Is β the α Dog in Estrogen Receptor–Mediated Protection From Hypertension?

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The onset of hypertension occurs earlier in men than in women. Moreover, the magnitude of hypertension is greater in men than in women across diverse mammalian species and experimental models. 17β-estradiol (E₂) is implicated in this female protection because ovarian hormone loss is associated with increased arterial pressure while E₂ replacement can prevent this effect. Creation of mice deficient in estrogen receptors (ERα and ERβ) and the development of ER subtype-selective ligands have enabled investigation of ER subtypes in hypertension.

A study of Japanese women revealed an association between hypertension and a cytokine–adenine repeat polymorphism in the ERβ gene. This association was strengthened by studies in ERβ-deficient mice, which developed hypertension as they aged and exhibited abnormal ion channel function in vascular smooth muscle cells suggesting ERβ attenuated the age-associated hypertensin by preserving vascular function. Pharmacological studies supported these conclusions by demonstrating selective agonists of ERβ-reduced arterial pressure in ovariectomized spontaneously hypertensive rats under conditions in which ERα-selective agonists did not. Furthermore, activation of ERβ improved nitric oxide–dependent vasorelaxation, increased cardiac output, and attenuated cardiac hypertrophy; however, this study did not determine whether these effects were peripherally or centrally mediated.

Previously, Xue et al showed that central but not peripheral infusions of a nonselective ER antagonist into mice augmented the pressor effects of angiotensin II (Ang II), thereby underscoring the importance of central ERs in blood pressure modulation. In this issue, Xue et al used small interference RNA (siRNA) scoring the importance of central ERs in blood pressure modulation. In this issue, Xue et al used small interference RNA (siRNA) to selectively knockdown ERβ in cultured PVN neurons treated over-night with aldosterone; however, these ER-observed effects on superoxide generation occurred in the absence of E₂ and were ER subtype independent. These cell culture studies suggest in vivo factors mask or prevent ERα in the PVN from exerting antihypertensive effects.

One-way ERβ in the RVLM could attenuate arterial pressure by modulating C1-adrenergic bulbospinal neurons because immunoelectron microscopy revealed that immunoreactive-ERβ was most frequently observed in the tyrosine hydroxylase–containing somata and dendrites. Furthermore, whole-cell patch-clamp recordings of bulbospinal RVLM neurons showed that ERβ- but not ERα-selective agonists reduced long-lasting L-type voltage-gated calcium currents. Thus, ERβ may decrease sympathetic tone by inhibiting calcium currents in the RVLM.

High aldosterone levels increase the risk of cardiovascular disease (CVD) in part through central control of blood pressure. Thus, this current study by Xue et al suggests that ERβ-specific agonists have therapeutic potential for treating women with hypertension because of mineralocorticoid excess. Primary aldosteronism was initially considered a rare cause of secondary hypertension with a prevalence <1%; however recently, studies indicate that the incidence is 10-fold higher. Thus, developing ERβ-specific agonists could have major clinical impact in women.

ERβ-specific agonists may also have therapeutic potential for treating men though given that circulating E₂ is 10- to 30-fold lower in men compared with ovarian hormone-replete women and that E₂ levels change dramatically through the menstrual cycle and as life progresses, there could be differences in ERβ agonist effectiveness, especially because sex differences in brain ER levels have been reported. Furthermore, ER expression is modulated by changes in circulating E₂. In Dahl salt-sensitive rats, ovariectomy resulted in reduced renal expression of ERα but increased ERβ whereas
Eβ replacement prevented these effects,9 and the Framingham Heart Study revealed that estrogen-related genes contribute to blood pressure variation in a sex-specific manner.10

ERβ may also be a pharmacological target for men with hypertension as long as any feminizing effects attributable to ERβ could be minimized. This therapeutic potential is illustrated by the drug raloxifen, which is a selective ER modulator that acts in a tissue-specific manner to antagonize ER action in breast tissue while activating ERβ in bone. Moreover, a study in ovariectomized spontaneously hypertensive rats demonstrated that an ERβ agonist was more effective than Eβ at lowering blood pressure while simultaneously avoiding the uterine growth-promoting effects of Eβ.3 Thus, it is conceivable that an ER-selective agonist could be developed that activated ERβ in key brain nuclei without exerting unwanted peripheral effects in men.

Although ERα does not seem to regulate arterial pressure in the PVN and RVLM, ERα could regulate other nuclei that contribute to autonomic control of pressure. In fact, earlier studies by Xue et al1 showed that central administration of Eβ prevented the augmenting effects of ovariectomy on Ang II–induced pressor effects in wild-type but not in ERβ knockout mice. Furthermore, central but not peripheral infusions of an ER-nonselective antagonist augmented the pressor effects of Ang II in wild-type females but not in central Eβ-treated ovariectomized ERα-deficient mice and, ganglionic blockade after Ang II infusion resulted in greater reductions in pressure in the ERα-deficient compared with wild-type mice. Future studies will need to elucidate the role of ERα and ERβ in other brain nuclei that play a critical role in pressure and baroreceptor function. Furthermore, we should determine whether central ERα and ERβ actions differ between Ang II–dependent and aldosterone-dependent hypertension, and we must not ignore the role of ER subtypes in critical end organs like the kidney and vasculature. The G-protein–coupled receptor 30 also warrants in-depth investigation, especially in mechanisms of postmenopausal hypertension because an agonist of this high affinity ER markedly reduced systolic blood pressure in ovariectomized mRen2.Lewis congenic rats but not in Eβ-replete intact females.11

Elucidating the ER subtype- and cell-specific effects of Eβ is critically important to our understanding of the complexities inherent in Eβ replacement therapy for treating ovarian hormone deficiency in women. The use of estrogen replacement therapy (ERT) in postmenopausal women markedly declined since 2002 because of the Women’s Health Initiative, which reported that ERT increased the risk of breast cancer and showed no benefit in reducing CVD risk. A major limitation of the Women’s Health Initiative was that the trial was not designed to study women who had recently entered menopause and the vast majority of women who had entered menopause ≥10 years before the start of ERT. A decade later, 2 key studies found that ERT can be of significant benefit to women who have recently entered menopause. Eleven years of continual ERT reduced the risk of heart failure and myocardial infarction by 50% in women who started treatment within 7 months of entering menopause and there was no evidence of increased risk of breast cancer, thrombosis, or stroke.12 The early results of the Kronos Early Estrogen Prevention Study also support these findings. These recent studies emphasize the clinical importance of delineating the biology of ER modulation of hypertension and associated disease to better inform ERT use.

In this issue, Xue et al9 provide strong evidence that β is the α dog in the PVN and RVLM in ER-mediated protection from mineralocorticoid excess, but the jury is still out on which ER subtype rules in other brain nuclei or how ERβ stacks up compared with the G-protein–coupled receptor 30. Given that hypertension is the major risk factor for CVD and that CVD is the leading cause of death in women, 1 thing is for sure, we need more elegant studies like this one to fully understand the role of Eβ and its receptors in blood pressure modulation so we can translate these findings into new therapeutics for the treatment of hypertension and associated CVD.

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References

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