma ET-1 concentrations returned to normal levels after surgical resection of the tumor.	Higher, but NS
Parrinello, 1996 [49]	ET-1 levels were significantly higher in obese hypertensives and obese normotensives than in lean normotensives. In addition, ET-1 levels were significantly higher in obese hypertensives than in obese normotensives.	$p < 0.05$
Amoroso, 1996 [50]	Patients with HTN had significantly higher plasma ET-1 concentration than normal subjects.	$p < 0.02$
Schneider, 2000 [51]	Basal ET-1 was significantly higher in hypertensive than in normotensive subjects, both in venous and arterial samples. There was no significant difference between venous and arterial ET-1 concentrations.	$p < 0.01$
Parissis, 2001 [52]	Patients with HTN showed significantly higher levels of ET-1 compared with normotensive controls.	$p < 0.01$

Table 1. *Cont.*

Study	Results	Significance
Kostov, 2014 [53]	Serum levels of ET-1 are significantly higher in patients with mild and severe HTN compared to the control group.	$p < 0.02$
Gu, 2015 [54]	Plasma ET-1 levels were higher in hypertensives than in controls.	$p < 0.001$
Kostov, 2016 [55]	Serum ET-1 concentrations were significantly higher in hypertensive patients with type 2 diabetes than in prehypertensive patients with diabetes and healthy normotensive controls.	$p < 0.05$

Abbreviations: ET-1, endothelin-1; HTN, hypertension; NS, not significant.

3. Role of ET-1 in the Pathogenesis of HTN

Based on the accumulating data from experimental and clinical studies, it can be assumed that there is a link between the increased biological activity of ET-1 and the development of HTN [44,55–58]. Probably, ET-1 is causally related to high BP through synergistic interactions of the following mechanisms: (1) participation in the development of oxidative stress and low-grade inflammation in the vascular wall with the occurrence of ED; (2) participation in the pathogenesis of arterial stiffness; (3) participation in the processes of arterial remodeling; (4) participation in the mechanisms regulating BP.

3.1. Participation of ET-1 in the Development of Oxidative Stress and Low-Grade Inflammation in the Vascular Wall with the Occurrence of ED

ET-1 is linked to the pathogenesis of HTN by means of oxidative stress in the vascular wall [59–62] and low-grade vascular inflammation [63–65], which are the main drivers of ED (Figure 2). The relationship between oxidative stress in the vessel wall and the development of HTN is shown in many experimental models, including in human HTN [66–69]. Various studies support the role of ET-1 in the formation of reactive oxygen species (ROS) and its relationship with oxidative stress and ED in humans. ET-1 stimulates the production of ROS in human endothelial and vascular smooth muscle cell cultures [70,71], as well as in isolated vessels [72–74]. It is assumed that the main mechanism for the increased production of ROS in HTN is increased expression of vascular NAD(P)H oxidase [60,62,75–77]. Increased production of ROS in the vascular wall leads to the activation of nuclear factor kappa B. This, in turn, stimulates the synthesis of pro-inflammatory cytokines, chemokines, and adhesion molecules, which are associated with the development of vascular inflammatory response. Low-grade inflammation localized in the vascular tissue is an important factor in the pathophysiology of HTN [78–80]. Actually, oxidative stress and inflammation form a vicious cycle in the development of ED, which is implemented with active participation of ET-1 [81–83]. ET-1 can activate macrophages that lead to the release of pro-inflammatory and chemotactic mediators, such as tumor necrosis factor alpha, interleukin (IL)-1, IL-6, and IL-8 [84–87]. In turn, these pro-inflammatory cytokines can stimulate the production of ET-1 [88], and this could lead to increased BP [51,89,90]. It is assumed that under physiological conditions, the vasodilating action of ET-1 may predominate, whereas under pathophysiological conditions, ET-1 may behave as a vasoconstrictor and play a role in the pathophysiology of HTN [19].

