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Role of endothelin in hypertension: a review

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Abstract

Throughout, the global population hypertension is increasing at a tremendous rate day by day. A number of behavioral and genetic factors are responsible for essential hypertension. Numerous risk factors like obesity, smoking, dyslipidemia, insomnia and the lack of physical exercise are the contributing risk factors to the development of hypertension. Endothelin-1 is considered to be a powerful vasoconstrictor. The activity of the endothelin is regulated by its receptors ETA and ETB which both are G- protein-coupled receptors. Vascular calcification, fibrosis, and perivascular inflammation are core aspects of hypertension that really are important in vascular aging and lead to vascular stiffening. Preliminary research has implicated T lymphocytes in hypertension's pathogenesis. The remodeling of resistant arteries and aberrant vascular function are both significantly influenced by ET-1. Endothelial dysfunction and arterial remodeling in sunitinib-induced hypertension involved ET-1/ETAR-mediated vasoconstriction and vascular oxidative stress. ET-1 can raise blood pressure by disturbing, in particular, maintaining intravascular fluid volume, contraction of the heart, and resistance in the peripheral vascular system.

Keywords*:* Endothelin Type A Receptor, High Blood Pressure, Pathophysiology, Reactive Oxygen Species, Vasoconstriction

Introduction

Hypertension is a malady growing constantly worldwide (Forouzanfar *et al.*, 2017), as it is among the first five causes of mortality (Nahimana *et al.*, 2018), and is a severe disease that elevates the risk of ischemic stroke, myocardial infarction, hemorrhagic stroke, cardiac arrhythmias including atrial fibrillation heart failure, sudden death, etc., and even cognitive

decline and dementia (Luo *et al.,* 2021; Whelton *et al.,* 2018; Williams *et al.,* 2018; Pusuroglu *et al.,* 2016). A quarter of the global population of adults is supposed to constitute hypertensive individuals, and it is estimated that this proportion will increase to 1.5 billion by 2025 (Tabrizi *et al.,* 2016). Around 7.5 million deaths or 12.8% of the total of all annual deaths worldwide occur due to high blood pressure (WHO, 2010). Which increases up to 10.7 million deaths worldwide every year (Gungor & Derici *et al.,* 2019). Meanwhile, according to a recent study, the number of persons aged 30–79 years old with hypertension has risen from 650 million to 1.28 billion in the last 30 years, with more than 700 million of them uninformed of their condition. At a global level, hypertension affects 59% of women and 49% of men (Zhou *et al.,* 2021). Dong *et al.* (2022) reported that around 4% of urban Chinese children and adolescents aged 6 -17 years were hypertensive after three separate BP screenings in 2012 -2015. ISH was the most frequent form of hypertension in children.

Hypertension is the greatest cause of early death worldwide, according to the World Health Organization (WHO), with the majority of people (two-thirds) residing in low- and middle-income nations (WHO, 2021). For example, in 2018, a study in Peru found that the age-standardized prevalence of hypertension was 20.6 %, with 43.5 %, 20.6 %, and 5.3 % of people having disease knowledge, treatment, and management of arterial hypertension, respectively (Villarreal-Zegarra *et al.,* 2021). In Pakistan, however, hypertension affects 26.34 % of the population. Subgroup analysis revealed that urban dwellers had a greater prevalence of 26.61 % than rural dwellers which had a prevalence of 21.03 % (Shah *et al.,* 2018).

In most of the cases, 90% of the patients were affected with essential and only 10% with secondary hypertension. Essential is caused by a combination of genetic, and behavioral factors like increased saturated fat, nutritional sodium intake physical activity, and mental stress, and environmental variables (Carey *et al.,* 2018; Bolívar, 2013). Renal disease, endocrine diseases as well as other medical conditions, are results secondary to hypertension (Lin *et al.,* 2016).

