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**Serotonin 5-HT_{2A} receptor gene polymorphism, 5-HT_{2A} receptor function
and personality traits in healthy subjects:**

A negative study

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Running title: 5-HT_{2A} receptor and personality

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Abstract

Background--Central serotonin-2A (5-HT_{2A}) receptor dysfunction is regarded as an important factor in the etiology of affective disorders. The relations between some personality traits and the vulnerability of affective disorders are also implicated. Moreover, there are several reports which describe the association between 5-HT_{2A} receptor gene polymorphisms and mental disorders. We therefore examined the relationship between personality traits, the 5-HT_{2A} receptor function, and 5-HT_{2A} receptor gene polymorphisms.

Methods-- 5-HT-induced intraplatelet calcium (Ca) mobilization, 5-HT_{2A} receptor gene polymorphisms (A-1438G, T102C, T516C, C1340T, C1354T), and Temperament and Character Inventory (TCI) scores were examined in 133 healthy subjects.

Results-- Neither 5-HT-induced Ca mobilization nor 5-HT_{2A} receptor gene polymorphisms (A-1438G, T102C) appear to be associated with seven

personality dimensions including Harm Avoidance. There was no significant difference in the Ca response among the subjects with -1438A/A, A/G and G/G genotypes. Since the appearance of the other types of the 5-HT_{2A} receptor gene polymorphisms (T516C, C1340T and C1354T) was quite rare in our sample, we were unable to examine the relationship between these polymorphisms, and the TCI score or the Ca response.

Limitations-- Our failure to find a significant association may reflect the false negative results due to the small sample size and low statistical power. Further studies in depressed patients may clarify the complicated relationship between personality traits and the vulnerability of affective disorders.

Conclusions-- Personality traits detected by TCI may not be directly related to the 5-HT_{2A} receptor function or 5-HT_{2A} receptor gene polymorphism which may be involved in the vulnerability of affective disorders.

Key words: Calcium, Temperament and Character Inventory (TCI), Serotonin-2A receptor function, Serotonin-2A receptor gene polymorphism, Personality trait, Healthy subject

Introduction

There has been extensive interest in central serotonin-2A (5-HT_{2A}) receptor dysfunction as an important factor in the etiology of affective disorders (see review, Kusumi & Koyama, 1998). By measuring 5-HT-induced intraplatelet calcium (Ca) mobilization, we have already indicated that the 5-HT_{2A} receptor function is increased in some types of depression such as bipolar disorder and melancholic major depression compared to normal controls, and that the enhanced Ca response is trait dependent (Kusumi et al., 1991b; 1994). Although these findings were confirmed by many studies (Mikuni et al., 1992; Eckert et al., 1993; Okamoto et al., 1994; Konopka et al., 1996; Tomiyoshi et al., 1999), it was found that the range of the 5-HT-

stimulated Ca response in normal subjects was widely distributed and fairly overlapped with that in depressed patients. Since the relationship between some personality traits and depression has previously been implicated in various psychopathological studies, we postulated that the 5-HT-induced Ca mobilization might be related with some personality traits that are involved in the vulnerability of affective disorders.

The Temperament and Character Inventory (TCI) is a self-rating questionnaire which measures four temperament dimensions, Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P), and three character dimensions, Self-Directedness (SD), Cooperativeness (C) and Self-Transcendence (ST), as defined by Cloninger's psychobiological model of personality (Cloninger et al., 1993). According to this model, each temperament dimension is postulated to be associated with a specific central neurotransmitter. That is, NS is theoretically related to dopaminergic activity; HA with serotonergic activity; and RD with noradrenergic activity (Cloninger, 1987). In fact, using the Tridimensional Personality Questionnaire (TPQ), prototype of the TCI, most of the studies have indicated a significant association between HA score and severity of depressive symptoms or response to antidepressants (Joffe et al., 1993; Nelson & Cloninger, 1997;

Tome et al., 1997). Thus, in this study, we investigated the correlation between the 5-HT_{2A} receptor-mediated Ca response and TCI scores using healthy control samples. If some personality traits are related with the vulnerability of affective disorders, it is interesting to examine this relationship not only in depressed patients but also in healthy subjects.

