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Effects of estrogen on vascular function and health: Controversies in hormone replacement therapy

There is a longstanding debate about whether hormone replacement therapy (HRT) is protective against heart disease in postmenopausal women. This is in light of non-randomized epidemiological data demonstrating an increased incidence of coronary heart disease in premenopausal women, compared to age-matched males, and protection of ovariectomized women by estrogen use. Secondary and primary prevention trials of HRT have been conflicting and controversial. Most recent data have been supportive of estrogen preventing or delaying CV pathology, when therapy is started early, i.e., in the perimenopausal period. It is imperative to understand the mechanisms by which estrogen can be protective. Indeed, estrogen has potent effects on the vascular endothelium. Normal homeostasis of a healthy endothelium is critical to maintain an anti-atherosclerotic state. The key, athero-protective molecule of this homeostatic endothelium is nitric oxide (NO). Estrogen is a potent activator of the endothelial enzyme that generates NO, eNOS, through activation of plasma membrane estrogen receptors and a sequential signaling cascade involving the kinases c-Src, PI-3 kinase and Akt. This is therefore mediated through the "nongenomic" pathway of steroid hormone activation, mediated most notably by a splice inform of the estrogen receptor, ER46, in human endothelial cells (ECs). In fact, there is a transmembrane version of endothelial ER46, demonstrated by elegant plasma membrane imaging studies. It is this transmembrane version that creates a huge selective therapeutic targeting opportunity. The molecular features of this receptor will be discussed, as will the controversy of HRT use in postmenopausal women, for cardiovascular protection.

Biography

Jeffrey R Bender graduated from the University of California, San Francisco School of Medicine in 1979. He works in New Haven, CT and specializes in Cardiovascular Disease. Jeffrey R Bender is affiliated with Yale New Haven Hospital.

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