Risk factors of hypertension

In genome-wide association studies (GWAS), a number of 120 loci have been associated to BP regulation, accounting for 3.5 percent of trait variations (Liu *et al.,* 2016). Hypertension is a silent killer (Prabakaran *et al.,* 2013). Although the majority of hypertensive individuals are asymptomatic, some suffer from headaches, loss of vision, lightheadedness, dizziness, or collapsing episodes (Singh *et al.,* 2017). HNT has many risk factors as it is reported by Niiranen *et al.* (2017) that family history of having hypertension before 55 years of age represents as the

strongest risk factor for hypertension in the offspring, independently of numerous known environmental variables. In the majority of studies, heritability estimates range from 35% and 50% percent in hypertensive patients (Ehret & Caulfield 2013). Blacks and non-Hispanic Black adults have more chance to develop Hypertensive compare to whites (Thomas *et al.,* 2018; CDC, 2010). In gender, men had a high risk of HNT than women at specific ages. The prevalence of HNT in older women eventually surpasses that of men (Choi *et al.,* 2017), especially after menopause, or after the age of 60. The older the participants were, regardless of gender, the more likely they were to have hypertension (Cutler *et al.,* 2008)

Obesity is increasingly recognized as one of the most critical risk factors, especially for hypertension and type-2 diabetes (Petrie *et al.,* 2018). Jiang *et al.* (2016) reported that obesity greater risk of premature death in HNT patients. Barath *et al.* (2007) reported that ET-1 plays a role in the development of juvenile hypertension associated with obesity because it enhanced ET-1-mediated vasoconstriction (Weil *et al.,* 2011) According to estimates, every 5% increase in weight leads to a 20–30% increase in the risk of HNT (Droyvold *et al.,* 2005). High sodium intake (Livingstone *et al.,* 2017; Margerison *et al.,* 2020), oily/ fried and fast food (Kang & Kim *et al.,* 2016; Shin *et al.,* 2013; Liu *et al.,* 2021), sugar-sweetened beverages (SSB) (Xi *et al.,* 2015; Kazi *et al.,* 2020), smoking (Bernabe & Carrillo, 2021; Bai *et al.,* 2017; Li *et al.,* 2021, Sedentary lifestyle (Kurjogi *et al.,* 2021; Al-Raddadi *et al.,* 2021) are the associated risk factors of HNT.

The Endothelin system

ET-1 constituted 21 amino acids and the other two isoforms of endothelin i.e. ET-2 and ET-3 had also been identified (Inoue *et al.,* 1989). ET-1 and ET-2 are very similar but ET-3 differs from ET-1 at 6 positions out of 21. In human chromosome 6, 1 and 20 contain the gene that encodes for ET-1, ET-2, and ET-3 respectively (Kawanabe & Nauli, 2011). ET-1 is the predominant endothelin isoform that is expressed in the cardiovascular system.

Endothelin-1 is a pleiotropic hormone, characterized in 1985 by Hickey. Yanagisawa *et al.* (1988) identified this endothelium-derived constrictor from the supernatant of porcine aortic EC and named endothelin (now named endothelin-1 or ET-1). Endothelin-1 (ET-1) was considered to be the strong vasoconstrictor yet discovered, capable of contracting a wide spectrum of mammalian blood vessels in vitro, containing arteries and veins of humans (Motte *et al.* 2006). The position of endothelin-1 rs5370 is on exon 5 (Dubovyk *et al.,* 2018). It is 100 times more powerful as compared to noradrenaline (Luscher & Barton, 2000).

Biosynthesis

Vascular smooth muscle cells VSMCs or cardiovascular cells are the most prevalent source of endothelin-1 synthesis as compared to other cells (Davenport *et al.,* 2016). Pre-endothelin levels (preproET-1) are predominantly regulated at the transcriptional level, with evidence involving numerous transcription factors including nuclear factor kappa B, activator proton 1 (AP- 1), FOXO1, HIF-1, GATA2, and VezF1. Endothelial cells consistently manufacture and secrete ET-1. Prepro-ET-1 cleaved to the inactive 38-amino-acid precursor big-ET-1 by an enzyme furin convertase. Mature ET-1 is then produced by the action endothelin-converting enzyme (ECE) (Chester & Yacoub, 2014).

