Molecular Etiology of Alzheimer's Disease: Aberrant Splicing of APP Gene Transcript and Linkage to Apolipoprotein ε4 Allele

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Aberration of alternative splicing of amyloid precursor protein (APP) gene transcript was found in AD brains, which may cause an imbalance between protease(s) and inhibitor, and possibly lead to deposition of amyloid as a result of incomplete digestion of APP. The ε4 allele of apolipoprotein E (APOE) gene was found more frequently in late-onset cases of AD than in control, indicating that apolipoprotein E4 is a risk factor of AD.

Keywords: Amyloid precursor protein/ Alternative splicing/ Aging/ Apolipoprotein E

Alzheimer's disease (AD) is one of the most common cause of dementia, and pathologically characterized by the deposition of βA4 protein in senile plaque cores and cerebral vessels as amyloid. The βA4 protein is generated from larger precursors (amyloid precursor proteins; APPs) that have structual features of cell surface receptors (Fig. 1). Three (or reportedly four) types of APP mRNA [APP770, APP751, (APP714) and APP695 mRNAs] are produced from a single gene transcript by alternative splicing of exons 7 and 8. The former exon encodes a Kunitz-type serine protease inhibitor (KPI) domain; APP770 and APP751, but not APP695 (nor APP714), have this KPI domain in the extra-cellular region. Our previous study [1] showed that the proportion of APP770 mRNA (or APP770 mRNA+ APP751 mRNA) is higher in the brain of AD than in control, particularly in the cerebral cortex and hippocampus. Additionally, AD patients showing histologically a high density of senile plaques exhibited a high ratio of (APP770 mRNA+APP751 mRNA)/ APP695 mRNA.

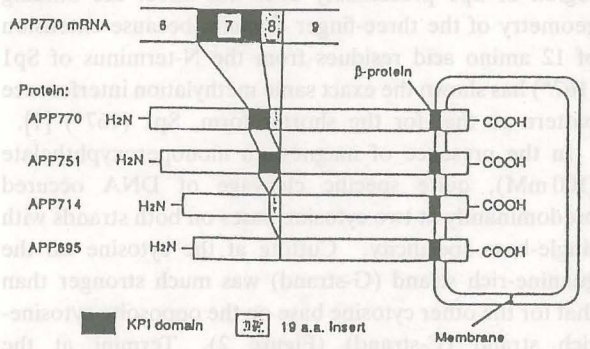

Figure 1. Structures of APP770 mRNA and four types of APPs that have structual features of cell surface receptors. The number of each domain corresponds to that of exon in the APP gene. Exon 7 encodes the KPI domain.

In this study, we analysed, by the method of RNase protection assay, the proportion of APP mRNAs in

BIOORGANIC CHEMISTRY —Molecular Clinical Chemistry—

Scope of research

This laboratory was founded in 1994, aiming at linkage between chemical / molecular sciences and basic / clinical medicine. Thus, our research effort is focused on elucidation of patho-physiological significance of various bioreactions, such as poly(ADP-ribosyl)ation of nuclear proteins and alternative splicing of amyloid precursor protein gene transcript, in etiology of diseases, such as malignancies and Alzheimer's disease. Gene diagnosis, particularly its laboratory technology and application to pathogenic genes, is another subject of our current research.

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various neurological disorders with special reference to aging. We found that the ratio of (APP770 mRNA+APP751 mRNA)/APP695 mRNA increased approximately 1.5-fold in the frontal cortex of AD compared with other neurodegenerative or cerebrovascular disorders [2] (Fig. 2). Furthermore, we found a positive correlation between the ratio (y) and age (x) both in AD and non-AD groups (Fig. 3). The relationship between the ages of AD (x_{AD}) and non-AD ($x_{non\text{-}AD}$) giving the same ratio was $x_{AD}=0.8x_{non\text{-}AD}-10.2$, indicating that the AD brain reached the same ratio of KPI-harboring to lacking APP mRNAs more than 20 years earlier than the non-AD brain in senescence. This age-related change of APP mRNAs proportion is prominent in the gray matter of cerebral cortex, where senile plaques abound, compared with the white matter [3]. These findings led us to the idea that an imbalance between protease(s) and inhibitor, caused by the aberrant splicing of APP gene transcript, may perturb normal degradation of APPs, thereby leading to deposition of βA4 protein as amyloid. The proportion of APP mRNAs may serve as a molecular index of brain aging or a marker of AD.

