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Vascular effects of estrogens: rapid actions, novel mechanisms, and potential therapeutic implications[1]

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KEY WORDS estrogens; bradykinin; arteries; endothelins; nitric oxide; postmenopause; vasodilation

ABSTRACT

Although estrogen-dependent effects on the vasculature were first observed more than a century ago, many of the mechanisms by which estrogens interact with the vascular wall have been identified only in the past 15 years. Estrogens bind to vascular estrogen receptors (ER), including the ERα, the novel ERβ as well as to membrane-bound receptors. Estrogens have direct effects in human coronary and internal mammary arteries by inducing rapid, endothelium-independent relaxation, enhancement of endothelial function and inhibition of vasoconstriction by vasoactive agonists. Furthermore, estrogens contribute to vascular homeostasis through modulation of gene expression, changes in membrane potentials, as well as expression and function of receptors. In addition, estrogens interfere with the activity of vasoactive peptides and vascular enzymes and act as natural antioxidants. Some of these effects have also been observed for phyto-estrogens, which are important dietary components in Asian countries. In the vasculature, the sum of these actions of estrogens results in vasodilatation and inhibition of vascular cell growth. Accordingly, estrogens have been shown to improve vascular function of animals and humans and to inhibit the response to injury after balloon angioplasty and the progression of atherosclerosis. Prospective clinical studies are ongoing to determine whether replacement therapy with estrogen or derivatives provides an alternative to lower cardiovascular mortality in postmenopausal women.

INTRODUCTION

Cardiovascular disease accounts for the majority of morbidity and mortality in postmenopausal women in Western societies and is comparable to that of men after age 75[1]. Epidemiologic data suggest a beneficial effect of hormone replacement therapy on cardiovascular risk[2,3]. High estrogen levels in pre- and postmenopausal women are associated with favorable changes in lipid metabolism[4] which, however, only in part explain the cardioprotective effects[5]. In recent years evidence has been accumulated indicating that estrogens have numerous effects on vascular homeostasis including the modulation of endothelium-dependent vasomotion[6]. Furthermore, they modulate the expression of endothelial and non-endothelial genes including those of the renin-angiotensin system[7,8], the clotting system[9,10], growth factors[11,12], and NO synthase[13,14]. Most of these effects are independent from plasma cholesterol levels indicating that estrogens exert specific actions protecting against vascular dysfunction.

Investigating the role of estrogens as potential "vascular" hormones goes back to the 1930s[15], however many studies regarding the action of estrogens were initiated only after the discovery of the regulatory role of the vascular endothelium by Furchgott and Zawadzki[16]. Functional integrity of the endothelium, a large endocrine organ, ensures the release of several humoral factors maintaining blood flow and fibrinolysis, vascular smooth muscle relaxation and contraction, as well as platelet activation and inhibition of thrombus formation. Thus, an intact vascular endothelium contribute to blood pressure and vessel

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patency. The most important endothelium-derived vasoactive substances are vasodilators such as nitric oxide (NO)[17] and prostacyclin[18], counterbalanced by vasoconstrictors, particularly endothelin-1 and angiotensin II[19]. Stimulation of endothelial cells by neurotransmitters, hormones, and substances derived from platelets and the coagulation system causes release of NO, relaxation of underlying vascular smooth muscle[16] and inhibition of platelet aggregation[20,21]. Expression of the endothelial nitric-oxide synthase (NOS 3) gene although constitutively activated[22] can be up-regulated by shear stress and estrogens[13,22-28]. The most potent endothelium-derived contracting factor known today is endothelin-1 (ET-1)[29,30] followed by components of the renin-angiotensin system and vasoconstrictor prostanoids[31]. Three distinct endothelin receptors have been identified: ET_A- and ET_B-receptors[32], and an ET_{BC}-receptor. In the vasculature, ET_A-receptors mediate contraction and proliferation[32,33] whereas endothelial cell-mediated ET_B-receptor activation is linked to the formation of NO and prostacyclin which acts as a negative feedback mechanism to reduce endothelin production in the endothelium[34] and to oppose the vasoconstrictor action in smooth muscle. In addition, ET_B-mediated endothelium-independent vasodilatation has been recently reported[35]. Endothelin synthesis is regulated by NO/cGMP-dependent mechanisms[34], cAMP-dependent inhibition[36], an inhibitory factor produced by vascular smooth muscle cells[37], through shear stress[38] and via an estrogen-receptor dependent mechanism[39,40]. Recent data suggest that the endothelin system contributes to endothelial dysfunction, vascular remodeling and hypertrophy and the progression of atherosclerosis[41-43].

