The epigenetic effects of amyloid-B1-40 on global DNA and neprilysin genes in murine cerebral endothelial cells

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摘要

Abstract

Amyloid-b (Ab) is the core component of senile plaques, which are the pathological markers for Alzheimer′s disease and cerebral amyloid angiopathy. DNA methylation/demethylation plays a crucial role in gene regulation and could also be responsible for presentation of senescence. Oxidative stress, which may be induced by Ab, is thought to be an important contributor of DNA hyper-methylation; however, contradicting this is the fact that global DNA hypo-methylation has been found in aging brains. It therefore remains largely unknown as to whether Ab does in fact cause DNA methylation/demethylation. Neprilysin (NEP) is one of the enzymes responsible for Ab degradation, with its expression decreasing in both Alzheimer and aging brains. Using high-performance liquid chromatography (HPLC), we explore whether Ab is responsible for alteration of the global DNA methylation status on a murine cerebral endothelial cells model, and also use methylation-specific PCR (MSPCR) to examine whether DNA methylation status is altered on the NEP promoter region. We find that Ab reduces global DNA methylation whilst increasing NEP DNA methylation and further suppressing the NEP expression in mRNA and protein levels. Our results support that Ab induces epigenetic effects, implying that DNA methylation may be part of a vicious cycle involving the reduction in NEP expression along with a resultant increase in Ab accumulation, and that Ab may induce global DNA hypo-methylation.