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Role of the Endothelin System in Sexual Dimorphism in Cardiovascular and Renal Diseases

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Abstract

Epidemiological studies of blood pressure in men and women and in experimental animal models point to substantial sex differences in the occurrence of arterial hypertension as well as in the various manifestations of arterial hypertension, including myocardial infarction, stroke, retinopathy, chronic kidney failure, as well as hypertension-associated diseases (e.g. diabetes mellitus). Increasing evidence demonstrates that the endothelin (ET) system is a major player in the genesis of sex differences in cardiovascular and renal physiology and diseases. Sex differences in the ET system have been described in the vasculature, heart and kidney of humans and experimental animals. In the current review, we briefly describe the role of the ET system in the cardiovascular and renal systems. We also update information on sex differences at different levels of the ET system including synthesis, circulating and tissue levels, receptors, signaling pathways, ET actions, and responses to antagonists in different organs that contribute to blood pressure regulation. Knowledge of the mechanisms underlying sex differences in arterial hypertension can impact therapeutic strategies. Sex-targeted and/or sex-tailored approaches may improve treatment of cardiovascular and renal diseases.

Graphical Abstract

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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In the current review, we will briefly describe the role of the ET system in the cardiovascular and renal systems, and update information on sex differences at different levels of the ET system including synthesis, circulating and tissue levels, receptors, signaling pathways, ET actions, and responses to antagonists in different organs that contribute to blood pressure regulation.

Keywords

endothelin; sex; cardiovascular system; kidney; cardiovascular diseases

1. Introduction

According to the definition provided by the Department of Reproductive Health and Research, World Health Organization (source: WHO, Gender mainstreaming for health managers: a practical approach, 2011, available at: <http://www.who.int/gender-equity-rights/knowledge/glossary/en/>), “sex” refers to the different biological and physiological characteristics of males and females, such as reproductive organs, chromosomes, hormones, etc, whereas “gender” refers to the socially constructed characteristics of women and men – such as norms, roles and relationships of and between groups of women and men. Therefore, because the current review is focused on biological rather than social topics, the word “sex” will be used throughout this review.

Arterial hypertension is the single most important contributing factor to cardiovascular morbidity and mortality worldwide [1, 2]. Epidemiological studies of blood pressure in men and women and in experimental animal models point to substantial sex differences in the occurrence of arterial hypertension [3, 4]. In addition, sex differences are found in the various manifestations of arterial hypertension, with men having a higher risk of coronary heart disease than women, especially at younger ages [5], and women having greater susceptibility for developing stroke [6] and heart failure [7, 8].

The endothelin (ET) system is an important contributor to sex differences in arterial hypertension [9]. Sex differences in the ET system have been described in the vasculature

and heart of human subjects and animals with arterial hypertension. Extensive evidence supports the central role of the kidney in the control of blood pressure and sodium (Na^+) homeostasis. Elevated blood pressure is associated with a rightward-shift in the pressure-natriuresis curve. Sex differences in multiple intra renal signaling systems that contribute to blood pressure control, including ET, renin-angiotensin-aldosterone and nitric oxide signaling systems, have also been described.

In the current review, we focus on the ET system as a major player in the genesis of sex differences in cardiovascular and renal diseases. We will briefly review the role of ET in the cardiovascular and renal systems, and update information on sex differences in the ET system that may impact development and progression of arterial hypertension and renal diseases.

2. Role of ET-1 in the cardiovascular and renal systems

Since the discovery of endothelin-1 (ET-1) in 1988 [10], research has shown that the ET system includes a family of three endogenous 21-amino-acid peptides, ET-1, ET-2 (or vasoactive intestinal contractor, the mouse analogue) and ET-3, which interact with two G-protein-coupled receptors (GPCR) subtypes, ET_A and ET_B . ET-1 is generated from its precursor pre-pro-ET-1 in a two-step enzymatic pathway to produce the 38-amino-acid precursor big ET-1 or pro-ET-1, which is subsequently cleaved to yield ET-1 by an endothelin-converting enzyme (ECE). Alternatively, chymase, an enzyme found in mast cells, as well as matrix metalloproteinases (MMPs) can cleave big ET-1 to yield a 31-amino-acid ET-1(1-31) and a 32-amino-acid ET-1(1-32), respectively.

ET-1 is continuously released by constitutive pathways and most ET-1 actions are paracrine or autocrine in nature. Whereas most of ET-1 effects are produced by activation of ET_A receptors, ET_B receptors on vascular endothelial cells are particularly important in terminating ET-1 actions. ET_B receptors remove ET-1 from the circulation, a process followed by ET-1 internalization and lysosomal degradation by the carboxypeptidase cathepsin A (reviewed by Barton and Yanagisawa [11]).