Molecular mechanisms of estrogen action

Estrogen binding occured in target tissues such as organs of the reproductive tract, however it could also be observed in non-target cells where binding is not restricted to the nucleus[44]. Vascular tissue is a target for steroids including estrogens indicating a local role for these hormones[3,45]. In agreement with these findings, messenger RNA and protein for the "classic" nuclear estrogen receptor (ER) α has been identified in human endothelial and vascular smooth muscle cells[46-50], and their expression is altered in atherosclerotic arteries[51]. Furthermore, ERα isoforms in vascular smooth muscle cells lacking transactivational activity have been reported[52]. Recently, a second transcriptionally active receptor has been cloned from prostate tissue and was named ERβ[53,54]. The ERβ exists in at least five different isoforms[55] and is expressed and functionally active in the vasculature[56-59]. Cross talk between the ERα and ERβ has been reported[55], an observation that may have important implications for the action and particularly for therapeutic application of estrogens and estrogen antagonists. In recent years, it has become clear that estrogen binding also occurs independently from nuclear receptors[44]. Binding of estrogen has been found in the cytosol of endothelial cells[60], a cell compartment containing an estrogen receptor activator protein[61]. Some of the rapid actions of estrogen[62-67] are thought to be mediated through steroid membrane receptors[68-71]. However, ERα-in contrast to current theories of its function as a "pure" nuclear receptor- is involved in rapid modulation of NOS[13,14], particularly NOS 3[12,72,73], involving translocation of NOS 3 from the cell membrane close to the nucleus[74]. Since the first description of vascular effects of estrogen more than a hundred years ago[15,75] several mechanisms by which estrogens indirectly and directly modulate vascular function have been identified. Estrogens inhibit the transcription of vascular genes[8,12,23,73,76-78], membrane potentials and ion currents[66,67,79-81], protein phosphorylation[67], expression of receptors[82-84] and activity of vasoactive peptides. Furthermore, estrogens modulate the activity of vascular enzymes[13,85,86] and act as antioxidants due to their phenolic structure[87-90]. The majority of these effects result in inhibition of vascular growth and/or vasodilatation, thus improving organ perfusion.

Estrogens and vascular function

In addition to first observations in uterine tissue[15,75], dilatation by estrogens in human vascular tissue was first observed in a venous vessel, the umbilical artery[91]. In 1993, we reported that 17β-estradiol relaxes human coronary arteries by an endothelium-independent mechanism[64,92,93] (Fig 1, 2), a finding independently confirmed by Chester and

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coworkers[91]. This direct, rapid effect of 17β-estradiol, which is also present in porcine coronary arteries[95], was also observed in isolated human internal mammary arteries, however the relaxant effect was less pronounced[92]. In addition to the direct effects on the vascular wall, estrogens exerted rapid as well as chronic effects on the endothelium affecting epicardial coronary[65,96-98] and resistance arteries[99] as well as the peripheral circulation[100], where estrogens are involved in flow-mediated and shear-stress-induced release of NO[101]. In human coronary arteries, we have recently demonstrated that endothelium-dependent relaxation to bradykinin, a vasodilator substance released by endothelial cells, was acutely potentiated by short-term incubation with 17β-estradiol[65]. In addition, contraction to vasoconstrictors such as angiotensin II, serotonin, and histamine was markedly attenuated in the presence of 17β-estradiol in human internal mammary arteries[102]. Interestingly, similar effects are observed using phyto-estrogens which were shown to improve coronary artery endothelial function[103] and to also inhibit atherosclerosis[104]. The vascular actions of phytoestrogens have been recently discussed in an excellent review[105].

