Endothelin in the female vasculature: a role in aging?

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Lekontseva O, Chakrabarti S, Davidge ST. Endothelin in the female vasculature: a role in aging? Am J Physiol Regul Integr Comp Physiol 298: R509–R516, 2010. First published January 6, 2010; doi:10.1152/ajpregu.00656.2009.—Cardiovascular diseases are the leading cause of morbidity and mortality in the world. Aging is associated with an increased incidence of cardiovascular disease. Premenopausal women are relatively protected from vascular alterations compared with age-matched men, likely due to higher levels of the female sex hormones. However, these vasoprotective effects in women are attenuated after menopause. Thus, the vascular system in aging women is affected by both the aging process as well as loss of hormonal protection, positioning women of this age group at a high risk for cardiovascular diseases such as hypertension, myocardial infarction, and stroke. The endothelin system in general and endothelin-1 (ET-1) in particular plays an important role in the pathogenesis of vascular dysfunction associated with aging. Evidence suggests that the female sex steroids can interfere with the vascular expression and actions of ET-1 via several mechanisms, which may further contribute to pathological processes in the vasculature of aging women. In this review, we have summarized hormone-dependent vascular pathways whereby ET-1 may mediate the deleterious effects of aging in postmenopausal females.

ET-1; menopause; estrogen; vasoconstriction; inflammation

AGING OF THE VASCULAR SYSTEM is a complex process characterized by sustained proinflammatory and proconstrictor changes in the vascular microenvironment. The resulting structural and functional alterations in systemic vasculature lead to increased risk of cardiovascular diseases such as hypertension, myocardial infarction, and stroke in the aging population (12, 18, 51, 70). In the absence of chronic preexisting conditions, such as diabetes, premenopausal women express a favorable cardiovascular phenotype compared with age-matched men, largely due to the vasoprotective role of ovarian steroids such as estrogen (92). An alteration in circulating sex hormones at menopause, such as the decrease in estrogens and a relative excess of androgens, is associated with the conversion from a low- to high-risk cardiovascular profile (19, 56). Although the mechanisms underlying the pathogenesis of vascular dysfunction in postmenopausal women are not completely understood, it is believed to result from a complex interplay between the aging process and the decline in ovarian hormones like estrogen.

Endothelin has emerged as one of the key mediators of vascular dysfunction and remodeling in aging. Interestingly, there is evidence that female sex steroids (in particular, estrogen) can regulate the endothelin system at various levels from gene transcription and posttranslational modification of the peptide to expression of its vascular receptors and postreceptor signaling events. This review will summarize current knowledge on the impact of aging and female sex hormones on the endothelin system, as well as outline directions where further research is needed. A better understanding of the role of endothelin in the pathogenesis of vascular dysfunction in postmenopausal women may lead to the development of novel sex-specific cardiovascular therapies.

Vascular Changes in Aging Women

Vascular system in aging. In aging, increased oxidative stress and inflammatory activity lead to changes in the cardiovascular system (21, 98, 105). This impacts vessel wall structure and passive mechanical properties, as well as functional vasoactive mechanisms. One of the early events in the process of vascular aging is endothelial dysfunction (14). The vascular endothelium closely interacts and modulates functions of the underlying vascular smooth muscle cells (VSMC) and the extracellular matrix, thereby controlling vascular tone and diameter (which define peripheral resistance and, hence, the blood pressure). The endothelium also carries out important synthetic and metabolic functions and acts as a nonthrombogenic and selective permeable barrier under normal physiological conditions (40, 84). Endothelial cell activation by stressful stimuli, such as proinflammatory cytokines and reactive oxygen species (ROS), may impair many endothelium-dependent
vasoprotective functions, which precede the onset of symptomatic cardiovascular disease. For example, a progressive decline in nitric oxide (NO)-mediated vascular relaxation with age has been documented by numerous studies in humans and animal arteries (34, 65, 113). In addition to impaired endothelial vasodilatory pathways, increased endothelial generation of vasoconstrictor products such as endothelin (as detailed in the next section) contributes to a net proconstrictor vascular phenotype (91). Furthermore, a vicious cycle can be formed where dysfunctional vascular cells themselves become a major producer of proinflammatory and growth-stimulating molecules, thus being both a target and a source of noxious stimuli. In summary, aging elicits multiple alterations in the vascular system, largely mediated by the locally generated pathological factors such as endothelin. Altogether, it allows for a gradual transition from an anti-inflammatory, antithrombotic phenotype to a proinflammatory, proatherosclerotic, and prohypertensive state.

