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Association of cognitive performance with interleukin-6 receptor Asp358Ala polymorphism in healthy adults

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Abstract Wechsler adult intelligence scale-revised was performed in 576 healthy adults to examine whether a functional polymorphism (Asp358Ala) of the IL-6 receptor (IL-6R) gene is associated with cognitive performance. Verbal intelligence quotient in Asp homozygotes was significantly higher compared to Ala carriers ($P = 0.005$). Compared to Ala carriers, Asp homozygotes performed better in the verbal subtests requiring long-term memory stores. Elevated IL-6 and soluble IL-6R levels in Ala carriers may have negative impact on acquiring verbal cognitive ability requiring long-term memory.

Keywords Cognitive function · Interleukin-6 · Genetic polymorphism · Intelligence

Introduction

Accumulating evidence has suggested a negative effect of interleukin-6 (IL-6) on learning and memory. Previous studies have shown that increased peripheral IL-6 levels are associated with age-related cognitive decline in well-functioning elders (Weaver et al. 2002; Yaffe et al. 2003; Lekander et al. 2011) as well as in patients with Alzheimer's disease (Huberman et al. 1995; Singh and Guthikonda 1997). Marsland et al. (2006) have shown that higher plasma IL-6 levels are also associated with lower cognitive performance in the healthy middle-aged adults. A brain imaging study has shown that peripheral IL-6 levels were found to be inversely associated with hippocampal grey matter volume in the healthy adults (Marsland et al. 2008); further supporting the role of IL-6 on subclinical cognitive decline.

Animal studies have also shown an involvement of IL-6 in cognitive functioning. Studies using transgenic mice have reported that IL-6 deletion has a facilitatory effect on learning and memory (Braida et al. 2004), while chronic IL-6 expression from astrocytes in the brain results in a decline in avoidance learning performance (Heyser et al. 1997). These findings suggest that the persistence of excessive IL-6 signaling has a negative impact on the cognitive performance. Furthermore, some studies have shown that increased levels of hippocampal IL-6 interfere with long-term potentiation (LTP) (Bellinger et al. 1995; Tancredi et al. 2000).

A single nucleotide polymorphism (SNP) Asp358Ala (rs8192284) of the IL-6 receptor (IL-6R) gene, which substitutes an amino acid at the proteolytic cleavage site, is known to be strongly associated with the circulating levels of soluble IL-6R (sIL-6R) (Galicia et al. 2004; Rafiq et al. 2007; Reich et al. 2007; Sasayama et al. 2011b) and IL-6 (Rafiq et al. 2007; Reich et al. 2007; Jiang et al. 2010; Sasayama et al. 2011b). The Ala allele of this polymorphism is associated with increased levels of both IL-6 and sIL-6R, suggesting that possession of this allele may result in elevated levels of IL-6 signaling. The present study was

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aimed to examine the Asp358Ala polymorphism for association with cognitive functioning in the healthy adults.

Methods

Subjects

Subjects were 576 healthy volunteers without current or past history of psychiatric treatment (144 males, average age ± standard deviation (SD) = 41.7 ± 16.3 years; 432 females, 46.2 ± 14.4). All the subjects were biologically unrelated Japanese. They were screened using the Japanese version of the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al. 1998; Otsubo et al. 2005) by a research psychiatrist. Participants were excluded if they had a prior medical history of central nervous system disease or severe head injury, or if they met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria (American Psychiatric Association 1994) for substance abuse or dependence, dementia, or mental retardation. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan. After description of the study, written informed consent was obtained from every subject.

Assessment of cognitive functioning

All the participants were administered the Japanese version of Wechsler adult intelligence scale-revised (WAIS-R) (Wechsler 1981; Shinagawa et al. 1990) by a research psychologist.