2.1. In the myocardium

ET-1 plays key roles in many aspects of cardiac physiology and pathology. ET-1 is vital for aortic arch formation during development, is required for cardiomyocyte survival and prevents myocyte loss during aging. ET-1 modulates coronary blood flow by regulation of vascular tone as well as cardiac muscle function (please refer to Drawnel et al. [12], for a very in-depth and elegant review on the cardiac ET system).

In the heart, ET-1 is synthesized and secreted by endothelial cells, myocytes and fibroblasts. ET_A receptors are highly expressed in cardiac myocytes, and both ET_A and ET_B receptors are expressed in cardiac fibroblasts and endocardial endothelial cells. The human heart has a high density of ET receptors and endothelial cells generate the peptide within the lining of the coronary circulation and the endocardium [12]. Binding of ET-1 to ET_A receptors on cardiomyocytes activates many signaling pathways, including protein kinase C (PKC), mitogen-activated protein kinases (MAPK) and G-protein receptor kinase (GRK), which

produce intracellular calcium release, reactive oxygen species (ROS) generation and receptor internalization [13, 14]. ET-1 has positive inotropic and chronotropic effects, for example, ET-1 increases cardiac contractility and heart rate, and induces arrhythmias [15, 16]. ET-1 plays a role in cardiac remodeling, particularly maladaptive cardiac hypertrophy. Circulating plasma levels of ET-1 are positively correlated with severity of cardiac diseases and are considered a prognostic indicator of heart failure. It is well established that ET-1 induces left ventricular hypertrophy and congestive heart failure and that ET antagonists have positive effects in the treatment of pulmonary arterial hypertension, which is characterized by right ventricular heart failure (the most common cause of death in patients with this disease). However, ET antagonists have failed in the treatment of left ventricular heart failure [12, 17].

2.2. In the vasculature

In the vasculature, ET_A receptors are mainly expressed in vascular smooth muscle cells (VSMCs), favoring short-term control of muscle tone and contributing to vasoconstriction, as well as long-term control of cell growth, adhesion, migration and intercellular matrix deposition [18]. ET_B receptors are also expressed in VSMCs with similar actions. ET_B receptors are expressed in the endothelial cells and, upon activation by ET-1, induce release of endothelial-derived vasodilator substances, including nitric oxide (NO), to favor vasodilation. The overall effect of ET-1 on vascular tone results from a balance between a direct vasoconstrictor effect via ET_A and ET_B receptors on smooth muscle cells and the vasodilation mediated by endothelial ET_B receptors in endothelial cells (please refer to Rautureau & Schiffrin [19] for an in-depth and elegant review on the vascular ET system).

ET-1 also induces the production of growth factors and inflammatory mediators. ET-1 favors deposition of extracellular matrix components, including collagen and fibronectin, and stimulates ROS production by endothelial and smooth muscle cells. ET-1 activates transcriptional factors and stimulates the expression of many pro-inflammatory cytokines, including Interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor- α (TNF- α), and enzymes such as inducible nitric oxide synthase (iNOS), cyclo-oxygenase (COX), NADPH oxidases; and the production of adhesion molecules by endothelial cells leading to monocyte migration [19].

2.3. In the renal system

The renal ET-1 signaling system is involved in the control of renal hemodynamics as well as tubular function through activation of ET_A and ET_B receptors. ET-1 results in strong and sustained vasoconstriction, oxidative stress [20, 21], nephrin shedding, expression of pro-inflammatory factors in podocytes [22, 23], proteinuria [24], and reduces medullary blood flow through activation of ET_A receptors [25]. On the contrary, activation of renal ET_B receptors induces vasodilation and inhibits Na⁺ and water reabsorption resulting in subsequent natriuresis and diuresis. The ET_B receptor-mediated natriuretic effects are NOS1-dependent [26]. Pharmacological blockade and genetic modification of the ET_B receptor function induces salt-sensitive hypertension [27]. Collectively, ET-1 appears to have paradoxical effects on blood pressure regulation by acting either on the renal cortical ET_A receptors promoting hypertension or renal medullary ET_B receptors promoting hypotension.

2.4. In the immune system

A large body of evidence has accumulated over the last 10 years indicating that ET-1 is an important stimulus for inflammatory pathways. This is evident in a wide range of organ system diseases [28]. ET-1 induces proinflammatory mechanisms, superoxide anion production, cytokine secretion [29, 30], endoplasmic reticulum stress [31], and synthesis of cell adhesion molecules, such as soluble ICAM-1 [28]. Several studies have suggested a potential interaction between the ET and the immune systems in the pathogenesis of pulmonary hypertension [29], portal hypertension [32, 33], preeclampsia (elevated blood pressure in pregnancy) [34, 35], and myocardial infarction [36]. For example, TNF- α is an important stimulus for ET-1 in response to placental ischemia during preeclampsia [34]. In addition, chronic exposure to activated CD4(+) T cells in response to placental ischemia results in ET-1 activation as a mechanism to increase blood pressure during pregnancy [35]. In myocardial infarction patients, BQ-123 leads to reduction in plasma myeloperoxidase (MPO), a marker of neutrophil activation [36].

