Abeta(25-35) alters Akt activity, resulting in Bad translocation and

許重義
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Abstract

The amyloid-beta peptide (Abeta) induces apoptosis in cerebrovascular endothelial cells (CECs), contributing to the pathogenesis of cerebral amyloid angiopathy. We have previously shown that Abeta induces apoptosis in CECs. In the present study, we report that Abeta25-35-induced CEC apoptosis involves the inactivation of Akt, a signaling kinase important in maintaining cell viability. Akt prevents the activation of death-signaling events by facilitating the inactivation of proapoptotic proteins such as Bad. We applied three strategies to show that Abeta25-35 inactivation of Akt is causally related to Abeta25-35-induced CEC death by preventing Bad activation and subsequent mitochondrial dysfunction (reflected by the release of endonuclease G and Smac, two proapoptotic intermembranous proteins of the mitochondria). Wortmannin, a PI3-kinase inhibitor, enhanced Abeta25-35-induced Bad activation, mitochondrial dysfunction and CEC death. Enhancement of Akt activity by a Tat-Akt fusion protein, or by viral gene transfer of a constitutively active mutant of akt, reduced Bad activation, mitochondrial dysfunction, and CEC death. Using a siRNA strategy to knock down the bad gene, we showed that Bad activation is causally related to Abeta25-35-induced mitochondrial dysfunction and CEC death. Together, these results establish that the Akt-Bad cascade is altered by Abeta25-35, resulting in CEC apoptosis.