Genotyping

Genomic DNA was prepared from the venous blood according to standard procedures. The Asp358Ala polymorphism was genotyped using the TaqMan 5′-exonuclease allelic discrimination assay (Applied Biosystems, Foster City; assay ID: AHD1C2X). Thermal cycling conditions for polymerase chain reaction were 1 cycle at 95°C for 10 min followed by 50 cycles of 92°C for 15 s and 60°C for 1 min. The allele-specific fluorescence was measured with ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster City). Genotype data were read blind to the WAIS-R scores. Ambiguous genotype data were not included in the analysis.

Statistical analysis

Categorical variables were compared using χ^2 test. Mean differences between the groups were assessed by analysis of variance (ANOVA). Differences in the WAIS-R scores between the genotypes were also tested using analysis of covariance (ANCOVA), with age, gender, and years of education as covariates. Scaled scores were used in the analysis of the subtest scores. Post hoc tests were performed using Bonferroni's correction for multiple comparisons. Associations between age and the subtest raw scores were examined with a linear regression analysis. The difference between two regression coefficients was estimated by calculating the t value. Statistical analyses were performed using the statistical package for the social sciences (SPSS) version 11.0 (SPSS Japan, Tokyo). Statistical tests were two-tailed and statistical significance was considered when $P < 0.05$.

Results

The number of subjects, age, years of education, and the WAIS-R scores for each genotype are presented in Table 1. The genotype frequencies of the subjects were not significantly deviated from Hardy–Weinberg equilibrium ($\chi^2 = 2.3$, $df = 1$, $P = 0.13$). Gender distribution did not significantly differ across genotypes ($\chi^2 = 2.1$, $df = 2$, $P = 0.35$). The WAIS-R full-scale intelligence quotient (FIQ) ranged from 74 to 143 (average ± SD = 111.6 ± 11.9). ANOVA analyses revealed significant differences in mean verbal IQ (VIQ) and three verbal subtest scores (information, vocabulary, and similarities) between the genotypic groups. These differences remained significant even when age, gender, and years of education were controlled for in the ANCOVA analyses. However, there was no significant difference in performance IQ (PIQ), full-scale IQ, or any of the performance subtest scores across the three genotypic groups.

As shown in Table 1, subjects homozygous for the Asp allele showed better performance in VIQ and verbal subtest scores, compared with those carrying the Ala allele (i.e., individuals with a genotype of Asp/Ala or Ala/Ala). When genotypes were thus, dichotomized into carriers and non-carriers of the Ala allele, the latter showed significantly higher VIQ compared to the former ($F = 7.9$, $df = 1,567$, $P = 0.005$, by ANCOVA). Non-carriers of the Ala allele scored significantly higher than the carriers in information ($F = 10.0$, $df = 1,567$, $P = 0.0017$), vocabulary ($F = 6.4$, $df = 1,567$, $P = 0.012$), and similarities ($F = 6.1$, $df = 1,567$, $P = 0.014$) subtests controlling for age, gender, and years of education. When analyzed separately in two age groups, i.e. below and above 50 years old ($N = 348$ and 228, respectively), the scores of these subtests were higher in Ala non-carriers compared to carriers in both age groups but the difference reached statistical significance in only the older group ($P = 0.0048$, 0.0057,

Table 1 The number of subjects, age, years of education, and WAIS-R scores for each genotype of the Asp358Ala polymorphism of the IL-6R gene