3.2. Participation of ET-1 in the Pathogenesis of Arterial Stiffness

A number of experimental and clinical studies have shown that ET-1 is responsible for maintaining arterial stiffness [27,91,92]. In ED, where the production of NO is reduced and that of ET-1 is increased, the balance is changed to increase arterial stiffness [57]. Arteriosclerosis [93–95] and its most common form, atherosclerosis [96–98], are the main pathological processes associated with increased hardness of the arteries (Figure 3). They significantly reduce the elastic properties of the arterial wall, which leads to an increase in

the pulse wave velocity of the large conductive arteries [99,100] and to the manifestation of isolated systolic HTN [101,102].

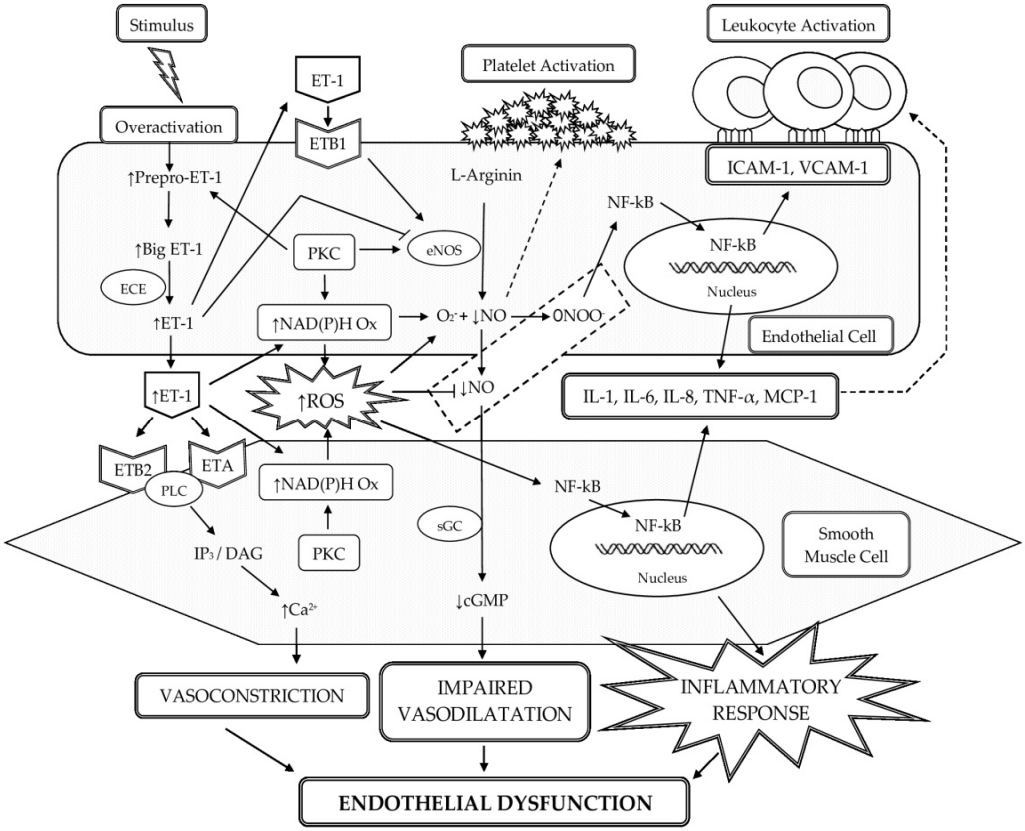

Figure 2. Schematic representation of the relationship of ET-1 with oxidative stress in the vascular wall, low-grade inflammation and ED. Increased production of ET-1 may decrease endothelial NO production by suppressing eNOS expression. In addition, ET-1 can mediate the formation of superoxide (O_2^-) by activating NAD(P)H oxidase, which may reduce the biological activity of NO in the vascular wall due to the formation of peroxynitrite ($ONOO^-$). In ED, the increased production of ET-1 shifted the balance of effects toward increased vasoconstriction, oxidative stress, and inflammation. Abbreviations: ET-1, endothelin-1; ECE, endothelin-converting enzyme; ROS, reactive oxygen species; ETA, endothelin receptor subtype A; ETB1, endothelin receptor subtype B1; ETB2 endothelin receptor subtype B2; PLC, phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PKC, protein kinase C; NAD(P)H Ox, nicotinamide adenine dinucleotide phosphate oxidase; ROS, reactive oxygen species; O_2^-, superoxide anion; $ONOO^-$, peroxynitrite; NF-κB, nuclear factor kappa B; IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor alpha; MCP-1, monocyte chemotactic protein-1; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule 1; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; Ca^{2+}, calcium ions; ↑, increased, enhanced activity; ↓, decreased.

3.2.1. Role of ET-1 in Arteriosclerosis

Arteriosclerosis is a pathological process of arterial aging that results from interactive genetic and epigenetic events within different cell types of vascular tissue and its extracellular matrix [95,103–105]. Increased ET-1 activity can contribute to vascular dysfunction and arterial aging through multiple pathways, such as direct hemodynamic effects, vascular oxidative stress, inflammatory activity, mitogenic VSMC stimulation, and fibrotic processes [106]. It has been found that the vasoconstrictor activity of ET-1 increases in the elderly [107,108] and that the synthesis of ET-1 is greater in cultured aortic ECs obtained from older compared with younger donors [109,110]. In addition, ET-1 can stimulate collagen synthesis by fibroblasts and the development of vascular fibrosis by activating ETA and ETB receptors [111–113]. In addition, ET-1 mediates transforming growth factor beta activation, which can further induce fibrosis [114].

