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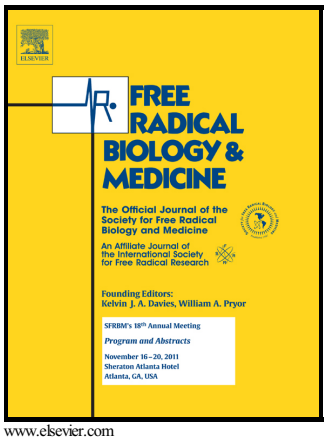

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ACCEPTED MANUSCRIPT

Activation of classical estrogen receptor subtypes reduces tight junction disruption of brain endothelial cells under ischemia/reperfusion injury

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Abstract

Ischemic stroke, which induces oxidative stress in the brain, disrupts tight junctions (TJs) between brain endothelial cells, resulting in blood-brain barrier (BBB) breakdown and brain edema. Estrogen reduces oxidative stress and protects brain endothelial cells from ischemic insult. The aim of this study was to determine the protective effects of estrogen on TJ disruption and to examine the roles of classical estrogen receptor (ER) subtypes, ERα- and ERβ, in estrogen effects in brain endothelial cells (bEnd.3) exposed to oxygen-glucose deprivation/reperfusion (OGD/R) injury. Estrogen pretreatment prevented OGD/R-induced decreases in cell viability and TJ protein levels. ERα- and ERβ-specific agonists also reduced TJ disruption. Knockdown of ERα or ERβ expression partially inhibited the effects of estrogen, but completely reversed the effects of corresponding ER subtype-specific agonists on the outcomes of OGD/R. During the early reperfusion period, activation of extracellular signal-regulated kinase1/2 and hypoxia-inducible factor 1α/vascular endothelial growth factor was associated with decreased expression of occludin and claudin-5, respectively, and these changes in TJ protein levels were differentially regulated by ER subtype-specific agonists. Our results suggest that ERα and ERβ activation reduce TJ disruption via inhibition of signaling molecules after ischemic injury and that targeting each ER subtype can be a useful strategy for protecting the BBB from ischemic stroke in

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