	Asp/Asp	Asp/Ala	Ala/Ala	Total	Statistical analysis[a]	
					F value	*P* value
N (Male/Female)	186 (51/135)	298 (67/231)	92 (26/66)	576 (144/432)		
Age (years)	45.1 ± 15.5	44.0 ± 14.8	48.4 ± 14.3	45.1 ± 15.0	3.03	**0.049**
Education (years)	15.1 ± 2.6	15.0 ± 2.7	14.8 ± 3.0	15.0 ± 2.7	0.43	0.65
WAIS-R						
Verbal subtests						
Information	11.7 ± 2.6	11.0 ± 2.8	11.0 ± 2.8	11.2 ± 2.8	5.523	**0.004**
Digit span	11.6 ± 3.0	11.2 ± 2.8	11.7 ± 2.6	11.4 ± 2.8	1.765	0.17
Vocabulary	12.1 ± 2.6	11.4 ± 2.7	11.5 ± 2.9	11.7 ± 2.7	3.356	**0.036**
Arithmetic	11.3 ± 2.9	11.0 ± 3.0	10.9 ± 3.1	11.1 ± 3.0	0.804	0.45
Comprehension	11.7 ± 2.8	11.5 ± 2.8	11.5 ± 2.9	11.6 ± 2.8	0.387	0.68
Similarities	12.8 ± 2.1	12.2 ± 2.4	12.3 ± 2.4	12.4 ± 2.3	3.042	**0.049**
Performance subtests						
Picture completion	10.4 ± 2.4	10.6 ± 2.2	10.8 ± 2.4	10.5 ± 2.3	0.434	0.65
Picture arrangement	11.3 ± 2.6	11.4 ± 2.6	11.7 ± 2.9	11.4 ± 2.7	0.368	0.69
Block design	12.3 ± 2.7	12.1 ± 3.2	12.0 ± 2.8	12.2 ± 3.0	0.209	0.81
Object assembly	11.6 ± 2.9	11.4 ± 3.0	10.9 ± 3.1	11.4 ± 3.0	1.100	0.33
Digit symbol	13.3 ± 2.8	13.1 ± 2.5	13.8 ± 2.8	13.2 ± 2.7	2.113	0.12
VIQ	112.4 ± 12.1	109.0 ± 12.8	109.6 ± 12.4	110.2 ± 12.6	4.008	**0.019**
PIQ	111.4 ± 12.1	110.9 ± 11.8	111.5 ± 12.7	111.1 ± 12.0	0.032	0.97
FIQ	113.1 ± 11.6	110.8 ± 11.8	111.4 ± 12.6	111.6 ± 11.9	1.588	0.21

Data are presented as mean ± standard deviation. *P* values < 0.05 are shown in boldface. WAIS-R scores were assessed with ANCOVA adjusted for gender, age, and years of education

IL-6R interleukin-6 receptor; *ANOVA* analysis of variance; *ANCOVA* analysis of covariance; *WAIS-R* Wechsler adult intelligence scale-revised; *VIQ* verbal intelligence quotient; *PIQ* performance intelligence quotient; *FIQ* full scale intelligence quotient

[a] Age and years of education were assessed with ANOVA

0.010, and 0.024 for VIQ, information, vocabulary, and similarities, respectively).

Age was significantly negatively correlated with the raw scores of every subtest except for information, vocabulary, and comprehension in each genotype group. Conversely, information and vocabulary scores showed significant positive correlation with age in Asp/Asp group, as shown in Table 2a. Regression coefficients were significantly higher in Asp homozygotes compared to Ala homozygotes in these subtests (Table 2b).

Discussion

Our results suggest that the Asp358Ala polymorphism of the IL-6R gene is associated with some aspects of cognitive functioning in the healthy adults. In particular, three of the verbal subtest scores and the total VIQ were lower in carriers of the Ala allele compared to non-carriers. Since the Ala allele is strongly associated with higher IL-6 and sIL-6R levels (Galicia et al. 2004; Rafiq et al. 2007; Reich et al. 2007; Jiang et al. 2010; Sasayama et al. 2011b); our findings support the possibility that excessive IL-6 signaling may have a negative impact on cognitive ability.

Some previous studies have shown that genetic variations in the gene encoding IL-1β, which stimulates IL-6 production (Van Damme et al. 1987) may be associated with cognitive performance (Baune et al. 2008; Tsai et al. 2010; Sasayama et al. 2011a). The present study showed for the first time, to our knowledge, that the IL-6R gene variation is also associated with cognitive performance; further supporting the involvement of pro-inflammatory genes in modulating the cognitive function.