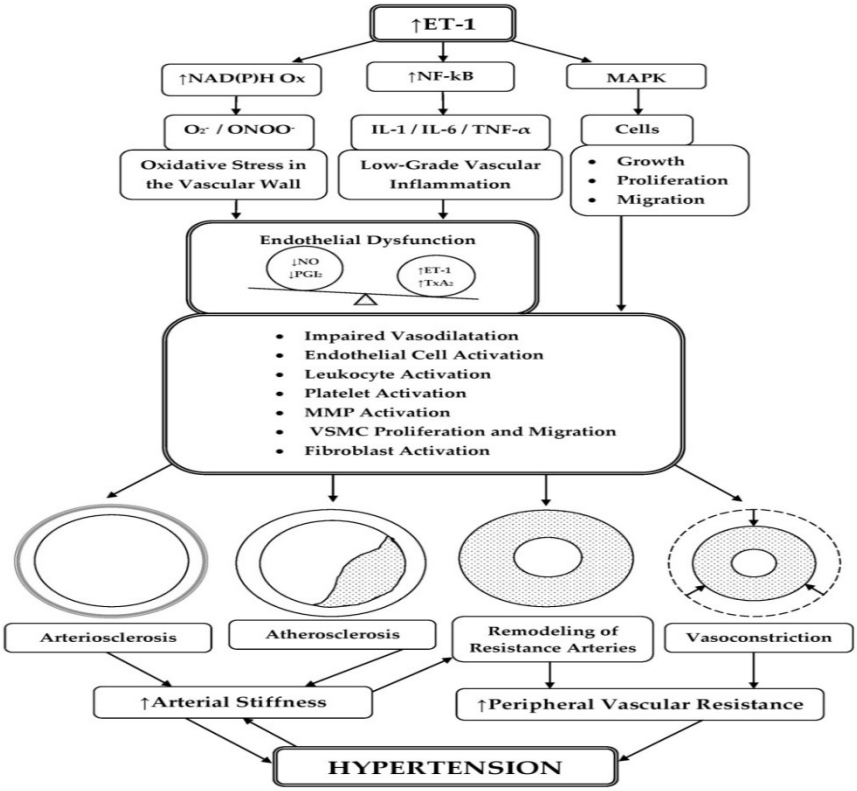

Figure 3. Schematic representation of the relationship of ET-1 with arterial stiffness and arterial remodeling as factors for the occurrence of HTN. Increased ET-1 activity may contribute to arterial stiffness in arteriosclerosis and atherosclerosis. These pathological processes significantly reduce the elastic properties of the central conduit arteries, which leads to the manifestation of isolated systolic HTN. Increased systolic and central pulse pressure may lead to eutrophic or hypertrophic remodeling of the small arteries. In particular, hypertrophic remodeling of resistance arteries is a signature of involvement of ET-1 in the hypertensive process. Abbreviations: ET-1, endothelin-1; NO, nitric oxide; PGI_2, prostacyclin; NAD(P)H Ox, nicotinamide adenine dinucleotide phosphate oxidase; O_2^-, superoxide anion; $ONOO^-$, peroxynitrite; NF-κB, nuclear factor kappa B; IL-1, interleukin-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; MAPK, mitogen-activated protein kinase; TxA_2, thromboxane A_2; ↑, increased, enhanced activity; ↓, decreased.

3.2.2. Role of ET-1 in Atherosclerosis

Atherosclerosis is a specific type of arteriosclerosis that is characterized by the build-up of intimal plaques inside the arteries and narrowing of their lumen. Previous studies on experimental animal models and humans have shown a key role of ET-1 in the pathogenesis of atherosclerosis [115–121]. In one classic experiment in which mice overexpressing human pre-proET-1 in the endothelium (eET-1 mice) have been crossed with atherosclerosis-prone mice (apolipoprotein E −/− mice) and fed a high-fat diet, the lipid-containing plaques in crossed animals (eET-1/apolipoprotein E −/−) have been increased dramatically more than in E −/− mice, along with an increase in BP. These findings suggest that increased endothelial expression of ET-1 accelerates the progression of atherosclerosis and may be the link between atherosclerosis and HTN [120]. Increased expression of ET-1 was also observed in human arteries