Recently, several reports have demonstrated the association between some 5-HT_{2A} receptor gene polymorphisms and mental disorders. For example, one of the 5-HT_{2A} receptor polymorphisms, A-1438G, has been reported to be associated with the susceptibility to anorexia nervosa (Collier et al 1997). It has been also suggested that the T102C polymorphism of the 5-HT_{2A} receptor gene and schizophrenia are positively associated (Inayama et al 1996; Williams et al 1996). However, these findings have not been replicated by other studies. Thus, it is possible that the etiology of these complex diseases might be elucidated by a genetic approach to personality traits rather than a direct association study between some genetic factors and the susceptibility to the diseases.

The distribution and reciprocal linkage of the 5-HT_{2A} receptor gene polymorphisms have been reported in Caucasian samples (Ozaki et al., 1996; Collier et al., 1997; Gutierrez et al., 1997), but there have been few studies in

Asian populations. Therefore, in this study, we first examined the distribution of five polymorphisms of 5-HT_{2A} receptor gene in Japanese healthy controls. And then we investigated the relationships between the TCI scores, and the 5-HT_{2A} receptor-mediated Ca response or 5-HT_{2A} receptor gene polymorphisms in healthy subjects. These methodological approaches, using psychological assessment, biological function and molecular genetics, may be useful for elucidating the vulnerability of affective disorders which is our final purpose.

Methods

One hundred thirty three nonrelated volunteers were all Japanese recruited from laboratory, office or hospital staff at Hokkaido University School of Medicine. They all underwent a direct interview to exclude psychiatric disorders classified according to DSM-IV (APA 1994). There were 87 males and 46 females, and the average age was 33.2 ± 8.6 (mean \pm S.D.) years. They were all drug free for at least 4 weeks before blood sampling and had no history of physical or psychiatric illness. After complete description of the study, informed consent was obtained from all subjects. The research protocol was approved by the ethics committee of Hokkaido University School of Medicine.

After collecting the blood samples, the subjects filled out a Japanese version of the TCI, which consists of 125 questions with four possible answers (Kijima et al 1996). Each score on the 4-point scale can range from 1 (strongly disagree) to 4 (strongly agree). The validity and reliability of the Japanese version of TCI have already been confirmed among different Japanese populations (Kijima et al 1996).

The isolation of platelets and the measurement of intraplatelet Ca concentration were performed as described previously (Kusumi et al 1991a; 1994). Briefly, platelet-rich plasma was incubated with 4 μM fura-2, a Ca sensitive fluorescent probe, for 15 min at 37°C. After centrifugation, the resulting platelet pellet was suspended at 1×10^8 cells/ml in Krebs-Ringer HEPES buffer. The samples were prewarmed in a cuvette at 37°C for 4 min and then 10 μM 5-HT was added to the incubation medium. Fluorescence was measured on a Hitachi F-2000 fluorometer with excitation at 340 and 380 nm, and with emission at 510 nm. Intracellular Ca concentrations were calculated from the ratio of fluorescence intensities at two excitation wavelengths in the platelet samples according to the method of Grynkiewicz et al (1985). We examined the maximum Ca response (% increase = initial peak (nM) / resting level (nM) X 100) induced by 10 μM of 5-HT.

DNA was extracted from 20 ml of whole blood by standard methods. Genotyping of 5-HT_{2A} receptor gene polymorphism, A-1438G, was performed as described by Collier et al (1997), and the other polymorphisms, T102C, T516C, C1340T and C1354T, were typed by the method of Ozaki et al (1996).

The associations between the TCI scores or 5-HT-induced Ca response, and the 5-HT_{2A} receptor gene polymorphism were assessed by one-way ANOVA for multiple comparison followed by Scheffe's test. The correlations between the TCI scores and the 5-HT-stimulated Ca response were analyzed using Pearson's correlation coefficient. P values less than .05 were considered statistically significant after Bonferroni's correction for multiple testing for six dimension subscales except HA since there was no prior hypothesis that these scales were related to serotonergic functions. However, P values for HA subscales were not corrected for multiple analyses because the prior prediction was that the HA scores might be affected by 5-HT_{2A} receptor gene polymorphism or 5-HT-induced Ca mobilization.