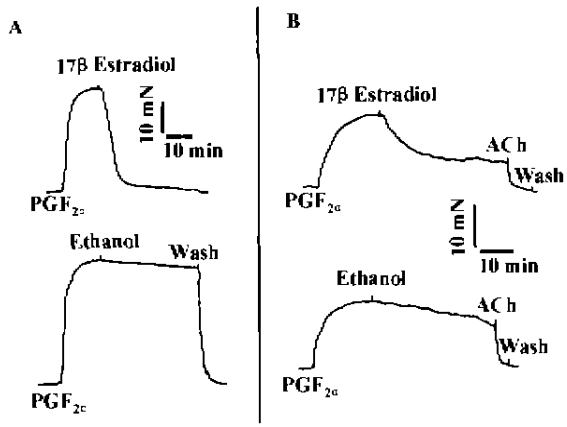

Fig 1. Original tracings of the effects of 17β-estradiol (upper panels) or solvent control ethanol (ETOH, 0.2 % vol/vol, lower panels) in isolated human coronary arteries (A) and human internal mammary arteries (B) precontracted with prostaglandin $F_{2\alpha}$. Note that in both coronary and internal mammary arteries 17β-estradiol 3 μmol · L^{-1} induces rapid relaxation, which is maximal after 15-20 min [from references (64, 92)].

Evidence suggesting physiological relevance of

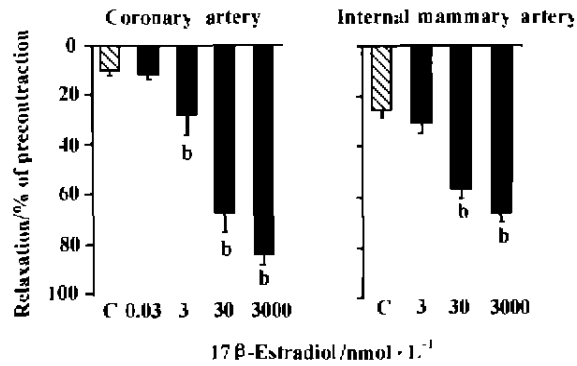

Fig 2. Concentration-dependent relaxation of isolated human coronary arteries (A) and human internal mammary arteries (B) precontracted with prostaglandin $F_{2\alpha}$ by 17β-estradiol. C, solvent control ethanol (0.2 % vol/vol, hatched bars). Note that in internal mammary arteries the solvent ethanol induces relaxation that is greater than in coronary arteries. $^bP < 0.05$. [Adapted from references (64, 92)].

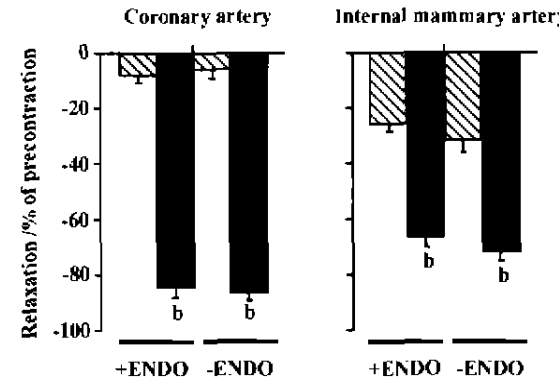

Fig 3. Direct relaxant effect of 17β-estradiol (3 μmol/L, black bars) and solvent control ethanol (0.2 % vol/vol, hatched bars) in human coronary arteries and internal mammary arteries with (+ENDO) and without endothelium (-ENDO). Note that in both vessels endothelial denudation had no effect on relaxation induced by 17β-estradiol. $^bP < 0.05$. [From references (64, 92)].

these *in vitro* findings in human arteries came from *in vivo* observations showing that physiological fluctuations of estrogen plasma levels during the menstrual cycle were directly related to endothelium-dependent vasodilatation[106], consistent with the concept of estrogens as physiological modulators of vascular tone. Thus, estrogens favored a state of vasodilatation, which may explain the onset of endothelial dysfunction due to

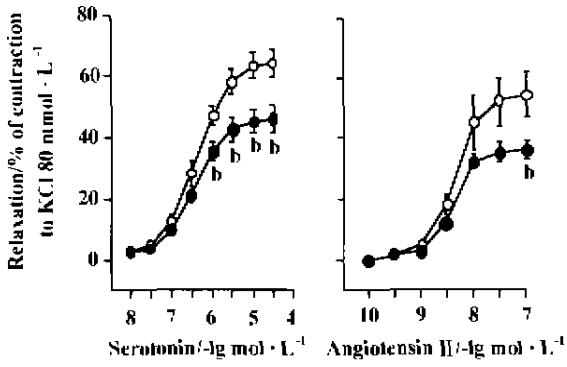

Fig 4. Acute effects of 17β-estradiol on contractions induced by angiotensin Ⅱ (left panel) and serotonin (right panel). Incubation with 17β-estradiol for 30 min attenuated the vasoconstrictor response to both agonists. $^bP < 0.05$. [Adapted from reference (102) Karger, Basel].