at various stages of atherosclerosis [122]. Plasma concentrations of ET-1 also showed a positive correlation with the stages of atherosclerosis [117]. In addition, the expression of Big ET-1 and ECE-1 was increased in atherosclerotic arteries [123], and the ETA and ETB receptors were highly expressed in smooth muscle cells and foam macrophages at the sites of atherosclerotic lesions [124]. ET-1 may also be involved in the inflammatory process and migration of VSMCs, as well as in the phenotypic transformation

of VSMCs into proliferative synthetic cells that produce the extracellular matrix of the plaque [125].

3.3. Participation of ET-1 in the Processes of Arterial Remodeling

In HTN, the change in the structure of resistance arteries involves two processes: inward eutrophic remodeling and hypertrophic remodeling [126]. In eutrophic remodeling, the outer diameter and the lumen are decreased and the cross-sectional area of the media is unaltered. This type of remodeling predominates in resistant arteries of SHR and 2K1C Goldblatt hypertensive rats in which the renin–angiotensin system plays an important role. In humans, eutrophic remodeling is found in mild, essential HTN. In contrast, hypertrophic remodeling involves increased medial cross-sectional area and decreased lumen [127]. Hypertrophic remodeling of resistance arteries has been a characteristic finding in most rat models of severe HTN in which the endothelin system is activated [128,129], such as deoxycorticosterone (DOCA)-salt hypertensive rats [130], 1-kidney 1 clip (1K1C) Goldblatt hypertensive rats [131], and Dahl salt-sensitive HTN [132]. In humans, it can be found in secondary HTN, for example, in renovascular HTN or HTN associated with pheochromocytoma [133]. ET-1 plays an important role in abnormal vascular function and remodeling of resistance arteries [27] (Figure 3). ET-1 has a direct hypertrophic effect on the vasculature, in particular on the small arteries, and hypertrophic remodeling is a sign of involvement of ET-1 in the hypertensive process [133].