Additionally, research on several immune-mediated models of renal damage has demonstrated that the ET-1 system is a central contributor in disease progression [28, 37, 38]. Chronic infusion of a non-pressor dose of ET-1 increases glomerular and plasma soluble intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein 1 (MCP-1) and increases renal infiltration of macrophages and lymphocytes [38]. These ET-1 induced proinflammatory effects are attenuated by ET_A receptor blockade. Similarly, ET_A receptor blockade in diabetic rats provides anti-inflammatory actions by reducing hyperglycemia-dependent increases in early inflammatory markers such as MCP-1 and ICAM-1 [24]. In addition, ET_A receptor activation mediates renal infiltration of T cells in angiotensin II-infused animals [39]. Furthermore, a recent clinical study has uncovered a new interaction between ET-1 and the immune system, with functional autoantibodies against ET_A receptors involved in atherosclerotic pathophysiology [40]. These studies highlight an important role for ET-1/ET_A receptor in inflammatory processes. However, the exact mechanism by which ET-1 induces inflammation and whether sex plays a role in this context remain undefined yet.

3. Sex differences in the ET-1 system

Sex-specific differences in age-related increases in blood pressure, in the prevalence of arterial hypertension [3, 4] and in the various manifestations of arterial hypertension have been consistently reported [1, 5–8]. Premenopausal women are largely protected against hypertension compared to age-matched men [4]. Experimental models of hypertension support the idea that males develop an earlier and more severe form of hypertension than females [41–44]. After menopause, blood pressure rises much faster in women, and, at this stage of life, the prevalence of hypertension is greater in women than men [45]. The prevalence of hypertension is higher in postmenopausal than premenopausal women, and the progression of renal diseases is less severe in women before menopause [46, 47], suggesting that gonadal hormones directly modulate sex differences in hypertension. Indeed, gonadal hormones modulate several pathways, including the ET system, that contribute to blood

pressure control, by regulating the cardiovascular, renal and neuronal systems function [4, 46, 48–55].

Sex differences in the ET system occur on different levels: expression of pre-pro-ET-1 and ECE activity/expression, plasma and tissue levels of ET-1, expression/activity of ET_A and ET_B receptors, effects of ET-1 on the cardiovascular and renal systems, responses to ET_A and ET_B receptors antagonists. Sex differences in the ET system also occur during the developmental programming of hypertension. This section will focus on the different aspects of sex differences in the ET system in the vasculature, heart and kidney. Whenever possible, the influence/contribution of sex hormones to these differences will be discussed.

3.1. Plasma and tissue levels of ET-1

Although sex differences are observed in blood pressure values in hypertensive adolescents, no significant changes in ET-1 levels have been found [56]. Sex differences in plasma ET-1 in hypertensive subjects are observed during the adult life, with men exhibiting higher plasma ET-1 levels than age-matched women [57, 58]. Healthy older women display higher ET-1 concentrations compared to healthy middle-aged women [59]. Indeed, aging is positively associated with increased ET-1 levels [60–63] and postmenopausal women exhibiting high testosterone levels also display high ET-1 levels, in comparison to those with lower testosterone levels, which may be relevant for increased blood pressure [64] and a proatherogenic profile [65].

Evidence points to a role for female gonadal hormones contributing to lower ET-1 plasma levels in females, compared to age-matched males. During the menstrual cycle, plasma ET-1 levels fluctuate. In the follicular and luteal phase, higher amounts of estrogen are secreted and lower plasma ET-1 levels are observed in comparison to the menstrual phase [63]. Pregnancy, another condition linked with increased levels of estrogen and progesterone, is also associated with decreased plasma ET-1 levels [57, 66–68]. Of importance, pregnant women with preeclampsia display increased levels of ET-1 [69, 70] and lower circulating progesterone, compared to normal pregnant women [71]. ET_A receptor blockade attenuates hypertension associated with preeclampsia [72].

Whereas low doses of a progestagen-only (etonogestrel) contraceptive do not change plasma ET-1 concentrations [73], hormone replacement therapy with 17 β -estradiol combined with progestins decreases plasma ET-1 in humans [74]. On the other hand, short-term administration of 17 β -estradiol with different progestins does not significantly change circulating ET-1 levels in healthy menopausal women [75, 76]. Male-to-female transsexual patients treated with estradiol and cyproterone acetate also exhibit decreased levels of ET-1 [57].

In experimental animal models, long-term replacement therapy with estradiol (6 months) prevents increases in ET-1 levels induced by ovariectomy. This effect of estradiol is also observed in female rats that received nicotine and in women subjected to environmental smoke, suggesting a protective role of this hormone via down-regulation of the ET system [77]. Raloxifene, a selective estrogen receptor modulator, decreases ET-1 levels in aortas from aged ovariectomized rats [78] and decreases plasma ET-1 in healthy postmenopausal

women [79, 80]. Raloxifene effects on plasma ET-1 are observed after 6-months of treatment [79, 80] but not after short periods of treatment (4 weeks) [81].

