Influences of Apolipoprotein E and 1-Antichymotrypsin Genotypes on Regional Cerebral Glucose Metabolism in Alzheimer's Disease

IV. 11. Influences of Apolipoprotein E and α_1-Antichymotrypsin Genotypes on Regional Cerebral Glucose Metabolism in Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that results in a progressive loss of intellectual functions. The aplolipoprotein E (APOE) ε4 allele has been demonstrated to have a strong association with late-onset familial and sporadic AD as a major susceptibility or risk factor gene[1]. Further, the α_1-antichymotrypsin (ACT) type A allele (ACT*A) also has been indicated to be a risk factor for AD[2,3]. However, the roles played by these risk factors in the functional impairment or death of neurons in specific groups during the AD process are still enigmatic.

The present study was aimed to elucidate the effects of the APOE and ACT genotypes on the neuronal functions in specific populations, examining cerebral glucose metabolism by using positron emission tomography (PET) and ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) for AD patients with defined APOE and ACT genotypes.

Subjects and methods

Twenty patients with sporadic AD (7 males and 13 females, mean age ±SD: 67.6 ±8.2 years, range 49 to 82 years) were examined. The profiles of these patients including the severity and progression of dementia assessed by Mini-Mental State Examination (MMSE) are summarized in Table 1.

Genomic DNA was extracted from peripheral leukocytes, and allelic polymorphisms of the APOE and ACT genes were determined as described elsewhere[2-4].

A PET scan with FDG and ECAT PT931 (CTI Inc, Knoxville, TN, USA) scanner was performed for each patient under a resting condition. Parametric images of the regional cerebral metabolic rate of glucose (rCMRglc) were constructed by means of the autoradiograpic method described by Hutchins et al.[5] Twenty-three regions of interest (ROIs) were placed on these calculated images by referring to the individual magnetic resonance (MR) images, and the rCMRglc values in these ROIs were determined.

A simple linear regression approach was employed for analyzing the correlations of the age, MMSE score and gene doses of the APOE ε4 and ACT*A with the rCMRglc value in each ROI. These relationships also were examined by a multiple regression analysis.

Results

The list of the APOE and ACT genotypes for the patients examined in this study is shown in Table 1.

The coefficients of correlation of the age, MMSE score and gene doses of the APOE ε4 and ACT*A with the absolute rCMRglc value by the simple regression analysis are contained in Table 2A. No relationships between the age and the rCMRglc value were observed in any of the ROIs examined. The MMSE score correlated significantly and positively with the rCMRglc value, particularly in the middle frontal areas ($p < 0.01$ by t-test). The rCMRglc value in the patients with the APOE ε4 allele was significantly higher than that in the non-APOE ε4 carriers in a dose-dependent manner, especially in the frontal areas ($p < 0.05$ by t-test). A typical example is depicted in Fig. 1A. There was a significant reduction of the rCMRglc with an increasing gene dose of the ACT*A allele, particularly in the temporo-parietal areas ($p < 0.05$ by t-test). Fig. 1B displays a typical example.

The results of the multiple regression analysis are shown in Fig. 2B, where the age and gene doses of the APOE ε4 and ACT*A alleles are employed as explanatory variables. A strong and positive correlation between the gene dose of the APOE ε4 allele was found, especially in the frontal and temporal areas ($p < 0.01$ or $p < 0.05$ by t-test). On the other hand, the gene dose of the ACT*A allele correlated strongly and negatively with the rCMRglc value in the temporal and parietal areas ($p < 0.01$ or $p < 0.05$ by t-test).

Little correlation between the gene doses of each allele and the rCMRglc value was observed in the paracentral and primary visual cortices, thalamus, striatum, pons and cerebellum in the simple and multiple regression analyses.

Discussion

Recent PET studies have indicated that the changes in cerebral glucose metabolism frequently present an anterior-posterior heterogeneity in AD patients[6]. Moreover, this heterogeneous pattern has been demonstrated to be associated with the clinical heterogeneity in AD, and to show no change with the progression of AD, suggesting that some 'stable' factors such as genetic factors may play a role in forming these functional and clinical heterogeneities[6].

The rCMRglc in the fronto-temporal areas were found to be preserved in the AD patients with the APOE ε4 allele. This suggests that the APOE gene alone does not affect the progression of AD adversely, once the disease is triggered. No or rather 'protecting' effect of APOE ε4 allele on the progression of AD also has been indicated in recent studies for evaluating the clinical correlates of this allele[7,8].

There was a significant reduction of the cerebral glucose metabolism in the patients carrying the ACT*A allele, especially in the areas typically involved in AD. Although the ACT protein consistently co-localizes with Aβ in senile plaques, the association of the ACT genotype with AD remains unsettled[9]. Further investigations for seeking pathological and / or clinical correlates of the ACT polymorphism are required.

The present study employed analyses with multiple ROIs, and there may be a problem of an excessive multiple comparison that produces a possibility of a spurious significance. The areas with a significant correlation, however, were spatially adjacent to form large areas, suggesting a biological meaningfulness of our results.