Results

A-1438G and T102C haplotype analysis of all 133 individuals revealed a linkage of the two polymorphic sites of the 5-HT_{2A} receptor genes. Allele -1438A and G were linked to 102T and C, respectively. The distribution of the 5-HT_{2A} receptor genotypes in our sample was different from those observed in caucasian populations (Ozaki et al., 1996; Collier et al., 1997; Gutierrez et al., 1997), but was almost same as in other Japanese samples (Inayama et al., 1996). The frequency of -1438G (or 102C) allele (45%) was a little lower than in Caucasian studies, whereas 516C, 1340T and 1354T alleles were extremely rare. The C allele of T516C and the T allele of C1354T were not observed in the 266 chromosomes. The T allele of C1340T was found in only one chromosome out of the 266 (allele frequency = 0.4%). Thus, we were unable to examine the relationship between T516C, C1340T or C1354T polymorphism and the TCI score in the present study.

The TCI scores sorted by 5-HT_{2A} receptor A-1438G genotypes are shown in Table 1. Observed genotype distributions were consistent with Hardy-Weinberg equilibrium. There was no significant relationship of the 5-HT_{2A} receptor A-1438G genotypes with seven personality dimension scores including HA. Although it appeared that there was a trend for a relationship

with NS total ($P=0.07$), NS total showed P value of $P=.42$ after Bonferroni's correction for multiple testing. In exploratory analyses, RD3 (attachment) and C1 (social acceptance) did show P values of $P=0.025$ and $P=0.004$, respectively. However, these results would not withstand correction for multiple testing.

The relationships between the TCI scores and the 5-HT-induced Ca response are shown in Table 2. There was a trend for a correlation with HA total ($P=0.07$), but the other six personality dimensions were not significantly related to the Ca response after Bonferroni's correction. No significant effect of sex and age on the Ca response was found in our present sample in agreement with earlier report (Kusumi et al., 1991a). In exploratory analyses, the 5-HT-stimulated Ca response showed a tendency to correlate with the purposeful (SD2) and pure-hearted (C5) subscale scores. However, these results would not withstand correction for multiple testing.

There was no significant difference in the 5-HT-stimulated Ca mobilization among the subjects with -1438A/A, A/G and G/G genotypes ($231.5 \pm 8.2\%$, the means \pm S.E. for A/A; $245.3 \pm 7.2\%$ for A/G; $241.0 \pm 14.8\%$ for G/G, $F=0.62$, $p=0.54$) (Fig. 1).

Discussion

In this study, we first examined five polymorphisms of 5-HT_{2A} receptor gene in Japanese populations. Some of the variations of the 5-HT_{2A} receptor, including T516C, C1340T and C1354T, appeared to be quite rare in our sample, even if they exist at all. The T and C allele of the T102C polymorphism were corresponded to the A and G allele of A-1438G, respectively, as reported in recent studies (Kouzmenko et al., 1999; Ohara et al., 1999).

The present results also suggest that neither 5-HT_{2A} receptor gene polymorphism A-1438G nor 5-HT_{2A} receptor function measured by the 5-HT-induced intraplatelet Ca mobilization appears to be associated with seven personality dimension of TCI including HA in which the serotonergic transmission is supposed to be involved (Cloninger 1987). According to the report by Zhu et al.(1995), the promotor region of human 5-HT_{2A} receptor gene comprising positions -1316 to -577, exhibited significant promotor activity. This promotor activity was not affected by the upstream sequence. On the other hand, downstream region, comprising positions -577 to -125, was found to contain the silencer activity for the gene expression. Moreover, it has recently reported that there was no significant difference in both basal and

induced promotor activities between the -1438A and G variants (Spurlock et al., 1998). No correlation was observed between the A-1438G genotype and the density of 5-HT_{2A} receptors in frontal cortex from postmortem brain (Kouzmenko et al., 1998). Although our failure to find a significant association may reflect false negative results from small sample size and low statistical power, these previous findings may suggest the possibility that this promotor polymorphism is not a major factor affecting the 5-HT_{2A} receptor expression. For subscale scores, the results of RD3(attachment) and C1(social acceptance) scores are interesting, although they are not significant data. It is possible that the present results may be related with the previous reports which showed the positive relationship between 5-HT_{2C} receptor polymorphism and RD (Ebstein et al., 1997), and increased social affiliation induced by SSRI administration (Knutson et al., 1998), respectively. However, considering the multiple testing, it should be carefully interpreted.