3.4. Participation of ET-1 in the Mechanisms of BP Regulation

BP regulation is an integrative process that involves complex interactions between the structures of the nervous system, cardiovascular system, hormones, and renal balance of fluids, which are in continuous feedback with specialized receptors related to monitoring the volume and hemodynamic parameters of blood circulation [134]. ET-1 can raise BP by disturbing some of these regulatory mechanisms (Figure 5), and in particular, maintaining intravascular fluid volume [24,25,135], peripheral vascular resistance [22,136,137], and cardiac contractility [138–140]. ET-1 is involved in maintaining intravascular volume by regulating the tubular reabsorption of water and electrolytes in the kidneys [24,25], affecting the production of aldosterone [141,142] and the secretion of vasopressin and natriuretic peptides [143,144]. ET-1 affects peripheral vascular resistance through its powerful vasoconstrictor effect, through the regulation of catecholamine secretion by the adrenal glands [145], as well as through its synergistic interactions with AT II [146,147] (Figures 4 and 5). In a number of pathological processes, overstimulation of ET-1/ETA signaling may upset the balance in the regulation of these mechanisms, which may subsequently lead to the development of HTN [24].

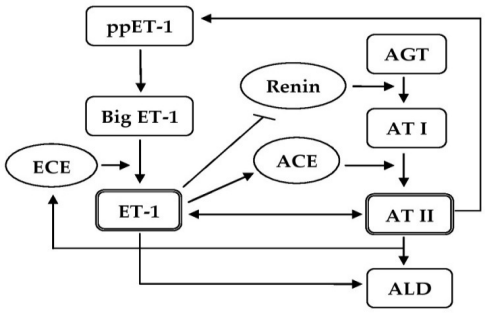

Figure 4. Schematic representation of synergistic interactions between ET-1 and AT II in the pathogenesis of HTN. ET-1 increases the formation of AT II by enhancing ACE activity. In turn, AT II increases the synthesis of ET-1 by enhancing ECE activity. ET-1 inhibits renin release, but can directly stimulate ALD production. Abbreviations: ET-1, endothelin-1; ppET-1, prepro-ET-1; ECE, endothelin-converting enzyme; AGT, angiotensinogen; AT I, angiotensin I; AT II, angiotensin II; ACE, angiotensin-converting enzyme; ALD, aldosterone.

