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Role of the endothelin system in sexual dimorphism in cardiovascular and renal diseases

Eman Y. Gohar [a,b,1], Fernanda R. Giachini [c,1], David M. Pollock [a], Rita C. Tostes [d,*]

[a] Cardio-Renal Physiology and Medicine, Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Alexandria University, Egypt
[c] Institute of Biological Sciences and Health, Federal University of Mato Grosso, Barra do Garças, MT, Brazil
[d] Department of Pharmacology, Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, SP, Brazil

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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.

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-

* Corresponding author at: Department of Pharmacology, Ribeirao Preto Medical School, University of Sao Paulo, Av Bandeirantes 3900, Ribeirao Preto, SP CEP 14049-900, Brazil.
E-mail address: rtostes@usp.br (R.C. Tostes).
[1] Authors have equally contributed to the manuscript.

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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), cyclooxygenase (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