Androgens seem to positively modulate ET-1 expression since female-to-male transsexual patients treated with testosterone display increased ET-1 levels [57]. Hyperandrogenism is common in women with polycystic ovary syndrome, and these patients display higher levels of ET-1, compared to healthy and age-matched women [82–85]. Antagonism of ET_A and ET_B receptors augments vasodilation in polycystic ovary syndrome patients [86]. Conversely, patients with various forms of hypogonadism display significantly higher ET-1 levels in comparison with age-matched healthy males and testosterone therapy decreased ET-1 levels in these individuals [87].

3.2. Expression of pre-pro-ET-1 and ECE activity

Whereas 17 β -estradiol inhibits ET-1 mRNA expression in various cell types, including endothelial cells, smooth muscle cells, cardiac myocytes, fibroblasts and mesangial cells [88–95], testosterone has been shown to increase ET-1 mRNA in human aortic endothelial cells [96]. Estrogen seems to modulate ET-1 gene expression and production also by indirect mechanisms. Estrogen increases nitric oxide synthase (NOS) activity and bioavailability of NO, an important factor that modulates ET-1 production [52], and inhibition of NOS partly attenuates the inhibitory effect of 17 β -estradiol on ET-1 production [88, 97].

The effects of gonadal hormones on ET-1 production are also observed in experimental animal models. Deoxycorticosterone acetate (DOCA)-salt hypertensive male rats exhibit higher pre-pro-ET-1 mRNA compared to hypertensive females [98, 99], and ovariectomy augments pre-pro-ET-1 mRNA [98]. Ovariectomy also augments plasma ECE activity whereas 17 β -estradiol replacement inhibits plasma ECE activity [100]. The negative modulatory effects of estrogen on ECE activity may be tissue-dependent, since acute 17 β -estradiol-induced inhibition of ECE is greater in internal mammary arteries compared to saphenous veins [101]. Phytoestrogens, such as genistein and daidzein, inhibit ECE-1 mRNA expression in rat mesenteric arteries [102]. To date, there is no evidence showing a regulatory role of testosterone on ECE activity in the cardiovascular system. Of importance, ECE polymorphisms have been associated with sex-dependent cardiovascular risks. For example, a genetic polymorphism located in the ECE-1 gene promoter (ECE-1b C-338A) is associated with increased risk of coronary artery disease [103], carotid atherosclerosis [104] and ischemic stroke [105] in Chinese women.

3.3. ET receptors

Tissue distribution of ET receptors is different between males and females, generally favoring vasodilation in females, that is, relatively fewer ET_A receptors compared to ET_B. Both ET_A and ET_B receptors, as well as their ratio, are increased in saphenous veins from men, compared to women [106]. Vascular ET_B receptors mRNA is increased in male DOCA-salt rats, compared to females [98, 99]. ET_A receptor activation is modified by age in a sex-dependent manner. Middle-aged and older normotensive men are more responsive to vasoconstriction elicited by ET_A receptors, compared to women, as demonstrated by forearm blood flow experiments [107].

Ovarian hormones also modulate ET_B receptors. 17 β -estradiol down-regulates ET_B receptor mRNA in isolated rat cardiomyocytes of spontaneously hypertensive rats (SHR) [108]. Ovariectomy up-regulates ET_B receptors in the ventricular myocardium of SHR [108] and in vessels from DOCA-salt rats [98].

Hormonal therapy with 17 β -estradiol or conjugated equine estrogens reduces ET_A receptors in rabbit thoracic aorta. However, the reduction of pre-pro-ET-1 (RNA expression) is only achieved when conjugated equine estrogens are administered in combination with norethisterone acetate [109]. In rabbit coronary arteries, long-term estrogen treatment selectively attenuates ET-1-induced vasoconstriction, possibly by increasing ET_B gene expression. This effect is abolished by progestins, suggesting that progestins may oppose the beneficial effects of estrogen on the arterial wall [110]. In portal veins, expression of ET_B receptors and ET-1 levels are enhanced in orchidectomized rats, and testosterone-replacement therapy completely reversed this effect [111].

Experiments conducted in the spotting-lethal (sl) rat, which carries a natural deletion in the ET_B receptor gene, indicate that ET_B receptor protects females during development of hypertension. Whereas elevation of systolic blood pressure by DOCA-salt treatment in wild-type rats is higher in males than in females, in the homozygous spotting-lethal (sl/sl) rats treatment with DOCA-salt similarly increases systolic blood pressure in male, female and ovariectomized rats [112]. Potential mechanisms involved in the protective effects of ET_B receptors include modulation of vascular ROS generation [112] and renal NOS activity [113].