Angiotensin II (Ang II), thrombin, hypoxia, and other factors can trigger the release of ET-1 (Stow *et al.,* 2011). Atrial natriuretic peptide (ANP), prostaglandin E2 (PGE2, prostaglandin E1), and nitric oxide (NO) are all inhibitors of endothelin production. Recent research indicates that EC, which is the primary biological producer of ET-1, may store the created ET-1 (Kisanuki *et al.,* 2010).

ET-1 performed its biological effect via signal transduction mechanism by two specific receptors in the circulation, i.e. ETA and ETB. The ETB receptors are similarly responsive to all three ETs while the ETA receptors are extremely selective for ET-1 (Schneider *et al.,* 2007). The VSMCs have the ETA receptor, which is primarily used by ET-1 to initiate contraction (Kowalczyk et al., 2015). The ETB receptors are found on the endothelium, where they mediate relaxation by releasing PG (prostacyclin) and NO as well as on VSMCs, where it promotes vasoconstriction (Aflyatumova *et al.,* 2018).

Signal Transduction Pathway

Two distinct receptors in the circulation, ETA and ETB, used a signal transduction pathway to carry out ET-1's biological function (Zhang et al., 2011). The α and βγ subunits of one of many potentially related G-proteins get dissociated when ET-1 binds to the ETA receptor (Smrcka, 2008).

Activation of the ETA receptor stimulates phospholipase C (PLC) that results in the conversion of phosphatidylinositol 4.5-bisphosphate (PIP2) into inositol 1,4,5- triphosphate (IP3) and diacylglycerol (DAG). IP3 stimulates the outflow of Ca2+ intracellular stores from the sarcoplasmic reticulum (SR). Furthermore, the ETA receptor acts on nonselective plasmalemmal Ca2+ channels and also causes the in-word movement of Ca2+ from outside via Ca2+ channels. This results in increased concentrations of Ca2+ that lead to the contraction of VSMC.

Additionally, the ETA receptor that actively promotes cell proliferation. Protein kinase C (PKC), which controls endothelin's mitogenic activity, is activated by the production of DAG. PKC also triggers a Ca2+-independent mechanism for VSMC contraction that involves calponin phosphorylation. The Ras/Raf/MEK/MAPK cascade is activated by PKC, which then impacts on gene transcription. Caldesmon is phosphorylated by MAPK, also increasing VSMC contraction. (Hynynen & Khalil 2006; Khalil 2011; Lima *et al.*, 2011; Kastin 2013; Gomez *et al.*, 2014).

ETB receptors include two subtypes: ETB_1, which is expressed on endothelial cells and evokes NO-mediated vasodilation (Aflyatumova *et al.,* 2018), and ETB_2, also present in VSMC, which causes contraction (Hynynen & Khalil 2006; Yanagisawa *et al.*, 1988). Stimulation of ETB_1 receptors also results in the release of other vasodilatory factors such as prostacyclin (PGI_2) and endothelium-derived hyperpolarizing factors. Furthermore, it is hypothesized that endothelial ETB receptors participate in the clearance of ET-1; however, the results are not conclusive (Kawanabe & Nauli 2011; Ohkita *et al.* 2012).

Mechanism

The normal plasma level of ET-1 is low (0.4–8.1 pg/ mL), which is insufficient to activate endothelin receptors. Activation of ET_A and ET_B receptors on VSMCs initiates vasoconstriction and cell proliferation, whereas activation of the ET_B receptor on endothelial cells mediates vasodilation by releasing nitric oxide (NO) and prostacyclin (Lüscher & Barton 2000; Mazzuca & Khalil 2012). However, in pathological conduction, the balance between the vasodilator and vasoconstrictor is impaired, among them ET-1 and NO play the most important role. It is believed that the ET-1 levels are higher in the intercellular space between endothelial cells and vascular smooth muscle cells (Piechota *et al.,* 2010). The plasma level of ET-1 is also high in HNT patients, it is observed in various studies but a contradiction is also noticed. The up-regulation of endothelin-1 inhibits the NO production and leads to vasoconstriction and multiple pathological conditions.