Female sex steroids and the vascular system. It is well known that vascular health declines earlier in aging male subjects compared with female subjects (15). It is also known that sex steroids are important in the regulation of vascular homeostasis (64, 76, 85). Thus, in females, estrogen regulates a number of signaling pathways in the vascular cells that are protective to the vessel structure and function, both rapidly and in the long term. These include modulation of vascular tone via both the endothelium-dependent mechanisms, as well as the mechanisms inherent to the VSMC (81). In addition, antioxidant, anti-inflammatory, and antiproliferative pathways modulated by estrogen protect against vessel injury from exposure to the vascular risk factors (16). This has been a subject of recent reviews (as indicated above), and will not be covered in detail here. Major hormonal changes associated with cessation of ovulatory function or menopause, such as decreased circulating estrogen and progesterone levels, contribute to vascular dysfunction in women via the loss of the aforementioned beneficial mechanisms. Together with aging, hormone deficiency plays a critical role in the vascular system in postmenopausal women. Being an important mediator of vascular dysfunction in aging, endothelin has also been identified as one of the targets for estrogen action in the vasculature (61). Given its potent proconstrictor, proinflammatory, and growth-promoting effects, it appears likely to make a substantial contribution to vascular alterations in aging women. This is an emerging area of research that will be highlighted in this review.

Endothelin: Background

Endothelin exerts potent vasomotor, proinflammatory, and proatherogenic effects on the vascular system with important physiological and pathological outcomes mediated through its specific receptors. The structure, production, and vasoconstrictor role of endothelin were described in the seminal publication by Yanagisawa et al. (111).

Endothelin: synthesis and activation. In humans, of three different proteins in the endothelin family (ET-1, ET-2, and ET-3) (47), ET-1 has been established as the principal isoform in the vascular system (59). Classically, it is generated in the endothelial cells via a number of intermediates with varying (typically low) biological activities. Thus, preproET-1 (ppET-1) gene transcription yields mRNA encoding for 212-amino acid peptide, which after removal of its signal sequence forms proET-1, which is further cleaved to big ET-1 (a 38-amino acid molecule). The latter can be found in systemic circulation at low levels, but lacks significant bioactivity. Further proteolytic removal of COOH-terminal residues, classically, by endothelin-converting enzymes (ECEs) results in formation of the mature ET-1[1–21] (29, 46, 108, 110). Alternative cleavage of big ET-1 by matrix metalloproteinase or chymase leads to production of extended-length isoforms, ET-1[1–32] and ET-1[1–31], respectively (33, 107). Although endothelial cells are considered the primary physiological source of vascular ET-1, it is now recognized that the vascular smooth muscle cells (VSMC), fibroblasts, and inflammatory cells (such as macrophages and leukocytes) are capable of ET-1 production under pathological conditions (28, 45, 50, 52, 88, 101).

Endothelin: receptors. The downstream effects of ET-1 are mediated by the two G protein-coupled receptors, ET<sub>A</sub> and ET<sub>B</sub>, which are encoded by different genes but share certain structural homology. In the vasculature, ET<sub>A</sub> receptors are typically expressed by VSMC, whereas ET<sub>B</sub> receptors are located on both VSMC and endothelial cells. ET<sub>A</sub>- and ET<sub>B</sub>-initiated signaling cascades in the vascular cells have been reviewed elsewhere (43). The vasopressor, mitogenic and inflammatory activity of ET-1 has principally been associated with the VSMC ET<sub>A</sub> receptors (and to a lesser extent, VSMC ET<sub>B</sub> receptors). In contrast, endothelial ET<sub>A</sub> receptors mediate release of endothelial-derived vasodilator substances (such as NO) contributing to vascular relaxation. In normal conditions, the balance between ET<sub>B</sub>-dependent proconstrictor and proliferator pathways is thought to be predominated by the endothelial ET<sub>B</sub> signaling (42). In addition, endothelial ET<sub>B</sub> receptors mediate antiproliferative pathways and ET-1 clearance (27, 72). However, this vasoprotective mechanism can be impaired in endothelial dysfunction commonly associated with aging.