References

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Table 1. Summary of the patients' profile examined here.

Patient No.	Age (years)	Sex	MMSE (/30points)	Genotypes APOE	ACT
1	49	F	18	4/3	-
2	56	M	25	4/3	A/A
3	59	M	26	3/3	A/T
4	62	F	18	4/3	A/A
5	62	M	6	3/2	-
6	64	F	22	3/3	T/T
7	66	F	21	4/4	T/T
8	66	M	20	3/3	A/A
9	67	F	17	4/3	-
10	67	F	21	4/3	A/T
11	67	F	26	4/3	-
12	67	M	24	4/3	A/T
13	68	F	20	4/3	T/T
14	70	F	23	4/4	T/T
15	70	F	24.5	4/4	T/T
16	71	F	14.5	4/3	T/T
17	79	F	11	4/3	A/T
18	79	F	5	4/4	A/T
19	80	M	17	3/3	-
20	82	F	24	3/3	-
mean	67.6		19.2		
S. D.	8.21		6.10		

- : Data not available

Table 2. 2A) Simple correlation coefficients of rCMRglc to the age, the MMSE score and the gene doses of APOE ε4 and ACT*A. Significance of each coefficient is tested by t- statistic.
2B) Partial correlation coefficients and determination coefficients calculated by multiple regression analysis for rCMRglc values. R^2 means coefficient of determination. The age and the gene doses of APOE ε4 and ACT*A are used as predictor variables without selection.

2A

ROI	Age	APOE ε4	ACT*A	MMSE
Upper lateral frontal	0.126	0.472 *	-0.545 *	0.508 *
Middle lateral frontal	0.099	0.482 *	-0.389	0.597 **
Lower lateral frontal	0.046	0.511 *	-0.368	0.492 *
Upper medial frontal	0.134	0.486 *	-0.498	0.517 *
Middel medial frontal	0.096	0.535 *	-0.515	0.565 **
Lower medial frontal	0.016	0.534 *	-0.500	0.530 *
Upper lateral temporal	0.029	0.282	-0.517	0.404
Middle lateral temporal	0.015	0.300	-0.492	0.455 *
Lower lateral temporal	0.044	0.372	-0.601 *	0.428
Medial temporal	-0.048	0.400	-0.563 *	0.401
Upper lateral parietal	0.188	0.263	-0.802 **	0.316
Lower lateral parietal	0.166	0.238	-0.708 **	0.462 *
Temporo-parietal junction	0.143	0.223	-0.727 **	0.407
Upper medial parietal	0.119	0.243	-0.675 **	0.242
Lower medial parietal	0.157	0.216	-0.557 *	0.349
Lateral occipital	0.240	0.205	-0.646 *	0.279
Medial occipital	0.094	0.308	-0.481	0.377

2B

ROI	Age	APOE ε4	ACT*A	R^2
Upper lateral frontal	-0.6495 *	0.6908 *	-0.6275 *	0.6781 **
Middle lateral frontal	-0.6416 *	0.7161 **	-0.4314	0.6271 *
Lower lateral frontal	-0.4960	0.6850 *	-0.3206	0.5528 *
Upper medial frontal	-0.5745	0.6344 *	-0.5390	0.5922 *
Middel medial frontal	-0.8373 **	0.8617 **	-0.7333 **	0.8460 **
Lower medial frontal	-0.6851 *	0.7383 **	-0.5955 *	0.7010 **
Upper lateral temporal	-0.5982 *	0.6146 *	-0.5774 *	0.6011 *
Middle lateral temporal	-0.6560 *	0.7109 **	-0.5696	0.6684 **
Lower lateral temporal	-0.5572	0.6828 *	-0.6435 *	0.6783 **
Medial temporal	-0.5962 *	0.7017 *	-0.6174 *	0.6781 **
Upper lateral parietal	-0.3502	0.6129 *	-0.8102 **	0.7781 **
Lower lateral parietal	-0.4962	0.5620	-0.7347 **	0.6825 **
Temporo-parietal junction	-0.4306	0.4365	-0.7379 **	0.6459 *
Upper medial parietal	-0.2468	0.3678	-0.6426 *	0.5346 *
Lower medial parietal	-0.2124	0.2715	-0.5189	0.3695
Lateral occipital	-0.2220	0.3352	-0.6070 *	0.4868
Medial occipital	-0.3581	0.5355	-0.4366	0.4600