In rats, pregnancy increases the expression of endothelial ET_B receptors in mesenteric arteries, which is followed by enhanced ET_B receptor-mediated vasodilation. Increased endothelial ET_B receptor function may be an important contributor to decreased vascular resistance during pregnancy [114]. The expression of ET_A and ET_B receptors during pregnancy may be modulated differently in pathological conditions, since pregnant rats submitted to chronic hypoxia develop preeclamptic symptoms, via enhancement of ET-1 and ET_A receptor mediated signaling [115]. Male, but not female, rats under chronic infusion of Ang II display an attenuated natriuretic response to sarafotoxin 6c, an ET_B receptor agonist, compared to normotensive rats, indicating impairment of ET_B receptors function in male hypertensive rats. ET receptors function is maintained in female rats infused with Ang II [116]. Under high salt intake, administration of A-192621, an ET_B receptor antagonist, increases blood pressure in both sexes, confirming that ET_B receptors are important to limit blood pressure increases during high salt feeding. When high salt intake is associated with Ang II infusion, male rats have significantly higher mean arterial pressure compared to females and, in this case, ET_B receptor antagonism abolishes sex differences in blood pressure control [117]. These studies reinforce the idea that in some forms of hypertension, female protection is conferred by differential ET_B receptors function/expression. Female rats lacking functional ET_B receptors everywhere except sympathetic nerves (ET_B deficient rats) have a greater blood pressure response to acute stress than males when placed on high salt [118]. More work needs be performed to fully elucidate the role of ET_A and ET_B receptors in the sympathetic control of blood pressure in males and females.'

3.4. ET-1 effects in the cardiovascular system

During the reproductive age, vascular reactivity is functionally different between sexes. Competitive binding studies conducted in saphenous veins from patients who underwent coronary artery bypass graft surgery demonstrated a higher ratio of ET-1 binding both in ET_A and ET_B receptors in men, as compared to women [106]. Administration of the ET_B receptor antagonist BQ-788 into the forearm skin of human subjects, by intradermal microdialysis, revealed that ET_B receptors in men mediate tonic vasoconstriction, whereas ET_B receptors in women mediate tonic vasodilation [119]. Human cerebral arteries from women, collected from patients undergoing neurological surgery of brain tumors or epilepsy, are significantly less responsive to ET-1, compared to arteries from men. Interestingly, expression of ET_B receptor mRNA is higher in cerebral arteries from female subjects [120].

Increased sensitivity to ET-1 and to the selective ET_B receptor agonist IRL-1620 has also been reported in conductance and resistance arteries from male, compared to female, DOCA-salt rats [121, 122]. *In vivo*, IRL-1620 induces vasodilation in mesenteric microvessels from control rats, marked vasoconstriction in male DOCA-salt rats and a very mild constriction in vessels from female DOCA-salt rats [122]. Changes in ET_B-mediated vascular responses are associated with increased ET-1 and ET_B receptor gene expression in male, but not in female, animals [99]. Furthermore, ovariectomy increases the vasoconstrictor responses to the ET_B agonist, and estrogen-replacement therapy restores IRL-1620-induced responses [98], reinforcing the suggestion that the ovarian hormones modulate ET-1/ET_B receptor vascular responses in salt-sensitive hypertension.

Intracellular pathways may also be sex-regulated during hypertension, resulting in differential vascular contractility. Augmented constriction in aorta and resistance mesenteric arteries from DOCA-salt male rats, compared to females, is associated with increased phosphorylation of ERK 1/2, a pathway activated by ET-1, and decreased mitogen-activated protein kinase phosphatase 1 (MKP-1) [41].

Sexual dimorphism in vascular reactivity to ET-1 is evident in other experimental models of hypertension. In SHR, aorta and mesenteric arterioles from males exhibit greater sensitivity to ET-1 compared to females. Vascular sensitivity to ET-1 is similar between female SHR and their normotensive controls [123]. Skeletal muscle arteries from female Yucatan pigs develop greater contractile force in response to ET-1 compared to arteries from males. Exercise training increases ET-1-induced contractions in arteries from males, but not in arteries from females [124]. Additionally, exercise training reduces vascular sensitivity to vasoconstrictor responses to ET-1, with the adaptation response being greater in male than in female [125].

Intracoronary infusion of estrogen mediates a greater increase in the coronary blood flow in angiographically normal middle-aged women, who simultaneously exhibit lower ET-1 levels [126]. In addition, 17 β -estradiol attenuates ET-1-induced coronary artery constriction both *in vitro* and *in vivo* [127–129], whereas testosterone significantly potentiates responses elicited by ET-1 [129]. Testosterone effects are not inhibited by androgen receptor antagonists (flutamide or cyproterone acetate), indicating that testosterone effects are not mediated by classical genomic activities [129].