Endothelin System in Aging

Physiologically, the ET-1 system plays an important role in the maintenance of vascular tone. Given its potent and long-lasting proconstrictor actions (compared with other known endogenous vasoconstrictors), the baseline in vivo ET-1 synthesis is characteristically low. However, normal aging appears to be associated with augmented ET-1 system activity, although the vast majority of the studies have only investigated this in male subjects.

Aging and endothelin synthesis. Aging is associated with higher endogenous ET-1 levels (mRNA and protein) in both plasma and vascular tissue in males and females (10, 36, 53, 57) together with an altered ET<sub>A</sub> to ET<sub>B</sub> ratio (48). Functionally, an increase in ET-1-dependent vascular tone has been demonstrated in clinically healthy older men (99). Another recent study in healthy volunteers reported impaired endothelium-dependent dilation in older compared with young men, which was inversely correlated with ET-1 protein expression in the brachial artery endothelial cells (25). Surprisingly, neither endothelial NO synthase (eNOS) protein nor its activation was found reduced with age in this study. In a similar vein, the authors observed improved endothelium-mediated vasodilation upon ET<sub>A</sub> receptor blockade in aged male mice (25). In addition, ET-1 appears to contribute to renal injury in aged male rats, suggesting that the effects of a hyperactive endothelin system extend beyond the vasculature into organs like the
kidney (77). The mechanisms stimulating the ET-1 system in aging are not fully understood. In activated endothelial cells, ET-1 yield can increase via upregulated transcription, rapid release of the preformed intracellular stores and/or by the means of posttranslational proteolytic maturation (87). For instance, ppET-1 mRNA can be markedly induced by various age-related mechanical and chemical stimuli to the endothelial cells, including disturbed shear stress, cytokines, and ROS (68, 109, 115). In addition, a greater activity and/or expression of ECE and non-ECE [such as matrix metalloproteinase (MMP)-2 and -9] proteases that cleave big ET-1 has been detected in the aging vascular tissue and may lead to increased ET-1 bioavailability (38, 44, 55).

**Endothelin and vascular dysfunction.** Increased bioactive ET-1 may contribute to vascular dysfunction in aging (regardless of sex) via multiple pathways. Beyond its direct hemodynamic effects, endothelin has been implicated in the vascular oxidative stress and inflammatory activity, oxidized low-density lipoprotein (oxLDL) uptake, mitogenic stimulation of the VSMC, and fibrotic processes. A reciprocal relationship between ET-1 and NO is known. For example, although ET-1 can mediate a transient release of NO via endothelial ET\(_{A}\) receptors, in the long-term ET-1 reduces eNOS expression and NO production in endothelial cells (82, 83). In vivo, intrabrachial infusion of ET-1 during 30 min impairs endothelium-dependent relaxation in healthy men, which can be prevented by coadministration of an antioxidant (13). ET-1 can generate ROS through activation of NADPH oxidase; and conversely, ROS appear to stimulate ET-1 production, leading into a vicious cycle of oxidative stress, inflammation, and vasoconstriction (22). Indeed, among many deleterious effects of increased oxidative stress is rapid consumption of NO in the reaction with superoxide radical, which yields peroxynitrite (ONOO\(^-\)), a reactive nitrating and inflammatory molecule. ET-1 has been further implicated in the inflammatory processes in the vessel wall via direct activation of macrophages and induction of numerous proinflammatory mediators (5). Importantly, cytokines provide a positive feedback to further stimulate the ET-1 system, components of which are found highly expressed in areas undergoing active atherosclerotic remodeling (9, 58). Similar bidirectional interactions have been described with other ET-1 targets in the vasculature. For example, ET-1 augments endothelial uptake of oxLDL, which in turn stimulate ET-1 production (67, 73). Accordingly, ET receptor’s antagonism improves endothelial function in hyperlipidemic animals (96), whereas lipid-lowering statin therapy inhibits production of ppET-1 mRNA in endothelial cells (41) and ET-1-dependent vasoconstriction in aortic rings (71). Another example of reciprocal relationships is MMP activation via ET\(_{A}\) receptors, which contributes to the profibrotic effects of ET-1 on the vascular extracellular matrix. On the other hand, MMPs are known to mediate bioactive ET-1 production via the specific big ET-1 cleavage, which may become a dominating processing pathway under certain vascular conditions in females (54, 55).

