

〈2〉閉経後女性の心血管性疾患の予防と治療法開発を目的とする、エストロゲンの心保護作用の解析

－血管内皮細胞増殖因子（VEGF）との関係を基軸とする研究－

Effects of estrogen on cardioprotection in postmenopausal women
through VEGF signaling system

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Estrogen has widely been credited for cardioprotection in women. However, the exact mechanisms that underlie these beneficial estrogenic effects are not completely understood. Here, we sought to: 1) elucidate estrogen's influence on levels of vascular endothelial growth factor (VEGF), a key regulator of cardiovascular processes, and components of its basic signaling machinery (VEGF receptors, Akt, and eNOS) in the heart, and 2) delineate the specific estrogen receptor signaling pathway that mediates its beneficial effects using mice lacking either estrogen receptor alpha or estrogen receptor beta. We analyzed pattern of VEGF signaling and the associated coronary capillary density in the hearts of wild-type (WT), estrogen receptor alpha knockout (ER α -KO), and estrogen receptor beta knockout (ER β -KO) female mice. Deletion of estrogen receptor alpha causes a marked decrease in coronary capillary density compared to wild type (WT) mice, while that of estrogen receptor beta had a minimal effect. Consistent with reduced coronary capillary density, cardiac expression levels of VEGF and its signaling molecules (two receptors, phosphorylated Akt, and eNOS) in ER α -KO mice were reduced to half of WT, in contrast to ER β -KO mice that only showed a slight decrease. Moreover, activity of eNOS was greatly lowered in ER α -KO mice. These data suggest that estrogen acts largely via estrogen receptor alpha to regulate VEGF transcription and possibly components of its basic signaling and ultimately, the development of coronary microvasculature in the heart. This molecular and histological data, in part, sheds some insights into potential mechanisms that may likely underlie estrogen's cardioprotective effects.

参考文献

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