All organ systems experience a natural decline in function as people age. However, cardiovascular pathologies like hypertension have been shown to hasten and initiate this process at an earlier age (Sun *et al*., 2015; Cunha *et al*., 2017). This is characterized by changes in collagen and elastin found in the extracellular matrix (ECM) (Duca *et al*., 2016) that lead to progressive pathological remodeling and stiffening in the vascular system (Wilk *et al*., 2013). Both cellular senescence as well as growth arrest plays a role in this (Cannata *et al*., 2016).

The Effects of Hypertension on Remodeling and Vascular Aging

It is clear that hypertension provides insight into the vascular remodeling that occurs with age because it is linked to accelerating vascular aging (Lakatta *et al*., 2007). Medical trials, such as MOBILIZE (maintenance of stability, independence, living, intelligence, and zest in the elderly), have shown that inflammatory and oxidative processes with reactive oxygen species (ROS) increased production are involved in this process. MOBILIZE found, in about 700 participants, that plasma concentrations of oxidative stress-regulated inflammation marker dissolved vascular cell adhesion molecule-1 were correlated with mobility problems (Tchalla *et al*., 2015).

Vascular calcification, fibrosis, and perivascular inflammation are core aspects of hypertension that really are important in vascular aging and lead to vascular stiffening (Guzik *et al*., 2017). Vascular smooth muscle cell (VSMC) stiffness and adhesion are both

elevated by hypertension, and these effects are amplified with advancing age (Sehgel *et al*., 2015). Endothelial dysfunction, oxidative stress, and endothelin-1 expression are all accelerated in elderly hypertensive mice. The induction of Galpha12/13, Galphaq/Galpha11, and Galpha12/13 in smooth muscle is a key mediator of these pathways (Wirth *et al*., 2016).

Additionally, it has been demonstrated that ascorbic acid improves individuals with essential hypertension's endothelium-dependent vasodilation (Guan & Wang, 2020). But increased ROS generation and a weakened antioxidant system may play a role in endothelial dysfunction in hypertensive individuals and causes arteriosclerosis along with the increase in peripheral resistance in hypertensive subjects. Instead of reduced NO generation, increased NO inactivation brought on by excessive ROS production may play a significant part in the impairment of endothelium-dependent vasodilation (Förstermann *et al*., 2017).

ET-1 Involvement in Arterial Remodeling Processes

Resistance artery structural changes in HTN occur as a result of two processes: inward eutrophic remodeling and hypertrophic remodeling (Lyle *et al*., 2019). The cross-sectional area of the media is unaffected whereas the outer diameter and lumen are reduced in eutrophic remodeling. In resistant arteries of SHR and 2K1C Goldblatt hypertensive rats, this kind of remodeling predominates, and the renin-angiotensin system is crucial in this process. In mild, essential HTN in humans, eutrophic remodeling is present. In contrast, hypertrophic remodeling results in a decrease in the lumen and an increase in the medial cross-sectional area (Intengan *et al*., 2000).

Most rat models of severe HTN in which the endothelin system is activated exhibit hypertrophic remodeling of resistance arteries (Schiffrin *et al*., 2001); examples include deoxycorticosterone (DOCA)-salt hypertensive rats (Li *et al*., 1994), 1-kidney 1 clip (1K1C) Goldblatt hypertensive

rats (Abdel-Sayed *et al*., 2003), and Dahl salt-sensitive (Ikeda *et al*., 1999). It can be discovered in secondary HTN in people, such as renovascular HTN or HTN linked to pheochromocytoma. The remodeling of resistant arteries and aberrant vascular function are both significantly influenced by ET-1 (Amiri *et al*., 2004). Hypertrophic remodeling is a marker of ET-1 involvement in the hypertension process since ET-1 has a direct hypertrophic effect on the vasculature, especially on the tiny arteries (Nishidi *et al*., 2012).