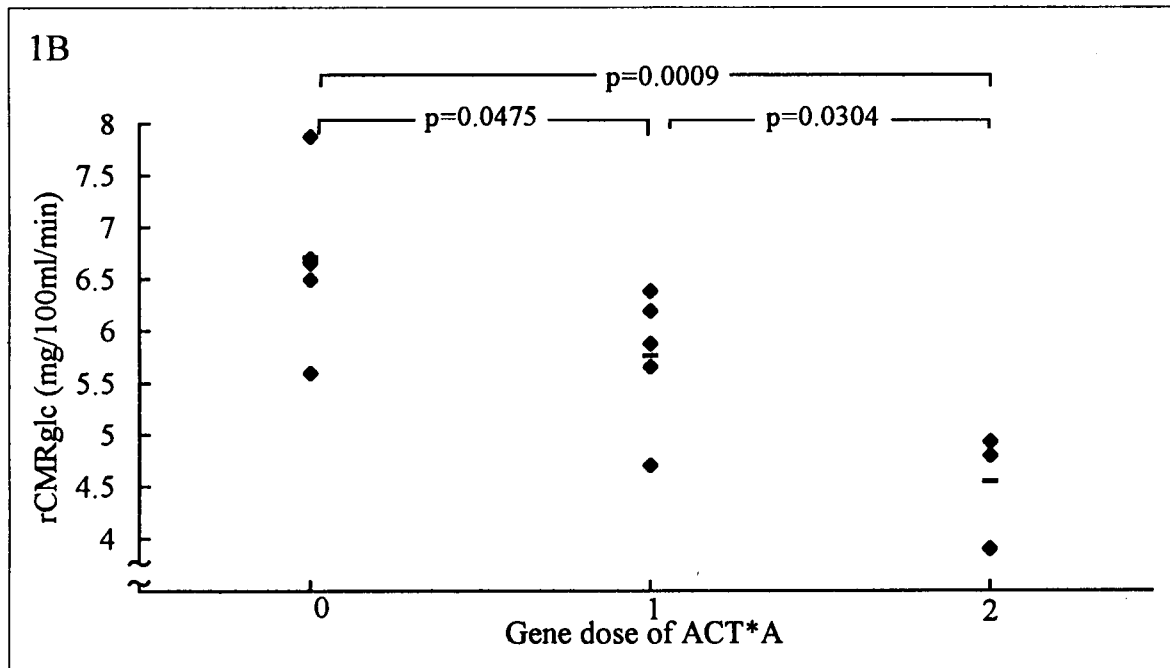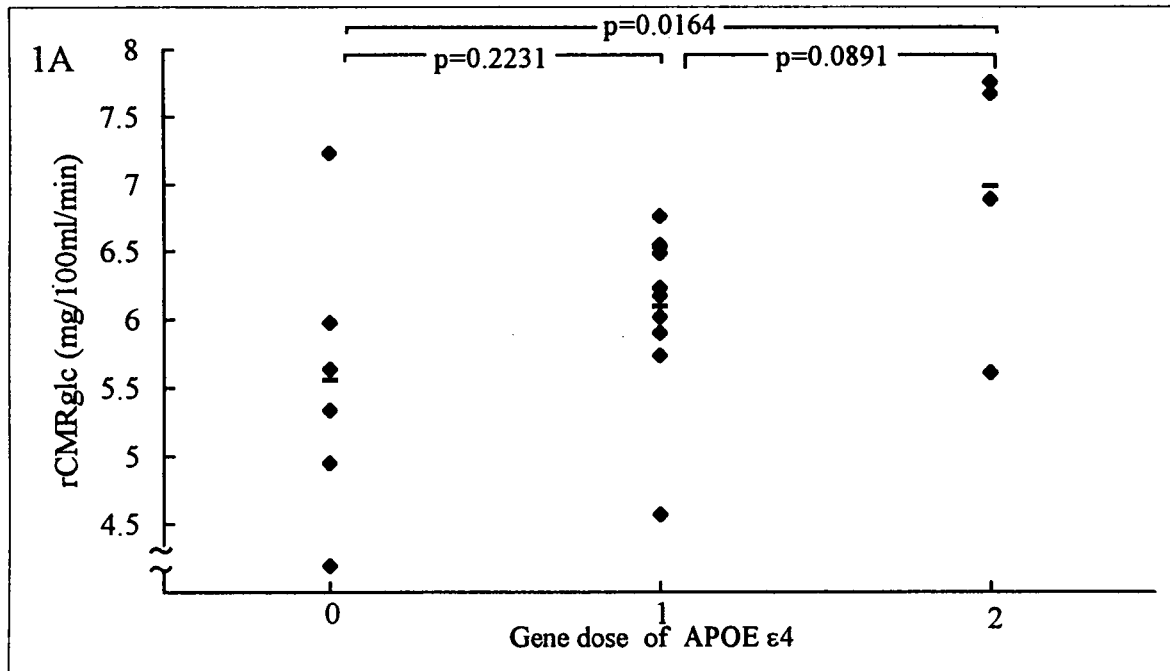*p < 0.05, **p < 0.01 by t-test (for each parameter) or by ANOVA (for R^2).

Fig. 1. Values of rCMRglc in the middle medial frontal area as a function of the dosage of APOE ε4 allele (1A, R = 0.535, p < 0.05) and in the upper lateral parietal area as a function of the dosage of ACT*A allele (1B, R = -0.802, p < 0.01). Horizontal bars represent mean values for the discrete conditions. Significance of difference is examined by analysis of variance (ANOVA).