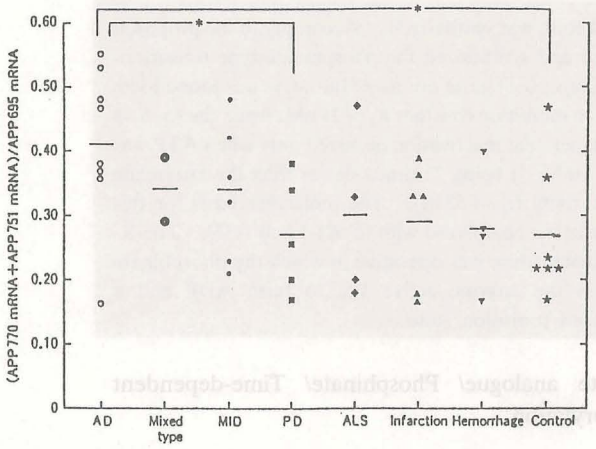

Figure 2. The ratio of (APP770 mRNA+APP751 mRNA)/APP695 mRNA in the frontal cortex in various neurological disorders and control. MID: multi-infarct dementia, PD: Parkinson's disease, ALS: amyotrophic lateral sclerosis.
* $p<0.05$ (Student's t-test).

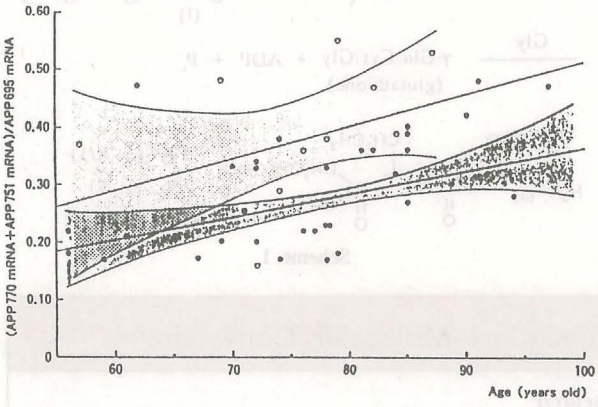

Figure 3. Correlation between the ratio of (APP770 mRNA+APP751 mRNA)/APP695 mRNA in the frontal cortex and age. The regression line for AD group (o, $n=10$) is $y=0.005x+0.014$ ($r=0.372$), and that for non-AD group (*, $n=33$) is $y=0.004x-0.037$ ($r=0.486$). The ≥90% confidence areas are indicated with shadowing. The AD group includes AD and mixed-type dementia.

Apolipoprotein E (apoE) is a structual component of chylomicron and lipoproteins and plays an important role in lipid metabolism. There are three major isoforms, referred to as apoE2, E3 and E4, that are encoded by ε2, ε3 and ε4 alleles, respectively, of a single gene located on the long arm of chromosome 19. The ε4 allele was reported to be associated with late-onset familial and sporadic ADs in the United States [4]. In this study, we analysed apoE genotypes in Japanese cases of sporadic AD by using PCR (polymerase chain reaction) coupled with RFLP (restriction fragment length polymorphism). We found a significant increase in the frequency of ε4 allele in late-onset cases (0.25), but not in early-onset ones (0.04), compared with control (0.09) [5]. The ε4 allele frequency was not so high among Japanese AD patients as reported for Caucasians, which could explain the relatively lower morbidity from AD in Japan. Thus, the apoE ε4 allele appears to serve as a risk factor of AD.

References

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