Oxidative stress links hypertension's inflammatory mechanisms

There is mounting evidence linking inflammation with hypertension (Nosalski *et al*., 2017). Inflammatory reactions and cytokines cause, and are a direct result of, oxidative stress, making it a pivotal factor in the pathophysiology (Mikolajczyk *et al*., 2016). Given the involvement of immunosenescent T cells in hypertension and the vulnerability of T cells to age-related alterations, this is of crucial importance (Czesnikiewicz *et al*., 2007). In addition to causing vascular alterations, the tumor necrosis factor- and interferon- that they produce functionally distinguish these cells from others (Itani *et al*., 2016). Even though, preliminary research has implicated T lymphocytes in hypertension's pathogenesis (Yodoi *et al*., 2015). Recent clinical research has shown that their function is linked to their strong cooperation with various components of innate, cellular, and humoral immunity. Specifically, B cells appear to play a pivotal role in hypertension, and their absence is linked to lower levels of oxidative stress in the blood vessels (Chan *et al*., 2015).

Recent research has linked pattern recognition receptors like TLR4 to controlling antigen-presenting cell activity in hypertension. Important in cardiac and renal damage and possibly in the development of high BP, this triggers inflammatory signaling via My88D and activation of nuclear factor-B (Biancardi *et al*., 2017,). In a TLR4-dependent fashion, adipokines like resistin may cause hypertension (Jiang *et al*., 2016). Toll-like receptor 4 (TLR4)-dependent activation of toll-interleukin receptor domain-containing adaptor protein-inducing interferon- contributes to angiotensin II-induced hypertension and cardiac hypertrophy, as reported in a recent issue of Hypertension. However, there is a contradiction in that the MyD88-dependent pathway can also suppress prehypertensive responses (Singh *et al*., 2015).

Recent breakthroughs in the study of hypertension have revealed unique oxidative and inflammatory pathways of vascular dysfunction that cause accelerated vascular aging in hypertension and related cardiovascular illnesses (Passacquale *et al*., 2016). These include microvascular dysfunction in the brain, heart, and systemically, along with the rapid progression

of atherosclerosis and an increase in cardiovascular risk. Creating innovative, selective inhibitors of NADPH oxidases that do not compromise Nrf2- or Nox4-dependent cardiovascular protective mechanisms is an urgent medical necessity. New treatment strategies against inflammation in cardiovascular disease and oxidative stress may be made possible by nanotechnologies (Lewis *et al*., 2016).

Overall, both pathogenically and phenotypically, vascular aging is associated with hypertension in the clinic. In addition, elevated BP itself has been shown to hasten the aging of the blood vessels, putting people at risk for issues in their target organs. For these reasons, various clinical trials are currently underway to discover biomarkers of accelerated vascular aging, validate the prognostic significance of vascular stiffness and allow vascular aging treatment and prevention (Sun *et al*., 2015; Sehgel *et al*., 2015).

The endothelin-induced vascular oxidative stress

Ang II and ET-1 are two circulating vasoactive factors that are particularly significant in the pathophysiology of hypertension (Beevers *et al*., 2011). In addition to activating Ca2+ channels, ET-1 and other vasoactive peptides also result in intracellular Ca2+ accumulation, which in turn activates Ca2+-sensitive Nox isoforms in the vasculature, particularly Nox5. This results in a feed-forward system that amplifies oxidative signaling and vascular damage.

In hypertension, many of these systems are over-regulated. Transient receptor potential melastatin 2 cation channel was recently discovered to be a crucial Ca2+ channel that links Ca2+ and redox signaling, a process that is heightened in VSMCs in hypertension (Lopes *et al*., 2020). Alterations in phosphatase activity are also linked to vascular oxidative stress, which enhances kinase signaling and causes vascular damage in hypertension (Camargo *et al*., 2018).