Several investigators have previously examined a relationship between serotonergic activity and the HA dimension. Pfohl et al.(1990) have reported higher HA scores in OCD patients compared to controls, but no association between this dimension and platelet imipramine binding. The HA scores in

female patients with bulimia were shown to be higher than in normal women, but the whole blood 5-HT levels were not related to this dimension (Waller et al., 1993). On the other hand, Ruegg et al.(1997) have indicated that cortisol response to intravenous clomipramine challenge was correlated with the HA scores in healthy subjects. The 5-HT_{1A} receptor activity measured by prolactin response to flesinoxan, which was blunted in depressed patients, has been shown to be correlated with the HA scores (Hansenne et al., 1997). Moreover, HA and RD scores were found to be useful for predicting the response to the 5-HT_{2A} receptor antagonist and 5-HT reuptake inhibitor antidepressant nefazodone in depressed patients (Nelson & Cloninger, 1997). Especially, the HA score has been reported to be significantly correlated with the severity of depressive symptoms (Nelson & Cloninger, 1997; Tanaka et al., 1997). Since the 5-HT-stimulated Ca response is not correlated with the Hamilton Rating Scale for Depression scores (Kusumi et al., 1994), the present results that the HA score did not have a significant relationship with the Ca response, support indirectly our previous findings that the 5-HT_{2A} receptor function may not be a state-dependent marker (Kusumi et al., 1994).

In this study, the 5-HT_{2A} receptor A-1438G genotype did not influence the 5-HT-induced Ca mobilization. Ozaki et al (1997) have indicated that the

subjects with missense 1354T (452Tyr) mutation of 5-HT_{2A} receptor exhibited lower Ca response to 5-HT than those without the mutation. However, there was no significant difference in 5-HT_{2A} receptor binding, G-protein, and protein kinase C function between two groups. These findings suggest the possibility that naturally occurring variant of 5-HT_{2A} receptor sequence may be capable of altering 5-HT_{2A} receptor function. Since both 1340T and 1354T mutations, which altered the predicted amino acid sequence, were extremely rare in Japanese sample, we could not examine the effect of the mutations on TCI scores in this study. It is needed to examine the effects of all 5-HT_{2A} receptor gene polymorphisms including these missense mutations on the TCI scores in both control and depressed patients using larger samples in future.

In conclusion, the present study suggests that neither 5-HT_{2A} receptor gene polymorphism A-1438G nor the 5-HT_{2A} receptor-mediated intraplatelet Ca mobilization appears to be associated with seven personality dimensions of TCI. Further studies of TCI in depressed patients with concurrent measurement of 5-HT_{2A} receptor gene polymorphisms and 5-HT_{2A} receptor function may clarify the complex relationship between personality traits and the vulnerability of affective disorders.

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Figure Legends

Fig. 1. 5-HT(10 uM)-induced intraplatelet Ca response in healthy subjects sorted by 5-HT_{2A} receptor A-1438G genotypes. Results are the means \pm S.E..

Table 1. TCI scores in healthy subjects sorted by 5-HT2A receptor A-1438G genotypes

