

Estrogen therapy replenishes vascular tetrahydrobiopterin and reduces oxidative stress in ovariectomized rats

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摘要

Abstract

Objective: We investigated whether the effect of estrogen therapy on vascular endothelial function is mediated through increasing the bioavailability of tetrahydrobiopterin (BH4) and associated antioxidant capacity in ovariectomized (Ovx) rats. Design: Aortas of sham-operated, Ovx, and Ovx plus estrogen therapy (Ovx + ET) female Sprague-Dawley rats were used to measure vascular reactivity. Plasma levels of nitric oxide (NO) metabolites, total antioxidant capacity, aortic superoxide anion (O₂⁻), and BH4 contents were determined. Results: Vascular reactivity, assessed on isolated aortic segments, indicated that phenylephrine-induced contraction in the Ovx group was significantly greater than that in the sham and Ovx + ET groups. The vasodilator responses to acetylcholine (10⁻⁹ to 10⁻⁵ M) and L-arginine (L-Arg; 10⁻⁴ M) in the sham and Ovx + ET groups were significantly greater than those in the Ovx group. Pretreatment with BH4 (10⁻⁵ M) enhanced the vasodilator responses to L-Arg in the Ovx group compared with the untreated Ovx group. An inhibitor of BH4 synthesis, 2,4-diamino-6-hydroxypyrimidine (2 mM), significantly attenuated the vasodilator response to L-Arg in the sham and Ovx + ET groups. In addition, Ovx significantly increased O₂⁻ production in aortic tissues and decreased plasma NO metabolites levels, whereas ET significantly prevented these effects. Pretreatment with BH4 also significantly decreased aortic O₂⁻ production in the Ovx group; both plasma total antioxidant capacity and aortic BH4 contents in the Ovx group decreased significantly compared with those in the sham group, which were also improved by ET. There were no significant differences in the protein expression of endothelial NO synthase in aortas in these groups. Conclusions: ET increases the availability of vascular BH4 to attenuate O₂⁻ production and restores total antioxidant capacity, leading to improved NO-mediated vasodilation in Ovx rats.