17b-Estradiol Inhibits Subarachnoid Hemorrhage-Induced iNOS Gene Expression by Interfering with the Nuclear Factor Kappa B Transactivation.

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Abstract

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Background and Purpose— Previously, we showed that 17ß-estradiol (E2) treatment prevented the subarachnoid hemorrhage (SAH)-induced cerebral vasospasm in male rats. The aim of this study was designed to further delineate the molecular mechanisms underlying E2-induced inhibition of inducible nitric oxide synthase (iNOS) upregulation and relief of vasospasm caused by SAH.

Methods— The 2-hemorrhage SAH model was induced by 2 autologous injections of blood into the cisterna magna of adult male rats. The rats were then subcutaneously implanted of a Silastic tube containing corn oil with or without 17ß-estradiol benzoate and received daily intraperitoneal injections of various doses of ICI 182,780, a nonselective estrogen receptor (ER) antagonist, for 7 days after the first hemorrhage. Basilar arteries were then removed for protein extraction, RNA isolation, and gel mobility assay. The protein levels of iNOS, p65, and ER were

examined by Western blot analysis, and that iNOS mRNA expression was evaluated by reverse-transcription polymerase chain reaction.

Results— E2 prevented the SAH-induced vasospasm and increases of the levels of iNOS protein and mRNA in basilar artery through an ER-dependent mechanism. Treatment of the SAH rat with E2 did not affect the nuclear translocation of p65 subunit of nuclear factor B, but caused an increase of the association of p65/ER, and reversed the SAH-induced increase of the p65 binding on iNOS promoter.

Conclusions— E2 inhibits the SAH-induced increase of iNOS by increasing the association of p65/ER, which in turn inhibits the binding of p65 to iNOS DNA. Our data suggest the potential applications of E2 in the treatment of SAH patient.