Editorial

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Alteration in Endothelial Estrogen Receptor Expression
A Potential Key of Vasculoprotection by Estrogens?

Jean-François Arnal, Francis Bayard

The results of the Women’s Health Initiative, a randomized controlled primary prevention trial evaluating the risks and benefits of estrogen plus progestin in healthy postmenopausal women, were published in July 2002.¹ After a mean of 5.2 years of follow-up, the data and safety monitoring board recommended cessation of the trial because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. More surprisingly, this trial revealed that hormone replacement therapy (HRT) does not confer vasculoprotection, but even slightly increases the risk of a cardiovascular event early after the start of HRT. These results are quite similar to those reported concerning the effect of HRT in secondary prevention (Heart and Estrogen/Progestin Replacement Study [HERS, 1998]).² These data clearly conflict with previous clinical observations and experimental studies. Indeed, the clinical rationale for these two large randomized controlled trials was based on the epidemiological evidence that women are protected against the clinical complications of atherosclerosis until menopause. However, this protection, probably attributable to sex hormones, is steadily lost within the years after menopause. In addition, all experimental studies that use animal models of atherosclerosis, by feeding monkeys, swine, or rabbits an atherogenic diet,³ have clearly demonstrated that estrogens prevent fatty streak deposit, the first step of atherosclerosis. More recently, the effect of estrogens was also studied in genetically modified mice, which allowed evaluation of the expression of various genes in physiological or various pathological processes. Mice deficient in apolipoprotein E demonstrate an endogenous hypercholesterolemia on a chow diet and develop fatty streaks, which are prevented by estradiol.⁴ Clinical studies have demonstrated that estrogens increase HDL-cholesterol and decrease LDL-cholesterol, thereby improving the lipoprotein profile. However, the fatty streak deposit in experimental atherosclerosis can be prevented even in the absence of changes in circulating cholesterol.³,⁴ Thus, only a minor part of the vasculoprotective effect of estrogens can be attributed to a beneficial effect on circulating lipoproteins. Accordingly, a number of recent studies strongly suggest a direct effect of estrogens on the vascular wall and, in particular, on the endothelium.⁵ The endothelium is recognized to play a crucial role in the physiology of circulation, because this cell monolayer is uniquely positioned at the interface between the blood and the vessel wall. As such, it could constitute a crucial estrogen target by regulating, for example, the generation of nitric oxide (NO)⁶ or stimulating reendothelialization of the carotid artery after endovascular injury.⁶ To date, expression of the two isoforms of estrogen receptor (ER), encoded by two different genes, ERα and ERβ, has been observed in endothelial cells.⁷ ERα, the first to be described, mediates most of the effects of estradiol (E2) in the process of reproduction. More recently, ERβ was characterized, but its role remains unknown. Thus, estrogens can directly influence endothelial physiology through a genomic mechanism, although nongenomic mechanisms responsible for short-term effects have also been demonstrated. Their respective importance remains to be clarified.⁸

Alterations of the cellular ER levels could then be of major importance in mediating the endothelial effect of E2. This aspect is investigated by Ihionkhan and coworkers in this issue of Circulation Research. In experiments using cultured ovine endothelial cells, they demonstrated that physiological concentrations of E2 induce an initial (2-hour) ERα downregulation. This observation fits well with the decrease initially described in the uterus after estrogen administration to rats,⁹ as well as in cultured uterine and breast cancer cell lines after estrogen exposure.¹⁰,¹¹ The mechanism of this downregulation has recently been investigated in transfected cells: ERα is degraded by the ubiquitin-proteasome pathway in a hormone-dependent manner, and such degradation is actually required for ERα to serve as a transcription factor.¹² Whether such a mechanism is also involved in endothelium was not investigated by Ihionkhan et al and will probably deserve further investigation in future studies. This group also reports that ERα downregulation is followed by an increase in ERα protein abundance that becomes evident after 6 hours of hormone exposure. Thus, the recovery of ERα in endothelial cells is more rapid at reaching receptor levels greater than baseline when compared with what is seen in reproductive tissues.¹³ Persistently elevated ERα levels under continuous estrogen treatment indicate a role of the hormone in maintaining the enhanced endothelial ERα expression. To what extent this dynamic gene regulation occurs in vivo, in endothelial cells from other vascular beds, and from other species, if it is modified by an associated progestin treatment, will require further investigation. Indeed, if similar kinetics occur in vivo, the route, dosage, and mode of E2 administration could greatly influence the biological activity of E2 in several ways. At least three routes of administration are currently proposed: oral, percutaneous, and, recently, nasal.¹⁴
The oral route and, more impressively, the nasal route elicit a sharp plasma peak followed by a rapid decline of the plasma concentration of the hormone, whereas the percutaneous route induces rather plateaued plasma levels, a profile close to that given by the subcutaneous pellets used in most of the experimental studies. Thus, in future studies, it will be of great interest to assess the ERα expression in tissues of the experimental models in response to both continuous and intermittent E2 administration. The intracrine or paracrine production of estrogens in the vascular wall by aromatization of androgen precursors and local metabolism will probably also have to be considered.14,15

Ihionkhan et al.10 reported that, in contrast to the upregulation in ERα after long-term E2 administration, the expression of ERβ was downregulated, which is the first evidence of contrasting ER isoform regulation by the hormone. It again raises the question of the role of ERβ in vascular biology, especially considering that this isoform is upregulated in the rat carotid artery after injury.16 Using gene targeting to investigate the function of the two receptors in vivo, it has been observed that E2 accelerates reendothelialization and increases endothelial production of endothelium-derived relaxing factor (EDRF)/NO in wild-type and in ERβKO mice. These effects of E2 are completely lost in ERαKO mice, unambiguously demonstrating that ERα, but not ERβ, mediates these endothelial effects of E2.18,19 The specific gene target(s) of ERβ are, if any, still to be characterized. Moreover, the full-length ERα at 66 kDa may not by itself mediate the complete range of activities of E2 in the endothelium. Human umbilical cultured endothelial cells contain two prominent ERα immunoreactive bands, one of the expected 66 kDa mass and the other at 45 kDa, which may separately trigger genomic or rapid signaling responses.20 Tissue-specific expression of such ERα mRNA variants, including aorta, have previously been described in the mouse21 and in humans.22 These observations in cultured cells recently found an in vivo counterpart when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensable when we demonstrated that the AF-1 activation function of ERα may be dispensible when the effect of estradiol on endothelial NO production in mice.23 At this point, it is also worth noting that the cellular level of the large series of nuclear receptor coactivators may play as great a role in estrogen action as the ER concentration itself.

Finally, in addition to the endothelium, the atherosclerotic process involves many other cell populations, such as smooth muscle, monocyte macrophages, and lymphocyte populations. In each of them, conditions of estrogen deficiency after surgical or natural menopause may also be characterized by altered ER expression, thereby potentially contributing to the increase in vascular disease associated with these states.5 Future studies will have to precisely define their specific roles. This assessment is required to understand the mechanisms by which estrogen can be vasoprotective (or not).

References


KEYWORDS: endothelium ■ estrogen receptors ■ estradiol ■ atherosclerosis ■ vasculoprotection
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