ANGIOGENESIS IN NEURODEGENERATIVE PROCESSES: LOSS OF REGULATORY Aβ FUNCTION CONTRIBUTES TO ENDOTHELIAL DEGENERATION

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Preservation of vascular functions are essential for neuronal integrity. Aβ peptides ($A\beta_{1-40}$, $A\beta_{1-42}$), cleavage products of the large precursor protein ubiquitously expressed, APP, may affect endothelial cell functions. Although Aβ peptides are naturally present in low nanomolar quantities as circulating soluble monomers in the cerebrospinal fluid and blood of healthy individuals, their function is not well delinated. We studied the activity of non fibrillary $A\beta_{1-40}$ and $A\beta_{1-42}$ on the endothelial cell functions related to angiogenesis. We demonstrated that Aβ peptides can affect the response of microvascular endothelium to physiological pro-angiogenic stimulation. Aβpeptides(0.5-500 nM) promote the formation of new capillaries by selectively controlling the fibroblast growth factor-2 (FGF-2) signaling cascade, without affecting the specific signaling of vascular endothelial growth factor (VEGF). In contrast, higher (μM) concentrations of Aβ result toxic for endothelial cells directly affecting FGF-2 expression and interfering with FGF-2 binding to its receptors. At these concentrations, in fact, Aβ peptide looses its ability to prime FGF-2 cycle and contributes to endothelial apoptosis. Our findings suggest that loss of the physiological regulatory function of Aβ peptideson FGF-2-induced effect on capillary brain endothelium, can contribute to the pathogenesis of Alzheimer's disease.
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