Estrogen-Independent Activation of Estrogen Receptors

Matthias Barton, Matthias R. Meyer, Eric R. Prossnitz

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Sex differences showing a lower prevalence and better outcome after ischemic stroke in women have been described, differences that are abrogated by natural or surgical menopause.1,2 High levels of endogenous estrogens in premenopausal women have been associated with reduced risk for a number of diseases, such as hypertension, diabetes mellitus, obesity, vascular disease, and stroke.2 The growing number of postmenopausal women attributed to shifts in world demographics also requires special action for the prevention and treatment of these conditions.3 Clinical and preclinical studies indicate that natural estrogens, such as 17β-estradiol, exert profound protective effects in the adult and the aging brain.3,4 Three proteins have been identified to mediate the effects of estrogens: estrogen receptor (ER) α, ERβ, and G protein–coupled ER (GPER).2,4 Although expression and function of ERα and ERβ have been well studied under physiological conditions, information about their function and expression under disease conditions, particularly in stroke,1 is still scarce.2,4

Interactions Between Estrogen and the Renin-Angiotensin System

Angiotensin is an important regulator of kidney function, inflammation, vascular tone, and, thus, cerebral perfusion.5,6 Estrogen inhibits the activity or expression of different components of the renin-angiotensin system such as angiotensin-converting enzyme (ACE), angiotensin II, or angiotensin II type 1 (AT1) receptors.6,7 Conversely, cessation of estrogen production after menopause activates the renin-angiotensin system.6 Previous studies indirectly suggested that the AT1 receptor, the predominant cellular target of angiotensin II, interacts with the function of estrogen receptors. Using a model of surgical menopause, Chappell et al8 found that the AT1 antagonist olmesartan is as effective as 17β-estradiol to suppress hypertension attributed to estrogen deficiency. Also, Tsuda et al9 reported that, in mice with atherosclerosis, neither low-dose 17β-estradiol nor olmesartan had an effect on its own on atherosclerotic lesion formation; however, in combination, lesion formation was almost completely suppressed. In addition, the AT1 antagonist losartan exerts central effects on thirst and sodium appetite in rats, which are inhibited by estrogen.9 Collectively, these findings indirectly suggested that both the renin-angiotensin system and estrogen-estrogen receptor signaling might share and/or amplify common modes of action that might be relevant for pathologies such as postmenopausal hypertension or its consequences, including myocardial infarction and stroke.

Estrogen-Independent Effects on Estrogen Receptor Signaling

In the present issue of Hypertension, Shimada et al10 have now taken this issue a step further. They assessed directly, using a model of surgical menopause, the potential involvement of estrogen receptors in the protective effects of the AT1 antagonist olmesartan on cerebral infarct size and the cellular changes associated with it. In addition, this comprehensive study reports several novel findings on the role of the brain renin-angiotensin system and regulation of estrogen receptors after ischemic stroke. The investigators found that, in the brain, ACE2 is expressed at higher levels than ACE1 and that all 3 of the estrogen receptors, ERα, ERβ, and GPER, are detectable. Ovariectomy had very distinct effects on stroke-induced changes: it increased infarct size and cerebral angiotensin II and AT1 receptor expression but reduced expression of ERα, ACE2, and the AT2 receptor. On the other hand, the expression levels of ACE1, ERβ, or GPER remained unaffected by menopause or stroke. These findings are important because they demonstrate that neither components of the RAS nor estrogen receptors are regulated uniformly under the same conditions (ie, physiological processes such as menopause or diseases such as ischemic stroke). The most important findings of the study by Shimada et al10 were that olmesartan treatment not only reduced infarct size but that these effects of olmesartan were estrogen receptor dependent, that is, olmesartan increased ERα in the peri-infarct zone, an effect that was blocked by the ER antagonist ICI 182 780 (Figure). Expression of ERβ and GPER remained unaffected by stroke or olmesartan treatment. Having discovered this new and important effect of a nonestrogenic drug on ERα signaling, the investigators went on to study whether olmesartan regulates ERα function and found that olmesartan stimulates both expression and phosphorylation of ERα, but only its phosphorylation was sensitive to ERα blockade by ICI 182 780. Given the previous observations of interactions between the RAS and estrogen,7–9 these important data are the first to demonstrate a direct interaction between an AT1 antagonist and ERα, compatible with the concept that ERα-dependent activation, molecular regulation, and organ protection may occur even in the absence of estrogen.

Implications and Perspectives

The findings presented by Shimada et al10 leave us with several questions. First, and perhaps most important, does activation of...
Figure. Estrogen receptor (ER)-dependent protective effects of olmesartan in ischemia-induced brain injury in estrogen (E2)-deficient states, such as menopause (natural or after ovariectomy). The angiotensin type II (AT1) receptor antagonist olmesartan (Olm) increases expression and phosphorylation of ERα. This results in upregulation of the angiotensin-converting enzyme (ACE) 2, Bcl-2, and Bcl-xL genes in an E2-independent manner, an effect that is blocked by the ERα antagonist ICI 182 780 (ICI). ICI also acts as an agonist of G protein–coupled ER (GPER), + indicates activation; −, inhibition.

ERα by an AT1 antagonist represent a class effect or is it simply because of the structural properties of this particular drug? Functional similarities with estrogen have been reported previously for other vasoprotective drugs, such as the β1 receptor-agonist nebivolol.11 Second, olmesartan attenuates atherosclerosis progression, a disease sensitive to ERα-activation;13 thus, the question remains as to how much of these olmesartan effects are mediated through ERα. In addition, novel estrogen receptors such as GPER may also affect olmesartan’s cellular target.14 Indeed, olmesartan was shown recently to reduce intimal angiogenesis,12 an effect that could be explained through antiangiogenic action of GPER activation.15 Finally, and most importantly, is the question of whether ERα-dependent effects of olmesartan are present and required for olmesartan’s effects in patients. Although olmesartan potentiates the antihypertensive effect of 17β-estradiol in postmenopausal women,16 most recently the Randomized Olmesartan and Diabetes Microalbuminuria Prevention Trial reported excess cardiovascular events and cardiovascular deaths in diabetes with cardiovascular disease.17 It can only be speculated whether the increased risk involved ERα-dependent effects of olmesartan. Also, whether the increased risk attributed to olmesartan is equally present in men and women is not known, because no sex-dependent subanalysis of this study is available. In any case, the work presented by Shimada et al10 provides surprising and important new pieces to the puzzle of how estrogen receptors and the renin angiotensin system interact. Whether olmesartan (or other angiotensin receptor blockers) also causes ERα activation in humans or in diseases distinct from ischemic stroke should be addressed in future studies.
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