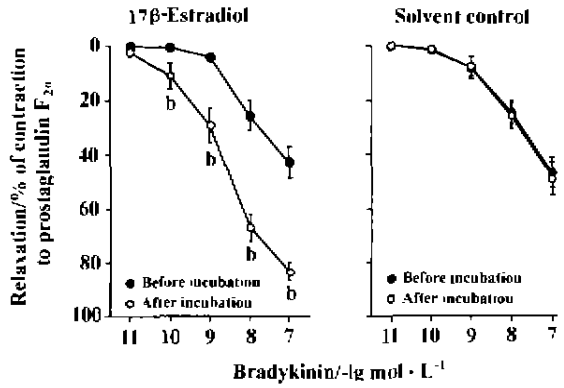

Fig 5. Acute effects of 17β-estradiol on endothelium-dependent relaxations to bradykinin in isolated human coronary arteries. Incubation with 17β-estradiolfor 30 min markedly potentiated relaxation to bradykinin (left panel). Incubation with the solvent control (0.2% vol/vol ethanol) had no effect on endothelium-dependent relaxations (right panel). $^bP < 0.05$. [Adapted from reference (65)].

"estrogen withdrawal" after menopause[6,107].

Estrogens and occlusive vascular disease

Antiproliferative effects of estrogens in the vasculature are well documented, including inhibitory effects on intimal hyperplasia after balloon angioplasty[108-111], and on the progression of atherosclerosis[106], two of the major clinical features of patients with coronary artery disease. Conjugated equine estrogens alone but not in combination with medroxyprogesterone acetate inhibit atherosclerosis in non-human primates[99,114,115]. In contrast to estrogens, raloxifene, a tissue-selective estrogen receptor agonist-antagonist which has been favored for postmenopausal hormone replacement therapy because of low cancer risk[116], had no effect on atherosclerosis in the same model[117]. The prospective HERS trial showed no effect after four-year combined estrogen/medroxyprogesterone acetate treatment on cardiovascular mortality in postmenopausal women with established coronary artery disease[118]. However, future studies are needed to determine whether natural progestogens, which are required to ensure protection of the endometrium, can maintain the beneficial effects of estrogen treatment on atherosclerosis and cardiovascular mortality.

Restenosis, a complex process, involving proliferation of cells in the intima, the media, and the adventitia[119,120], occurs in 30 – 50 percent of patients undergoing balloon angioplasty due to coronary atherosclerosis. Several studies have demonstrated that estrogens inhibit restenosis[108-111] and there is experimental evidence that medroxyprogesterone acetate antagonizes these effects[121]. Pregnancy, which is associated with a marked increase in estrogen levels in plasma and in tissue, completely prevented restenosis-even in the absence of a functional NOS 3-gene[122]. These data and the observation that the inhibitory effect of estrogen on restenosis is preserved also in the absence of the ERα suggest a different mechanism. Indeed, ERβ is rapidly up-regulated after balloon angioplasty in male mice[57] suggesting a role for this receptor in vascular injury and possibly protection.

Beneficial effects of estrogen-clinical evidence and relevance

Although experimental data has demonstrated a beneficial effect of estrogens on endothelial function and vascular structure, clinical data on the effects of hormone replacement therapy remain conflicting with some studies showing improvement[107,123,124] while others did not[125]. The different results may be related to the severity of pre-existing endothelial dysfunction[107] and on the use of synthetic progestogens

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such as medroxyprogesterone acetate (MPA). This compound has been commonly administered to postmenopausal women to oppose the side effects of estrogen. However, MPA also antagonizes the positive effects of estrogen on vascular function[99,126], an effect not seen for natural progesterone[123]. Recent advances such as the identification of novel modes of actions of estrogens, the discovery of ERβ will help in understanding the actions of estrogens and allow the design of new strategies for their therapeutic application to prevent cardiovascular disease and its sequelae.

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雌激素的血管作用：快速作用，新的机制和治疗潜力[1]

R972.1

关键词 雌激素类；缓激肽；动脉；内皮缩血管肽类；一氧化氮；绝经后；血管舒张

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