Blood pressure increased in mice with endothelial-specific overexpression of ET-1 in a way that was reliant on the ET type A receptor (ETAR). Reduced renal artery flow, stiffness of the mesenteric small artery, endothelial dysfunction, vascular inflammation, and oxidative stress were all linked to this (Coelho *et al.*, 2018). Cardiovascular and coronary microvascular dysfunction in mice with pressure overload and left ventricular hypertrophy brought on by transverse aortic coarctation was causally related to increased ET-1-induced vasoconstriction, Rho kinase activation, and oxidative stress (Tsai *et al*., 2017).

Endothelial dysfunction and arterial remodeling in sunitinib-induced hypertension involved ET-1/ETAR-mediated Nox activation and vascular oxidative stress (Colafella *et al*., 2020). Although ROS are produced as a result of ET-1, these ROS themselves control the endothelin system.

Plasma oxidative stress indicators and ET-1 levels were decreased in Fischer 344 rats given a superoxide dismutase mimic (AEOL 10150) in a dose-dependent manner (Ganesh *et al*., 2016). In hypertension patients, serum ET-1 levels are clinically linked with oxidative stress indicators (Plooy *et al*., 2017).

Effect of ET-1 on Blood pressure Regulation

The regulation of BP is contributed by complex relations between the CV system, hormones, part of the brain, and renal balance of water and electrolytes. They feedback with specialized receptors related to regulating the volume and hemodynamic factors of blood circulation (Nishida *et al.,* 2012). ET-1 can raise BP by disturbing, in particular, maintaining intravascular fluid volume (Speed *et al.*, 2015), contraction of the heart, (Drawnel *et al.*, 2013; Zolk *et al.*, 2014), and resistance in the peripheral vascular system (Cardillo, 1999; Nohria *et al.*, 2003). ET-1 is involved in maintaining intravascular volume by regulating water and electrolytes reabsorption in the tubular part of the renal system (Kohan *et al.*, 2011; Speed *et al.*, 2015) , affecting the production of aldosterone (Bernabe & Carrillo, 2021; Berillo *et al.*, 2021) and the secretion of vasopressin and natriuretic peptides (Fu *et al.*, 2018). Impaired regulation shifts the balance toward increased vasoconstriction as in the peripheral vascular system increased the resistance through its powerful vasoconstrictor effect, through synergistic interaction catecholamine and interactions with angiotensin II (Delong and Sharma, 2019)., increased reabsorption of fluid and electrolyte, increased sympathetic activity, and increased strength of cardiac contraction, which may lead to an elevation in BP. 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 (Kohan *et al.,* 2011).

Hypertension often leads to serious complications like cardiovascular disorders, cognitive decline, dementia, and sudden death as well. The plasma level of ET-1 is also high in HNT patients, it is observed in various studies but a contradiction is also noticed. The upregulation of endothelin-1 inhibits NO production and leads to vasoconstriction and multiple pathological conditions. Hypertrophic remodeling is a marker of ET-1 involvement in the hypertension process since ET-1 has a direct hypertrophic effect on the vasculature, especially on the tiny arteries. Reactive oxygen species (ROS) are produced as a result of ET-1; these ROS themselves control the endothelin system. Hence, increased ROS generation and a weakened antioxidant system may play a role in endothelial dysfunction and causes arteriosclerosis along with the

increase in peripheral resistance that leads to hypertension. In hypertension patients, serum ET-1 levels are clinically linked with oxidative stress indicators. ET-1 is involved in maintaining intravascular volume by regulating water and electrolyte reabsorption in the tubular part of the renal system affecting the production of aldosterone and the secretion of vasopressin and natriuretic peptides. Impaired regulation shifts the balance toward increased vasoconstriction which may lead to an elevation in BP.

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