Sex-related differences in other vascular effects of ET-1 have been reported. ET-1 inhibits proliferation of smooth muscle cells derived from female, but not male, pig coronary arteries [130]. In a rodent model of brain ischemic injury, injection of ET-1 adjacent to the middle cerebral artery induces brain injury, with males having greater damage compared to females [131]. However, upon ET-1 stimulation, both testosterone in males, as well as 17 β -estradiol in females prevent constriction-induced inward remodeling in isolated mesenteric arteries from rats, an effect dependent on NO and transglutaminase activity [132].

In the heart, cardiac adaptations to DOCA-salt hypertension display sex-specific dimorphism independent of blood pressure with male mice exhibiting greater left ventricular and renal hypertrophy compared with female mice [133]. On the other hand, DOCA-salt-treatment of estrogen receptor β deficient (ER $\beta^{-/-}$) mice produces greater cardiac hypertrophy in females than in males. Cardiac hypertrophy in female ER $\beta^{-/-}$ mice treated with DOCA-salt is associated with greater collagen deposition and differential activation of ERK1/2 and p38, proteins of the MAPK signaling pathways [134]. Importantly, ET-1 is a key player in mediating cardiovascular abnormalities associated with DOCA-salt hypertension [135, 136]. Figure 1 summarizes the sex differences in ET system in the vasculature.

3. 5. ET-1 effects in the renal system

In the several last years, studies have provided evidence that the renal medullary ET-1 system contributes to sex differences in blood pressure. Nakano and Pollock [137] demonstrated that infusion of ET-1 into the renal medulla results in enhancement of Na⁺ excretion only in female rats. This sexual dimorphism can be related to the reduction in medullary blood flow in male rats that was not evident in female rats. Interestingly, ovariectomy attenuates this male-female difference [137], suggesting an important role for ovarian hormones in mediating sex differences in renal medullary ET-1 function. Additionally, Kittikulsuth et al. [116] found that intramedullary infusion of the ET_B agonist, S6c, results in natriuresis in female Ang II hypertensive rats, but not in males. Moreover, renal medullary ET-1 infusion to female Ang II hypertensive rats stimulates natriuresis, which is partially blunted by ET_A receptor antagonism [116]. These two studies highlights that medullary ET_A receptors contribute to natriuresis in female rats lacking ET_B receptors or infused chronically with Ang II. However, ET_A receptor expression and Ca²⁺ signaling in inner medullary collecting duct (IMCD) are greater in male compared with female Sprague Dawley rats, whereas, IMCD ET_B receptor binding is not sexually dimorphic [138]. Taken together, it is postulated that ET_A dependent natriuresis demonstrated in female rats is related to ET_A receptors located on other cell types [138].

Despite the evidence that the renal ET-1 system is sexually dimorphic and gonadectomy eliminates this dimorphism in animal model [139]), the roles of male and female sex steroids in mediating sexual dimorphism in renal ET-1 system have been poorly studied. Few studies have explored a direct interaction between male sex steroids and renal ET-1 system. Kalk et al. [140] demonstrated that the renal histopathological phenotype in male ET-1 transgenic mice with regard to glomerulosclerosis, proteinuria, perivascular fibrosis and immune cell immigration is ameliorated by castration, suggesting that the effects of ET-1 overexpression

on renal tissue injury are modulated by androgens. Additionally, renal ET-1 system has been implicated in sex differences in renal ischemic susceptibility based on androgens particularly [141]. Thus, androgens may up-regulate ET-1 production promoting renal damage by causing renal vasoconstriction and mitogenesis that can contribute to kidney fibrosis [142].

A role for the female sex steroids, estrogen and progesterone, in mediating sex differences in renal ET systems has been also suggested. Estradiol suppresses renal ET-1 overproduction and the consequent renal damage in acute renal failure [143]. This suppressive effect of estradiol on renal ET-1 overproduction is closely related to the NO pathway and is probably involved in the beneficial effect of estradiol on ischemia/reperfusion-induced renal injury [144]. Ba and Chaudry demonstrated that the administration of estradiol protects different organs, including the kidneys, against ischemia-reperfusion damage through a mechanism that involves, at least in part, estradiol-induced reduction in ET-1 renal vasoconstriction probably through activation of renal estrogen receptor- β [145]. Estradiol attenuated the inhibitory effect of ovariectomy on ET_A and ET_B receptor expression in the renal cortex [146]. Additionally, supplementation of OVX rats with estradiol and progesterone prevented the increase in renal inner medullary ET_A and ET_B receptor expression demonstrated in OVX rats [146]. The female sex appears to be protective against the progression of autosomal-dominant polycystic kidney disease, in association with changes in renal expression of ET-1 [139]. The difference in renal ET-1 levels between male and female rats with autosomal-dominant polycystic kidney disease (ADPKD) is attenuated by ovariectomy, but not orchietomy [139], suggesting a central role for ovarian hormones in sexual dimorphism in renal ET-1 system in ADPKD. Moreover, an interaction between progesterone and the renal ET-1 system has been also suggested. Zhang et al. [147] showed that pregnancy and progesterone enhance renal ET_A receptor expression. Recent studies support a role of renal ET-1 in the pathophysiology of preeclampsia [115, 148]. However, further studies are required to clarify the link between progesterone and the renal ET-1 particularly in the context of preeclampsia. Figure 2 summarizes the sex differences in ET system in the kidney.