In summary, a vicious cycle of the ET-1 system activation, oxidative stress, and inflammation appears to play an important role in the pathogenesis of age-related vascular alterations. In women, ET-dependent vascular pathways can be intervened/ regulated by the hormonal (e.g., estrogen) status, both via the direct estrogen effects on the components of the ET-1 system, as well as indirectly via its capacity to impact vascular inflammation. The evidence demonstrating relationships between the hormonal milieu and ET-1 signaling will be summarized next.

**Sex Hormones and Endothelin**

Sex hormones exert important regulatory effects on blood pressure in health and disease. In menopausal women, there is a gradual fall in the levels of the female sex hormones estrogen and progesterone with a corresponding increase in relative levels of testosterone compared with estrogen. The deleterious effects of menopause on the cardiovascular system are well known. While healthy premenopausal women are relatively protected against cardiovascular diseases, such as myocardial infarction and stroke compared with age-matched men, this protection is lost upon reaching menopause (92). The factors regulating the female sex hormone-mediated cardiovascular protection are the subject of much basic and clinical investigation. It is increasingly apparent that alterations in both actual levels of and vascular responses to ET-1 play a major role in this process.

**Estrogen and ET-1 synthesis.** Estrogen is well known as a modulator of vascular function. In various in vitro, ex vivo, and in vivo experimental conditions, estrogen has been shown to exert anti-inflammatory, antioxidant, and antihypertensive effects on the vascular system (16). As ET-1 is a key proinflammatory and prohypertensive molecule in the vasculature, it is not surprising that estrogen can affect ET-1 levels. A seminal study by Polderman et al. (80) demonstrated higher plasma levels of ET-1 in healthy men compared with premenopausal healthy women. The ET-1 levels were even lower in pregnant women. Interestingly, the authors also studied groups of male-to-female as well as female-to-male transsexuals and showed a decrease in ET-1 in the former and increased ET-1 in the latter. Creatasas et al. (20) observed a decrease in plasma ET-1 in primary amenorrhic female teenagers following exogenous estrogen treatment. Similarly, plasma concentrations of ET-1 were found to be decreased on hormone replacement therapy with estradiol or estrone (with or without progesterone supplementation) in postmenopausal women (6, 11, 104, 114). These studies clearly suggest a link between increased female sex hormones and a corresponding decrease in ET-1.

Studies by various research groups have shown the ability of estrogens to inhibit ET-1 at both mRNA and protein levels in experiments using cultured vascular endothelial cells (106). Estrogen administration inhibited ET-1 synthesis both in resting endothelial cells as well as in cells stimulated by cyclic strain or proinflammatory mediators such as thrombin, TNF, and ANG II (26, 49, 69, 103). Various mechanisms have been proposed to explain the inhibitory effect of estrogen on endothelial ET-1 production. Some studies have indicated a role for specific estrogen receptors (ER\(_{a}\) and ER\(_{b}\)) in this process (2, 32). However, Wilbert-Lampen et al. (103) suggested a novel ER-independent effect of estrogen on ET-1 that was mediated through endothelial sigma-1/cocaine receptors involving the scavenging of ROS. Interestingly, Dubey et al. (26) have shown that the estrogen metabolites 2-hydroxyestradiol and 2-methoxyestradiol can suppress ET-1 synthesis through an ER-independent mechanism. This would both prolong and potentiate the effects of estrogen on ET-1 inhibition and may
explain some of the long-term effects of estrogen under in vivo conditions. The inhibitory effects of estrogen on ET-1 levels are further supported by evidence from animal studies. Ovariectomized female animals show an increase in ET-1 levels in both plasma and vascular tissues, while supplementation with exogenous estrogen negates this increase in ET-1, suggesting a key role for estrogen on ET-1 expression (3, 24, 95, 97, 102).