Our data indicated that Asp homozygotes performed better than Ala carriers in subtests requiring examinees to use long-term memory stores, such as information and vocabulary. Separate analyses in two age groups suggested that the difference was greater in those above 50 years old. Furthermore, these subtest raw scores were positively correlated with age in only Asp homozygotes. These findings suggest that Asp homozygotes have higher ability to transfer information into the long-term memory store,

Table 2 Results of the linear regression analyses in each genotype group with age as the independent variable and subtest scores associated with Asp358Ala genotype as dependent variables

Asp358Ala genotype	*N*	Variable	Information			Vocabulary			Similarities		
			β	95% CI	*P* value	β	95% CI	*P* value	β	95% CI	*P* value
(a) Regression coefficients (β) and *P* values											
Asp/Asp	186	Intercept	16.1	14.1 to 18.1	**<0.001**	35.1	30.3 to 39.9	**<0.001**	22.7	21.1 to 24.4	**<0.001**
		Age	0.061	0.019 to 0.10	**0.0046**	0.133	0.032 to 0.234	**0.010**	−0.068	−0.103 to −0.034	**<0.001**
Asp/Ala	298	Intercept	16.7	14.9 to 18.4	**<0.001**	36.9	32.9 to 40.9	**<0.001**	23.3	21.9 to 24.8	**<0.001**
		Age	0.022	−0.016 to 0.060	0.26	0.033	−0.053 to 0.118	0.46	−0.101	−0.133 to −0.069	**<0.001**
Ala/Ala	92	Intercept	18.9	15.2 to 22.5	**<0.001**	42.2	33.8 to 50.6	**<0.001**	24.1	21.1 to 27.2	**<0.001**
		Age	−0.031	−0.10 to 0.042	0.40	−0.081	−0.247 to 0.086	0.34	−0.119	−0.180 to −0.059	**<0.001**

Asp358Ala genotype	Information				Vocabulary				Similarities			
	$\lvert\beta_2-\beta_1\rvert$	95% CI	*t* value	*P* value	$\lvert\beta_2-\beta_1\rvert$	95% CI	*t* value	*P* value	$\lvert\beta_2-\beta_1\rvert$	95% CI	*t* value	*P* value
(b) The difference between regression coefficients obtained in each genotype group												
Asp/Asp versus Asp/Ala	0.039	−0.018 to 0.097	1.34	0.18	0.100	−0.033 to 0.233	1.48	0.14	−0.607	−2.88 to 1.67	0.52	0.60
Asp/Ala versus Ala/Ala	0.052	−0.029 to 0.133	1.27	0.20	0.113	−0.070 to 0.296	1.22	0.22	−1.410	−4.78 to 1.96	0.84	0.40
Ala/Ala versus Asp/Asp	0.092	0.012 to 0.172	2.26	**0.025**	0.213	0.024 to 0.403	2.22	**0.027**	−0.607	−3.91 to 2.70	0.47	0.64

P values < 0.05 are shown in boldface

95% CI 95% confidence interval

resulting in greater difference in built-up knowledge compared to Ala carriers as they age. On the other hand, we obtained no evidence for association between the polymorphism and the score of subtests requiring working memory, such as digit span and arithmetic. These findings may suggest that excessive IL-6 signaling due to the Asp358Ala polymorphism has a negative impact on acquisition/retention of knowledge rather than the short-term memory function. This may partly be explained by the impairment in hippocampal-dependent learning and memory related to IL-6. A number of animal studies have shown that IL-6 inhibits LTP in the hippocampus (Bellinger et al. 1995; Tancredi et al. 2000; Li et al. 1997). These findings raise the possibility that constantly elevated IL-6 signaling in Ala carriers may have impaired the acquisition of new memories. Future studies are necessary to confirm our findings by prospectively examining the longitudinal effects of the Asp358Ala polymorphism on acquiring cognitive ability requiring long-term memory.

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