Importance of Estrogen Metabolites

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The influence of estrogen on blood pressure is complicated and sometimes contradictory. Premenopausal women have a lower incidence of hypertension, but recent clinical trials suggest that postmenopausal hormone replacement therapy does not necessarily decrease the risk of cardiovascular disease. Sexually dimorphic hypertension is evident in multiple animal models, yet only some indicate a critical role for estrogen. These contradictions emphasize the importance of identifying the critical molecular signaling pathways in the cardiovascular system that are activated by estrogen and pursuing alternative pathways for their activation. One important factor that has been neglected in the study of estrogen’s cardiovascular effects is the conversion of 17β-estradiol, the most commonly studied ovarian estrogen, to metabolites that are capable of exerting discrete physiological effects (Figure).

In this issue of Hypertension, Jennings et al use a mouse model of angiotensin II (Ang II)–induced hypertension to demonstrate that the protective cardiovascular effects historically attributed to the predominant estrogen 17β-estradiol may instead reflect distinct actions by the metabolite 2-methoxyestradiol (2-MeE2). The critical enzymes include cytochrome P450 1B1 (CYP1B1), which metabolizes 17β-estradiol to the catechol estrogen 2-hydroxyestradiol (2-OHE), and catechol-O-methyl transferase, which subsequently converts 2-OHE to 2-MeE2. In comparison with wild-type controls, female CYP1B1-knockout mice display a significantly greater pressor response to Ang II accompanied by vascular and cardiac remodeling, vascular dysfunction, and oxidative stress. This genetic approach is nicely complemented by studies using the selective CYP1B1 inhibitor tetramethoxystilbene, which similarly increases the Ang II response. The ability of both CYP1B1 gene deletion and pharmacological inhibition to enhance Ang II–induced hypertension is absent in ovariectomized mice, emphasizing the necessity of endogenous estrogen as a substrate for CYP1B1’s protective actions.

Protection from Ang II–induced hypertension is restored in CYP1B1-knockout mice by administration of the CYP1B1 product 2-OHE and its catechol-O-methyl transferase–derived metabolite 2-MeE2. Interestingly, treatment with another catechol estrogen, 4-OHE, does not reduce blood pressure in Ang II–infused CYP1B1-knockout mice and exacerbates the Ang II response in wild-type female mice. The increased pressure may result from the actions of 4-OHE or its metabolite 4-MeE2. The contradictory actions of these 2 catechol estrogens indicate that in wild-type female mice, 17β-estradiol is predominantly metabolized to 2-OHE and 2-MeE2, which have beneficial actions on blood pressure. Whether disease or aging alter the predominant metabolic pathway and lead to increased production of detrimental metabolites is not yet known.

2-MeE2 may have direct actions on the renin–angiotensin system or may counteract hypertension via other mechanisms. Studies by Dubey and Jackson have established a role for this metabolite in estrogen’s protective cardiovascular effects, including vasodilation and inhibition of vascular smooth muscle cell growth. Although the estrogen receptor (ER) subtype that mediates the beneficial actions of this metabolite is unknown, membrane-initiated signaling events occurring independently of the classical steroid receptors ERα and ERβ have been implicated. Recently, the ability of 2-MeE2 to decrease angiotensin receptor binding was found to be mediated by the G protein–coupled ER. Additional studies using this Ang II infusion model using ER-knockout mice or pharmacological inhibitors will reveal the ER subtype that binds 2-MeE2 and facilitates its protective actions during Ang II–dependent hypertension.

The formation of catechol estrogens 2-OHE and 4-OHE via CYP1B1 and subsequent conversion by catechol-O-methyl transferase to methoxyestradiols is only 1 metabolic pathway for 17β-estradiol. This hormone is also subjected to 16α-hydroxylation, and all of the catechol estrogens (2-OHE, 4-OHE, and 16α-OHE) can be oxidized to form semiquinones and quinones. 17β-hydroxysteroid dehydrogenase converts 17β-estradiol to estrone, which can also be converted to catechol and methoxy estrogens. During pregnancy, 16-hydroxydehydroepiandrosterone sulfate in the placenta converts 17β-estradiol to estriol. Furthermore, cholesterol metabolites that are upstream of 17β-estradiol and formed independently of the enzymes 17α-hydroxylase and aromatase may be important in estrogen’s cardiovascular effects. Cholesterol is directly converted by cholesterol 27-hydroxylase to the metabolite 27-hydroxycholesterol, which acts as both an ER agonist and antagonist, depending on the tissue. Finally, catechol estrogens may directly participate in the formation of prostaglandins through the process of cooxidation in the absence of any receptor binding or activation.

For these findings to be translated into clinical therapies, the relative amounts of estrogen metabolites that are present in women and the influence of aging and disease on the metabolic pathway need to be established. In pulmonary
of 10 different equine estrogens obtained from the urine of pregnant mares. Half of these estrogens are not endogenous to humans and contain 1 or 2 additional double bonds in ring B. Not surprisingly, these equine estrogens have unique pharmacokinetic and receptor-binding profiles, which may contribute to the conflicting results of clinical trials. More sophisticated pharmaceuticals that selectively replace certain estrogen metabolites or are resistant to metabolism need to be developed. Alternatively, combining estrogens with enzyme inhibitors or selective ER modulators such as bazedoxifene may prove to be beneficial for cardiovascular function while avoiding estrogen’s deleterious effects.

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References

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