



Nagoya City University Academic Repository

学位の種類	博士 (医学)
報告番号	甲第1979号
学位記番号	第1390号
氏名	高原
授与年月日	令和5年9月25日
学位論文の題名	Presenilin 1 deficiency impairs A β 42-to-A β 40- and angiotensin-converting activities of ACE (プレセニリン1欠損がACEのA β 変換活性に及ぼす影響) Front Aging Neurosci. 2023; 15:1098034. doi: 10.3389/fnagi.2023.1098034.
論文審査担当者	主査： 齊藤 貴志 副査： 松川 則之, 飛田 秀樹

Abstract

Alzheimer's disease (AD) is associated with amyloid β -protein 1-42 ($A\beta_{42}$) accumulation in the brain. $A\beta_{42}$ and $A\beta_{40}$ are the major two species generated from amyloid precursor protein. We previously reported that angiotensin-converting enzyme (ACE) converts toxic $A\beta_{42}$ to neuroprotective $A\beta_{40}$ and reduces the $A\beta_{42}/40$. Inhibition of ACE or heterozygous ACE deletion significantly enhances $A\beta_{42}$ deposition and increases $A\beta_{42}/A\beta_{40}$ ratio in the brain of AD model mice. Most *PSEN1* mutations found in FAD induce an increase in the $A\beta_{42}/40$ ratio, but the underlying mechanism is unclear. Here we found that ACE protein purified from PS1-knockout (PS1-KO) fibroblasts shows altered glycosylation and markedly impaired $A\beta_{42}$ -to- $A\beta_{40}$ - and angiotensin-converting activities. Transfection of wild-type (WT) PS1 restored these activities in PS1-KO cells; however, some PS mutants could not restore the $A\beta_{42}$ -to- $A\beta_{40}$ -converting activity of ACE in PS1-KO cells. We also found that the glycosylation of ACE in adult mouse brain differed from that of embryonic brain and that the $A\beta_{42}$ -to- $A\beta_{40}$ -converting activity in adult mouse brain was lower than that in embryonic brain. Our data indicate that deletion of PS1 results in a significant decrease in both the $A\beta_{42}$ -to- $A\beta_{40}$ -converting activity and angiotensin-converting activity of ACE. Moreover, some FAD-linked PS1 mutations were shown to impair the $A\beta_{42}$ -to- $A\beta_{40}$ -converting activity of ACE. Our findings suggest that PS mutations increase the $A\beta_{42}/A\beta_{40}$ ratio by reducing the $A\beta_{42}$ -to- $A\beta_{40}$ -converting activity of ACE.