**Estrogen and posttranslational ET-1 activation.** ECE, which cleaves big ET-1 to release the active ET-1 molecule, is a target of estrogenic actions. Exogenous estrogen administration can decrease both ECE mRNA as well as ECE activity in ovariectomized rats (86, 95). A single study involving human subjects is available, which has shown an ex vivo effect of estrogen decreasing ECE activity in arteries but increasing it in veins (39). Further research is needed to study both the acute and long-term effects of estrogen on ECE regulation. In addition, previous work from our laboratory has demonstrated a key role for MMP-2 on the yield of bioactive ET-1 through the specific proteolysis of big ET-1 (33). Since estrogen can potentially affect activity of both MMP-2 and -9, an alternate mechanism of ET-1 regulation is also possible (74).

**Estrogen and ET receptors.** The vascular actions of ET-1 are mediated through its specific receptors, ET$_A$ and ET$_B$, which may be targets of estrogen. The data regarding the role of estrogen on these receptors is quite contradictory and may represent differential effects of estrogen in different species and/or vascular beds. For example, a study by Pedersen et al. (79) showed a reduction in levels of the ET$_A$ receptor in the thoracic aorta and epicardial arteries of estrogen-supplemented rabbits. However, a previous publication by the same group had demonstrated estrogen suppression of the ET$_B$ receptor in coronary arteries, an effect that could be blocked by concomitant administration of progesterone (78). Nuedling et al. (75) have shown upregulation of the ET$_B$ receptor in the heart of ovariectomized female spontaneously hypertensive rats (SHR), which could be reversed by exogenous estrogen. Surprisingly, a paper by Miller et al. (63) demonstrated increased high-affinity endothelin binding sites and increased vasoconstrictor response to ET-1 in coronary arteries of female pigs compared with male pigs. However, this study did not differentiate between ET$_A$ and ET$_B$ receptors, and it is possible that the changes in receptor binding sites might be secondary to changes in circulating ET-1 concentrations over a period of time. A study by Ergul et al. (31) showed increased levels of ET$_A$ receptors in saphenous veins of men compared with women with a corresponding increase in ET-1 responsiveness in male vascular tissue. Whether these effects hold true for other vascular beds in humans remains to be determined.

**Estrogen and postreceptor ET-1 effects.** ET-1 exerts profound vasoconstrictor, proinflammatory, and prooxidant effects on the vasculature (30, 35). Estrogen elicits both genomic and nongenomic responses in the vasculature that may counteract these effects of ET-1 through different pathways. For example, estrogen increases eNOS activity through a combination of genomic [i.e., protein upregulation (94)] and nongenomic [rapid phosphorylation (17, 89)] mechanisms, generating NO and promoting vasodilatation, thus opposing the vasoconstrictor effects of ET-1. Estrogen may also reduce ET-1-induced oxidative stress through upregulation of SOD or suppression of prooxidant enzymes like NADPH oxidase (23, 37, 62). Similarly, while ET-1 can upregulate leukocyte adhesion molecules and promote inflammatory cell recruitment at the endothelium, estrogens can inhibit these inflammatory processes through a number of anti-inflammatory mechanisms, such as inhibition of NF-kB (4).

