Hormonal Regulation of Normal Vascular Tone in Males

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“Shall it be male or female? say the cells, And drop the plum like fire from the flesh.”

—Dylan Thomas

The presence of steroid hormone receptors in the vasculature of male animals has been recognized for more than two decades, and the ability of vascular estrogen receptors (ERs) to activate gene expression in vascular smooth muscle and endothelial cells from both sexes is now well established. We know now that normal ER function is required for skeletal development in the human male, male fertility, and normal cardiovascular development and function in males as well as females. In men, circulating estrogen levels are quite low and substantially lower than androgen levels.

How do cardiovascular tissues in men become exposed to estrogen? Males generate estrogen by synthesizing it directly from testosterone in target tissues. The enzyme aromatase, a member of the P450 superfamily of enzymes, is responsible for the conversion of C19 androgenic steroids to the corresponding estrogens, a reaction known as aromatization, since it involves conversion of the A-ring of androgens to the corresponding phenolic A-ring characteristic of estrogens (Figure). Aromatase is widely expressed in ovary, placenta, hypothalamus, liver, muscle, adipose tissue, and of note, in vascular smooth muscle and endothelial cells. Estradiol is therefore generated directly in the male vasculature, where it can activate ERs in both the cells in which it arises and in neighboring vascular smooth muscle and endothelial cells.

Two new studies contribute substantially to our understanding of the autocrine and paracrine effects of aromatase-derived estrogen in the male vasculature. In the last issue of Circulation Research, Lew and colleagues report studies in healthy young men of the effect of estrogen replacement on endothelial function. Study subjects were given anastrozole, a nonsteroidal inhibitor of aromatase, to suppress local estrogen production. Anastrozole caused a significant decrease in flow-mediated brachial dilatation compared with placebo in these healthy subjects. In this issue of Circulation Research, Kimura and coworkers present animal studies complementary to these human studies. They report that endothelium-dependent vasodilation is significantly blunted in blood vessels from the male aromatase knockout (ArKO) mice. These studies thus both support the hypothesis that aromatization of testosterone to estrogen is required for the maintenance of normal endothelial function and vascular tone in males.

Prior Studies in Male Animals

There is substantial evidence that physiological testosterone levels have a beneficial effect on blood vessels and that this is due to conversion of testosterone to estrogen. Testosterone relaxes blood vessels in male animals of several species, as do selective ER modulators like tamoxifen and raloxifene. Injury of male blood vessels induces the expression of ER β, and disruption of the ER β gene in mice leads to abnormal vascular function and hypertension. The role of ERs in the vasculature extends as well to the more complex processes of the vascular injury response and atherosclerosis. In the rat carotid injury model, testosterone, estrogen, and selective ER modulators all can inhibit neointimal thickening after balloon injury. Using LDL receptor–deficient mice, Nathan and coworkers recently showed that castration of male animals increases the extent of atherosclerosis that develops in comparison to intact animals while aromatase inhibition with anastrozole reverses the protected status of intact male mice and increases the extent of atherosclerosis to the level observed in orchidectomized animals. Furthermore, testosterone was able to reduce lesion formation in castrated animals, an effect that was abrogated when mice were simultaneously treated with aromatase inhibitor. This study supports that vascular aromatase and local estrogen production mediate testosterone attenuation of early atherogenesis in this model. These investigators subsequently showed that aromatase-derived estrogen specifically inhibits expression of the proatherogenic vascular cell adhesion molecule VCAM-1.

Prior Studies in Human Males

Estrogen replacement therapy in men has been considered fraught with risk since 30 years ago when the Coronary Drug Project (CDP) study found that high-dose estrogen therapy in men was associated with an increased risk of myocardial infarction and death. The results of the CDP halted research of estrogen replacement in men. However, it was subsequently recognized that the high doses used in the CDP were likely to have contributed to the prothrombotic effects observed in study subjects. As both animal and human studies of sex steroid hormones in males...
gradually resumed, abundant evidence accumulated supporting that estrogen acts on the male cardiovascular system (reviewed in Reference 24). Physiological levels of E2 help maintain normal plasma levels of HDL cholesterol in men. A man lacking functional ER-H9251 has been reported to have a number of abnormalities of bone and mineral metabolism,4,24 as well as significant impairment of flow-mediated endothelial vasodilatation and early coronary arterial calcification.26,27