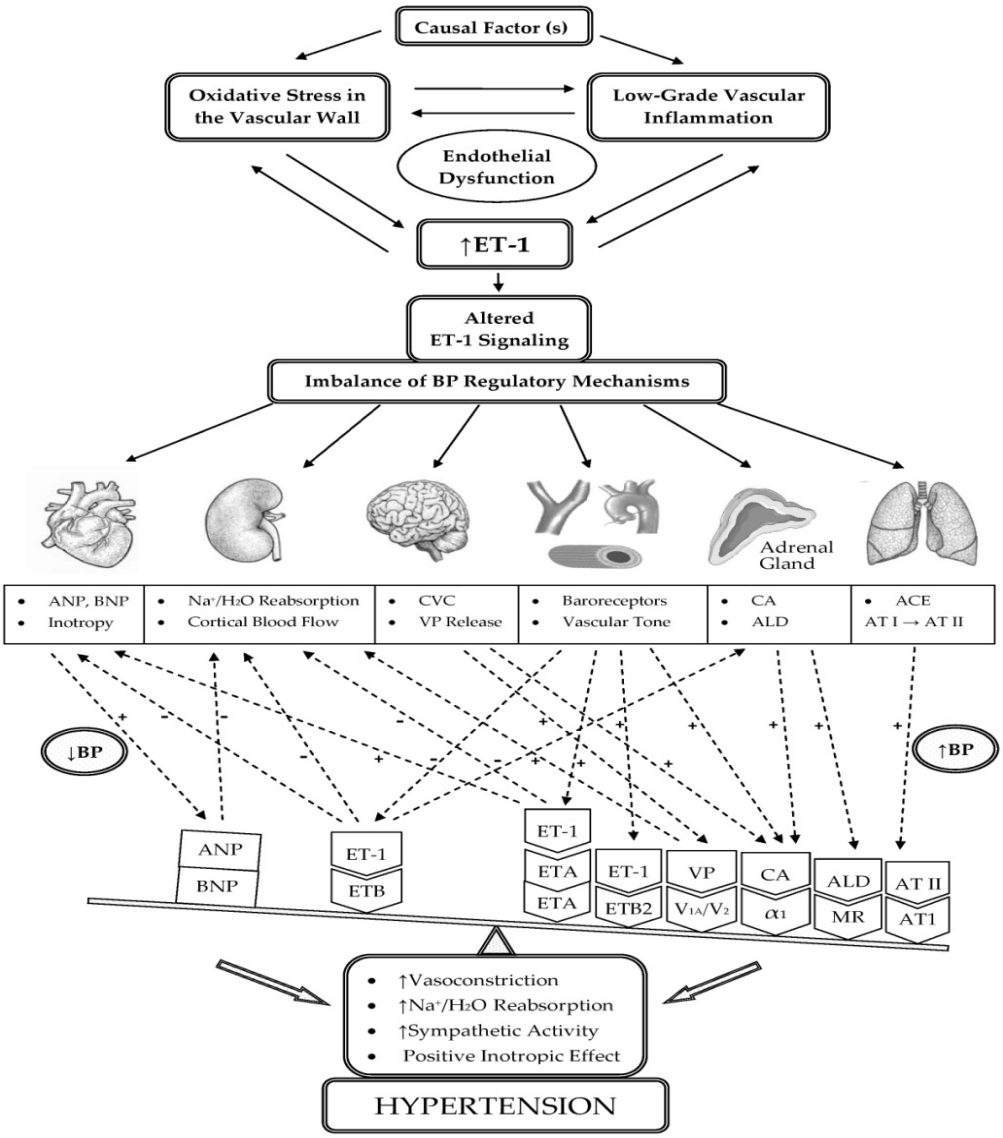

Figure 5. Schematic representation of integrated regulatory effects of ET-1 in HTN. Excessive activation of ET-1 leads to an increase in BP by enhancing the effects of ET-1/ETA signaling in the vasculature, adrenal gland, kidney, nervous system, and heart, which predominate over the BP-lowering effects of ET-1/ETB signaling. The cumulative effect is increased vasoconstriction, increased Na^+ and H_2O reabsorption, increased sympathetic activity, and a positive inotropic effect on the myocardium, which may lead to the development of HTN. Abbreviations: ET-1, endothelin-1; ETA, endothelin receptor subtype A; ETB, endothelin receptor subtype B; ETB2, endothelin receptor subtype B2; AT I, angiotensin I; AT II, angiotensin II; ACE, angiotensin-converting enzyme; AT1, angiotensin II receptor type 1; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; VP, vasopressin; V_{1A}, vasopressin 1A receptor; V_2, vasopressin 2 receptor; CA, catecholamines; α_1, alpha-1 adrenergic receptor; ALD, aldosterone; MR, mineralocorticoid receptor; CVC, cardiovascular center; H_2O, water; Na^+, sodium; +/−, activation/inhibition; ↑, increased.