3.6. Pressor effects and responses to ET receptor antagonists

Sex differences have been reported in the pressor effects of ET-1. In anesthetized rats, ET-1 produces rapid and transient falls in arterial blood pressure and hindquarter resistance, followed by long-lasting increases in blood pressure and hindquarter resistance. The initial ET-1-induced hypotension and vasodilation are similar in male and female rats. However, the pressor and hindquarter vasoconstrictor effects are significantly higher in male than female rats [149].

Bosentan, a mixed ET_A and ET_B receptor antagonist is more effective to reduce blood pressure in male, compared to female, DOCA-salt rats, supporting the idea that differential activation of ET-1 pathways contributes to higher blood pressure in male hypertensive subjects [122]. Ovariectomy augments the blood pressure-lowering effects of bosentan whereas estradiol replacement, combined or not with progesterone, restores ET-1 plasma levels and the blood pressure effects of bosentan [98]. Administration of ABT-627, an ET_A

receptor antagonist, to sl/sl rats for two weeks reduces blood pressure in a greater magnitude in females, compared to male rats [112].

A study looking at the pharmacokinetics and safety of macitentan, a dual ET-1 receptor antagonist, in healthy Caucasian and Japanese subjects, showed that C_{max} values¹ for macitentan and its active metabolite, ACT-132577, are approximately 25% higher in Caucasian women, compared to Caucasian men. Additionally, Caucasians and Japanese women display a 15% higher exposure to ACT-132577, when compared to men. Although these pharmacokinetic changes are not considered clinically relevant, since clinical laboratory and electrocardiographic parameters are similar among the groups [150], it is possible that sex-related differences in ET antagonists' pharmacokinetics may account for some of the differences in the effects of ET antagonists.

Obese female SHHF/Mcc-fa(cp) rats are resistant to the antihypertensive effects of irbesartan, an AT₁ receptor antagonist, compared with males. The resistance to the depressor effects of irbesartan in obese females is associated with increased urinary ET-1 excretion [151]. In addition, a G5665T gene polymorphism of pre-pro-ET-1 in humans modifies responses to antihypertensive treatments in men, but not in women [152]. Changes in systolic blood pressure, after 12 weeks of treatment with either irbesartan or atenolol, are more than 2-fold greater in men carrying the T allele compared with those with the G/G genotype, whereas no significant differences in blood pressure changes between G/G and carriers of the T allele are seen among women [152].

Sex hormones may contribute to the differential response to ET antagonists in males and females. Ovariectomized rats treated with J-104132, a mixed ET_A/ET_B receptor antagonist, for two weeks exhibit decreased neointimal formation after balloon injury. Combination of J-104132 with an Ang II antagonist, but not with 17 β -estradiol, further reduces neointimal formation, suggesting that the antagonism of ET receptors have estrogen-like vasoprotective actions in neointimal formation [153].

Several clinical studies showed that selective ET_A receptor antagonists and combined ET_A and ET_B receptor antagonists lower blood pressure in hypertensive patients [154, 155] and reduce proteinuria and albuminuria in patients with chronic kidney diseases and [156, 157] and diabetic nephropathy [158, 159]. Despite the high therapeutic potential of ET receptor antagonists as antihypertensive and renoprotective agents, none of these antagonists has been approved for management of hypertension or nephropathies. This is mainly attributed to their side effects, particularly fluid retention [160]. However, fluid retention appears to be managed by proper dosing of the ET receptor antagonist along with concomitant administration of diuretics [161]. In general, the therapeutic potential of ET receptor antagonism for treatment of cardiovascular and renal diseases has been recently reviewed by several elegant reviews in 2015 [162–166]. Clinical trials focusing on sex-associated differences and confirmation in humans of data on sex differences in the ET-1 system

¹C_{max} = maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body after the drug has been administered and prior to the administration of a second dose.

obtained in experimental animals will help to establish sex-targeted or sex-tailored interventions for the treatment of cardiovascular and renal diseases.

3.7. ET and sex specific developmental programming of hypertension

Events occurring early in life, comprising the fetal period, contribute to long-term modulation in the cardiovascular functions, including blood pressure control [167–170]. Therefore, sex differences in adult blood pressure may result from sex-specific developmental programming, through several mechanisms including the ET system [171] (See Ojeda 2014 for an in-depth review on sex differences in the developmental programming of hypertension).

