

## 論文の内容の要旨

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論 文 題 目 Conversion of A $\beta$ 43 to A $\beta$ 40 by the successive action of angiotensin-converting enzyme 2 and angiotensin-converting enzyme (アンギオテンシン変換酵素 II(ACE2)およびアンギオテンシン変換酵素(ACE)による A $\beta$ 43 から A $\beta$ 40 への変換機構解析)	
(論文の内容の要旨)  [背景と目的] The longer and neurotoxic species of amyloid- $\beta$ protein (A $\beta$ ), A $\beta$ 42 and A $\beta$ 43, contribute to A $\beta$ accumulation in Alzheimer's disease (AD) pathogenesis and are considered to be the primary cause of the disease. In contrast, the predominant secreted form of A $\beta$ , A $\beta$ 40, inhibits amyloid deposition and may have neuroprotective effects. We have reported that A $\beta$ 43 is the earliest-depositing A $\beta$ species in the amyloid precursor protein transgenic mouse brain. Here, we studied whether there are enzymes converting A $\beta$ 43 to A $\beta$ 42 and converting A $\beta$ 43 to A $\beta$ 40.  [材料と方法] C57BL/6J mouse brain and other tissues were homogenized in an equal volume (w/v) of lysis buffer and centrifuged. The supernatants were then collected to examine angiotensin converting enzyme (ACE) 2 activity, and then to examine the protein expression of ACE2 by Western blot and immunostaining. ACE2 activity was measured by an ACE2 activity assay kit, using Mc-Ala/Dnp fluorescence resonance energy transfer peptide. Converted A $\beta$ 40 and A $\beta$ 42 from A $\beta$ 43 were analyzed by Western bolt. The primary antibodies were anti-human amyloid $\beta$ (35-40) mouse monoclonal IgG, anti-human amyloid $\beta$ (1-42) rabbit polyclonal IgG and anti-human amyloid $\beta$ (1-43) rabbit polyclonal IgG. Angiotensin II levels in human serum were measured by enzyme-linked immunosorbent assay (ELISA).  [結果] A $\beta$ 40 and A $\beta$ 42 were generated from the mixture of A $\beta$ 43 and mouse brain lysate in a time dependent manner. The generation of converted A $\beta$ 42 was inhibited by EDTA and an ACE2 specific inhibitor, DX600. Furthermore, the combination of ACE2 and ACE converts A $\beta$ 43 to A $\beta$ 40. Notably, ACE2 activity showed a tendency to decrease in the serum of AD patients compared with normal control.  [結論] We found that ACE2 converts A $\beta$ 43 to A $\beta$ 42, and this activity is inhibited by DX600. Combination of ACE2 and ACE converts A $\beta$ 43 to A $\beta$ 40, suggesting a successive conversion of A $\beta$ 43 to A $\beta$ 40. ACE2 activity showed a tendency to decrease in the serum of AD patients compared with normal control, suggesting an association between lower ACE2 activity and AD. Therefore, maintaining ACE2 and ACE activities in the brain could act as a protective and defensive mechanism in the initial stages of AD to limit its pathological development.	