Estrogen has direct vasodilator properties in men as it does in women. In a study by Blumenthal and coworkers,28 conjugated estrogens enhanced acetylcholine-mediated coronary blood flow increases measured 15 minutes after intravenous hormone. Conjugated estrogens can also acutely abolish abnormal coronary artery constriction induced by cold pressor testing in male cardiac allograft recipients.29 Increased bioavailability of endothelial-derived nitric oxide is presumably responsible for these effects. However, at least one study found that estradiol modulates acetylcholine-induced coronary artery responses in female but not male atherosclerotic coronary arteries.30 In a study of hypogonadal men, estrogen supplementation to levels considered physiological in women was well tolerated, and vasoconstrictor responses to several agonists were markedly attenuated by estrogen treatment. Estrogen also reduced systolic and diastolic blood pressures and increased HDL cholesterol levels in these men, but interestingly did not alter vasodilator responses to acetylcholine.31 In another recent study, the selective ER modulator tamoxifen significantly increased endothelium-dependent, flow-mediated dilatation of the brachial artery in men with angiographically proven coronary artery disease and control subjects with normal coronary arteries.32 Chronic aromatase inhibition in elderly men has been associated with reduced endothelial function that is reversible after cessation of therapy.33 Studies of male to female transsexuals receiving long-term high-dose estrogen therapy have shown that estrogen treatment improves endothelium-dependent vasodilation.34,35 Finally, recent work supports that genetic variation in the ERα can substantially modify the risk for myocardial infarction in men. In studies of subjects from the Framingham Heart Study Offspring Study, Shearman and colleagues36 demonstrated very recently that a common ERα variant is associated with a 3-fold increase in the risk of myocardial infarction in men.

Testosterone levels, like those of estrogen, decline with age. Most cross-sectional studies show an inverse relationship between testosterone levels and the incidence of coronary heart disease in men (reviewed in Reference 37). Administration of physiological amounts of testosterone to men with coronary artery disease enhances coronary blood flow and endothelial function.37,38 It is important to bear in mind that administration of exogenous estrogens can alter the expression of components of the very hormone response system targeted. For example, estrogen induces an increase in sex hormone–binding globulin concentrations in blood, which in turn may reduce free testosterone levels and potentially tissue bioavailability. If this proves to be clinically relevant, it might be more effective to attempt to enhance aromatization of exogenous testosterone to estradiol instead of trying to increase tissue estrogen availability with estrogen supplementation. Consideration of such issues will be necessary if we desire to develop a rational approach to hormone replacement therapies for women and for men.37,39 However, tailored, selective hormone receptor and/or enzyme-directed therapies for testosterone and estrogen replacement have the potential to help us treat vascular disease in men and in women.

The two recent studies in Circulation Research13,14 use sophisticated approaches to shed important new light on our understanding of normal hormonal control of vascular tone in males. In the Lew et al study,13 the authors find significant attenuation of flow-mediated vasodilatation without significant changes in lipoproteins, homocysteine, or C-reactive protein. The ArKO mice used by Kimura and colleagues14 were made and characterized in the Simpson
laboratory and already have provided us with a wealth of information about estrogen in normal male physiology. Male ArKO mice have no detectable plasma estradiol and have marked elevations of circulating testosterone, lutetinizing hormone (LH), and follicle-stimulating hormone (FSH). They display impaired sexual behavior and spermatogenesis, and they develop obesity, hypercholesterolemia, hyperleptinemia, and insulin resistance, as well as osteoporosis. Kimura et al add vascular dysfunction to the list of abnormalities present in the male ArKO mice. Together, these two new studies support that conversion of aromatase-generated estrogen helps maintain normal vascular tone. These studies, and work on this pathway in females, suggest several important questions to explore next. First, does maintenance of normal tone by estrogen in males require ERs (which is very likely)? If so, are ERα and ERβ both involved? We know that ERαKO mice have abnormal decreases in basal nitric oxide production and that ERβKO mice have abnormal contractile responses in part due to diminished expression of inducible nitric oxide synthase (iNOS). However, it is not clear at present whether estrogen’s effects on vascular tone in males are mediated by endothelial NOS (eNOS), iNOS, or some combination of NOS isoforms. By combining the currently available pharmacological inhibitors for ER and NOS, as well as existing genetically modified mice for ERα, ERβ, eNOS, and iNOS, these questions can now be directly addressed. The relative contributions of rapid, “non-genomic” activation of NOS and genomic increases in NOS expression in male vessels, both of which are regulated by ERs, (Figure), also need to be understood, as does the relative contributions of local versus systemic aromatase activity to the male vascular dysfunction noted in these studies. However, the evidence for an important role for endogenous estrogens in vascular physiology continues to accumulate. These new studies add to the growing interest in developing tissue-specific sex steroid hormone receptor modulators as new therapies to modify the development and/or progression of vascular diseases in men and women.

References
Mendelsohn and Rosano  Hormonal Regulation in Vasculature of Male Animals


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