One factor that may modulate sex differences in the early life programming of ET system is stress. Stressors such as hypoxia are considered risk factors related to complications during pregnancy, and exposure to hypoxia during the fetal period augments cardiovascular disease in later-life [172]. Mesenteric resistance arteries from aged male rats, but not aged female rats, which were exposed to prenatal hypoxia during day 15 to 21 of pregnancy, display increased vasoconstriction to big ET-1, but not to ET-1, compared to their aged-matched controls. This response is almost completely abolished by an ECE antagonist (CGS35066). Interestingly, NOS inhibition potentiates big ET-1 contractility observed in male offspring that underwent intrauterine growth restriction (IUGR), demonstrating a modulatory role for NO. ET-1 antagonism results in more significant blood pressure-lowering effect in IUGR male offspring, compared to female IUGR offspring [173]. These findings indicate that hypoxia during the prenatal life favors vascular sex differences observed in the ET system, with long-term consequences [171, 173].

Male and female offspring from sheep administered the steroid betamethasone during pregnancy exhibit increased mean arterial pressure. Administration of ET-1 generates a more pronounced effect on vascular resistance and increases in blood pressure in female offspring compared to the male offspring [174]. These findings indicate that exposure to different drugs/agents during the antenatal phase can program vascular responses to ET-1 in adult, in a sex-specific manner.

Maternal separation, a model of early life stress, decreases expression of vascular ET_A and ET_B receptors in male rats. ET receptor blockade significantly blunts acute air jet stress-induced pressor response in control rats and in rats submitted to maternal separation. Acute air jet stress also increases plasma corticosterone levels in control, but not in rats submitted to maternal separation, an effect inhibited by ET receptor blockade [175]. Acute air jet stress-elicited pressor response involves ROS-dependent mechanisms, downstream of ET_B receptor activation [176]. These data reinforce the idea that early life stress modulates the ET-1 system, and augments stress-induced pressor responses later in life [175].

Human studies reinforce a positive relation between exposure to adverse childhood experiences and high ET-1 in young adults, but failed to show an interaction between sex-related adverse childhood experiences with ET-1 levels [177]. Therefore, it will be interesting in the future to describe which conditions may interfere in the sex-specific

programming of blood pressure through the modulation of the ET-1 system components. Figure 3 summarizes the sex differences in ET system in development programming.

3.8. ET and sex chromosomes

Importantly, sex differences in physiology and pathophysiology arise not only from direct effects of sex hormones, but also from sex chromosome genes. However, limited studies have addressed the potential role for the sex chromosomes in the development of cardiovascular and renal diseases. Using the four-core genotype model, Chen et al. have demonstrated that adiposity is linked to X chromosome [178]. Although blood pressure was not monitored in this particular study, it is well established that obesity has a hypertensive effect [179]. Recently, the use of the same mouse model has revealed that sex chromosome genes participate in the modulation of neural pathways underlying regulatory response to renin-angiotensin stimulation [180, 181]. Additionally, angiotensin-induced vasodilation and endothelium-derived hyperpolarizing factors require the XX chromosome sex complement [181]. It is very important to separate the contribution of the female sex steroids on the cardiovascular and renal ET system from the contribution made by sex chromosomal complement. However, this area has not been explored yet.

4. Conclusions and perspectives

Despite the fact that several studies have attracted the attention to sexual dimorphism in the molecular pathways involved in the pathophysiology of cardiovascular and renal diseases, the current national guidelines for treatments of hypertension and other cardiorenal diseases still recommend the same therapeutic approaches for both sexes. Thus, starting to think about the selection of sex-specific drugs for management of cardiovascular and renal diseases should be a central goal, which is even further supported by available data from clinical trials highlighting sex differences in the blood lowering capacity of some classes of antihypertensive medications [182–185].

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Figure 1.

Hypothetical scheme highlighting sexual dimorphism in ET system in the vasculature. Ca²⁺, calcium; DAG, diacylglycerol; ET-1, endothelin-1; ECE, endothelin converting enzyme; ET_A/ET_B, subtype A and subtype B endothelin receptors; IP₃, inositol trisphosphate; MAPK, mitogen-activated protein kinases; MMPs, matrix metalloproteinases; NO, nitric oxide; PGI₂, prostacyclin; PLC, phospholipase C; ROS, reactive oxygen species; VSMCs, vascular smooth muscle cells.

Figure 2. Hypothetical scheme highlighting sexual dimorphism in ET system in the kidney. ET-1, endothelin-1; ET_A/ET_B , subtype A and subtype B endothelin receptors; MBF, medullary blood flow; Na^+ , sodium; U_{NaV} urinary sodium (Na^{2+}) excretion.

Figure 3.

Stressors in the early life and sex specific developmental programming of hypertension. Ang II, angiotensin II; ET-1, endothelin-1; ECE, endothelin converting enzyme; ET_A/ET_B, subtype A and subtype B endothelin receptors; ROS, reactive oxygen species.