**Estrogen and an in vivo ET-1 role.** Studies in intact animals have shown a modulatory effect of estrogen on ET-1 effects in the cardiovascular system. While neither male nor cycling female SHR rats show a role for ET-1 on hypertension, ET-1 protein levels are upregulated in postcycling SHR females with a consequent effect of ET-1 modulation on blood pressure (90, 112). Similarly, in a rat model of DOCA-salt hypertension, ovariectomy worsened ET-1-mediated vasoconstriction, which could be reversed by supplementation with exogenous estrogen with or without progesterone (24). ET-1 levels were increased in both male and female ovariectomized DOCA-salt hypertensive rats with improvements in blood pressure and consequent renal lesions on treatment with either hormone replacement therapy (females only) or ET$_A$ receptor blockers (66). Further evidence of a protective effect of estrogen on ET-1-mediated vascular pathologies is shown in a rat model of trauma hemi-
orriage, which causes increased ET-1-dependent vasoconstriction following vascular trauma. Treatment with estrogen attenuated these ET-1-mediated vascular effects (8). Interestingly, from this model, the estrogen receptor subtypes ERα and ERβ appear to differentially modulate estrogen-induced vasorelaxation in an organ- and time-specific manner (7). Our own work using a rat model of menopause (12-mo-old ovariec-tomized Sprague-Dawley rats) found increased mesenteric artery reactivity to big ET-1 (an ET-1 precursor) compared with young cycling females, which was ameliorated in the “menopause” animals receiving chronic estrogen treatment (55). A study by Sudhir et al. (93) showed an attenuation of ET-1 responses in coronary arteries following acute intracoronary injection of a physiologically relevant dose of estrogen, suggesting the possibility of rapid nongenomic estrogen effect. These in vivo findings clearly show a key role for estrogen in protecting the cardiovascular system from ET-1-mediated pathological change, which may be lost during menopause.

Other sex hormones and ET-1. Progesterone, the other major female sex hormone, also inhibits ET-1 production in both resting and stimulated endothelial cells (69, 103). In addition, combined hormone replacement therapy containing progesterone has been shown to reduce ET-1 levels (6, 24). On the other hand, testosterone can increase ET-1 synthesis both in vitro and in vivo (100, 103). Indeed, a study of postmenopausal women in Brazil found a significant correlation between serum testosterone and plasma ET-1 levels (60). Not only does testosterone increase ET-1 levels, it can also modulate vascular responses to exogenous ET-1 (1). Thus, an altered balance between estrogens and testosterone in menopausal women may aggravate ET-1-mediated vascular pathologies.

Conclusions: Endothelin in Postmenopausal Women

Postmenopausal women are at a dual disadvantage regarding their cardiovascular health: aging by itself contributes to increased oxidative stress and vascular degenerative processes, and these changes can be further aggravated by the loss of vasoprotective effects of the female sex hormones at menopause. Given the role played by ET-1 in the pathogenesis of age-related adverse vascular events and the role of estrogen in modulating ET-1-mediated vascular effects, there appears to be a major role for endothelin signaling in the postmenopausal female vasculature as summarized in Fig. 1. Whereas this hypothesis is supported by the data gathered from animal models, studies involving postmenopausal human subjects are few. Although these studies have tended to demonstrate a reduction in ET-1 plasma levels as a measure of estrogen regulation of ET-1 effects, it is a matter of conjecture to state that plasma ET-1 is a good indicator of its vascular effects. A recent study has demonstrated an increased ET-1 vasoconstrictor tone in healthy aging males compared with younger males (99). If aging alone could cause such changes in males, the effects in females who simultaneously lose their estrogen-mediated vasoprotective function, could be even more significant.

Perspectives and Significance

In summary, the aging process appears to augment ET-1 contribution to dysfunction in the cardiovascular system. Aging women are positioned at an increased risk due to the loss of female sex hormone-mediated protection against ET-1. Despite this significance, investigations on ET-1 in the aging female vasculature are sorely lacking. Both clinical and basic studies need to be performed in postmenopausal women to assess the role of increased ET-1 signaling in the vasculature. In addition, sex-specific analysis may be warranted when testing the potential therapeutic role for endothelin system manipulation in cardiovascular disease.

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DISCLOSURES

No conflicts of interest are declared by the authors.

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