In addition, ET-1 is involved in maintaining BP by regulating the cardiovascular center [148] and baroreceptor activity [149]. The paraventricular nucleus (PVN) is an important integrative center in the control of the cardiac sympathetic afferent reflex, which is a positive-feedback, sympathoexcitatory reflex. Abundant ET-1 expression is found in the PVN, especially in the parvocellular PVN cells [150]. The projections from the PVN to brain stem loci lead to increases in sympathetic efferent output and BP [24]. The lesion of the PVN prevents the intracerebroventricular administration of ET-1-induced increase in BP [151]. Projections from the PVN and area postrema also modulate the nucleus tractus solitarius, which, in turn, sends inputs to the PVN. Collectively, these regions

function to regulate sympathetic and parasympathetic outflow to the heart and sympathetic output to the vasculature, kidney, and elsewhere. Interactions between these regions are complex, involving both excitatory and inhibitory signals. ET-1 and its receptors have been implicated in the enhanced sympathetic excitability observed in models of salt-sensitive HTN such as the DOCA-salt and ETB-deficient rats [24]. Endogenous ET-1 appears to have a sympathoexcitatory effect in both normotensive and hypertensive subjects through ETA receptors, contributing to basal sympathetic vasomotor tone. Moreover, HTN shows an increased susceptibility to the sympathoexcitatory effect of endogenous ET-1. The discovery of enhanced biological activity of ET-1 on autonomic cardiovascular regulation, beyond the known effects on vascular tone, further reinforces the fundamental role of the endothelin system in the pathophysiology of HTN. Thus, treatment options aimed at counteracting the effects of ET-1 could have a beneficial effect on the adrenergic overactivity observed in HTN [152].

4. ET-1 as a Potential Therapeutic Target in HTN

Considerable progress has been made during the last two decades in characterizing the pharmacology of the ET-1 signaling pathway with the development of key compounds, such as selective ETA and ETB receptor antagonists (ERAs), dual endothelin receptor/angiotensin receptor antagonists (DARAs), together with selective ETB receptor agonists and radiolabeled analogs to accurately describe the ET system and its role in human and animal models of HTN [13]. The development of orally active ERAs that had become available by the mid-1990s allowed to study whether and how endogenous ET-1 contributes to the pathophysiology of essential HTN. Treatment with bosentan, a nonselective ERA, or darusentan, an ETA-selective ERA, decreased arterial BP in patients with essential HTN. Antihypertensive efficacy in patients with essential hypertension has also been reported for the DARA sparsentan [153]. Aprocitentan is a novel, oral, dual ERA that has demonstrated a more favorable tolerability and safety profile in early clinical trials compared with other ERAs [154]. ERAs remain an important part of pulmonary arterial hypertension (PAH) treatment. Treatment with approved ERAs, such as bosentan, ambrisentan, and macitentan, slows down PAH progression and relieves symptoms. However, more studies are needed to assess the benefits and safety of ERA treatment in patients with arterial HTN [155]. ERAs could play a particular role in the treatment of high-risk patients, such as those with resistant and salt-sensitive hypertension, those with progressive chronic kidney disease, those who develop hypertension after transplantation, or those with hypertension as part of the metabolic syndrome or diabetes [26]. The general side effects of ERAs are related to the vasodilator properties, including flushing, nausea, headache, nasal congestion, and peripheral edema, as well as hypotension and palpitations. Peripheral edema can be observed with the use of ERAs. Reduced hemoglobin levels and anemia can also appear during ERA treatment, as well as a reversible, dose-dependent elevation in aminotransferases [155].

5. Conclusions

ET-1 is involved in the physiological regulation of BP, thus exerting its influence on various processes: (1) it regulates vascular homeostasis, (2) regulates renal–endocrine mechanisms maintaining sodium and water balance, (3) modulates systemic hemodynamics, (4) affects the stiffness of the arteries, and (5) activates the natriuretic peptide system of the heart in chronic volume overload. In HTN, these regulatory mechanisms are disbalanced due to enhanced ET-1/ETA signaling in the vasculature, adrenal gland, kidney, nervous system, and heart. Impaired regulation shifts the balance toward increased vasoconstriction, increased Na^+ and H_2O reabsorption, increased sympathetic activity, and increased strength of cardiac contraction, which may lead to an increase in BP. In the long term, to these effects is added the increased systolic arterial pressure as a result of the structural changes in central and resistance arteries potentiated by ET-1, which leads to a permanent increase in BP and the development of HTN.

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