Subscale	TCI Scales	Mean±SD			ANOVA
		A/A (N=39)	A/G (N=67)	G/G (N=27)	
Temperament scales					
NS	Novelty Seeking	51.6±7.3	49.4±6.2	47.9±5.6	F=2.75, p=0.07
NS1	Exploratory excitability	13.9±2.3	13.5±2.2	12.8±2.1	F=1.95, p=0.15
NS2	Impulsiveness	12.0±2.5	11.7±2.4	11.6±2.4	F=0.30, p=0.74
NS3	Extravagance	12.8±2.3	12.6±2.1	12.0±2.7	F=1.09, p=0.34
NS4	Disorderliness	12.1±2.4	11.7±2.2	11.6±1.9	F=0.42, p=0.66
HA	Harm Avoidance	51.1±7.5	52.5±8.7	54.0±6.1	F=1.14, p=0.32
HA1	Anticipatory worry	12.4±2.2	12.6±2.5	12.5±2.1	F=0.11, p=0.90
HA2	Fear of uncertainty	14.0±2.7	14.6±2.6	14.9±2.5	F=0.96, p=0.38
HA3	Shyness	12.5±2.2	12.5±3.1	13.1±2.2	F=0.54, p=0.59
HA4	Fatigability and asthenia	12.2±2.6	12.9±2.7	13.6±2.0	F=2.38, p=0.10
RD	Reward Dependence	43.2±4.5	42.2±5.0	44.1±4.3	F=1.67, p=0.19
RD1	Sentimentality	14.4±1.8	14.7±1.9	14.4±2.1	F=0.30, p=0.74
RD3	Attachment	13.9±3.0	13.0±2.9	14.8±2.3	F=3.81, p=0.025
RD4	Dependence	14.8±2.0	14.5±2.1	15.0±2.2	F=0.62, p=0.54
P/RD2	Persistence	13.3±2.6	13.0±2.7	12.5±2.7	F=0.61, p=0.54
Character scales					
SD	Self-Directedness	71.2±7.5	70.7±10.5	70.6±9.9	F=0.04, p=0.96
SD1	Responsibility	16.1±2.3	16.3±2.4	16.4±3.0	F=0.08, p=0.93
SD2	Purposeful	13.5±2.2	13.4±2.6	13.6±2.4	F=0.05, p=0.96
SD3	Resourcefulness	14.8±2.0	14.5±2.6	14.1±2.5	F=0.83, p=0.44
SD4	Self-acceptance	12.5±3.0	12.1±3.9	12.9±3.6	F=0.48, p=0.62
SD5	Congruent	14.2±2.3	14.3±2.5	13.6±2.2	F=0.90, p=0.41
C	Cooperativeness	70.5±7.0	71.9±7.3	74.0±5.9	F=2.01, p=0.14
C1	Social acceptance	14.9±1.8	15.8±2.1	16.5±1.5	F=5.87, p=0.004
C2	Empathy	12.1±1.6	12.6±1.8	12.3±1.8	F=1.00, p=0.37
C3	Helpfulness	14.7±1.7	14.9±2.2	15.1±2.0	F=0.45, p=0.64
C4	Compassion	15.2±2.4	15.0±2.8	16.0±2.0	F=1.45, p=0.24
C5	Pure-hearted	13.9±1.9	13.7±1.6	13.9±2.2	F=0.16, p=0.85
ST	Self-Transcendence	28.5±5.9	27.1±5.1	27.0±5.5	F=1.05, p=0.35
ST1	Self-forgetful	9.1±2.6	8.5±2.3	8.4±2.7	F=0.69, p=0.50
ST2	Transpersonal	9.7±2.4	9.2±1.9	9.1±2.0	F=0.79, p=0.45
ST3	Spiritual acceptance	9.7±2.0	9.3±2.3	9.4±2.0	F=0.53, p=0.59

Table 2. Correlations between TCI scores and 5-HT-induced Ca response in healthy subjects

TCI subscale		5-HT-induced Ca response	
		r	p
Temperament scales			
NS	Novelty Seeking	-0.05	0.64
NS1	Exploratory excitability	0.08	0.42
NS2	Impulsiveness	0.10	0.34
NS3	Extravagance	-0.09	0.38
NS4	Disorderliness	0.00	0.97
HA	Harm Avoidance	-0.18	0.07
HA1	Anticipatory worry	-0.09	0.37
HA2	Fear of uncertainty	-0.13	0.19
HA3	Shyness	-0.20	0.05
HA4	Fatigability and asthenia	-0.02	0.86
RD	Reward Dependence	-0.12	0.23
RD1	Sentimentality	-0.14	0.17
RD3	Attachment	0.02	0.84
RD4	Dependence	-0.18	0.08
P/RD2	Persistence	0.19	0.05
Character scales			
SD	Self-Directedness	0.08	0.42
SD1	Responsibility	0.04	0.66
SD2	Purposeful	0.21	0.03
SD3	Resourcefulness	0.03	0.75
SD4	Self-acceptance	-0.01	0.88
SD5	Congruent	0.05	0.61
C	Cooperativeness	-0.05	0.60
C1	Social acceptance	-0.03	0.80
C2	Empathy	0.05	0.65
C3	Helpfulness	-0.11	0.29
C4	Compassion	0.09	0.35
C5	Pure-hearted	-0.25	0.01
ST	Self-Transcendence	-0.08	0.40
ST1	Self-forgetful	-0.15	0.14
ST2	Transpersonal	-0.12	0.22
ST3	Spiritual acceptance	0.08	0.45

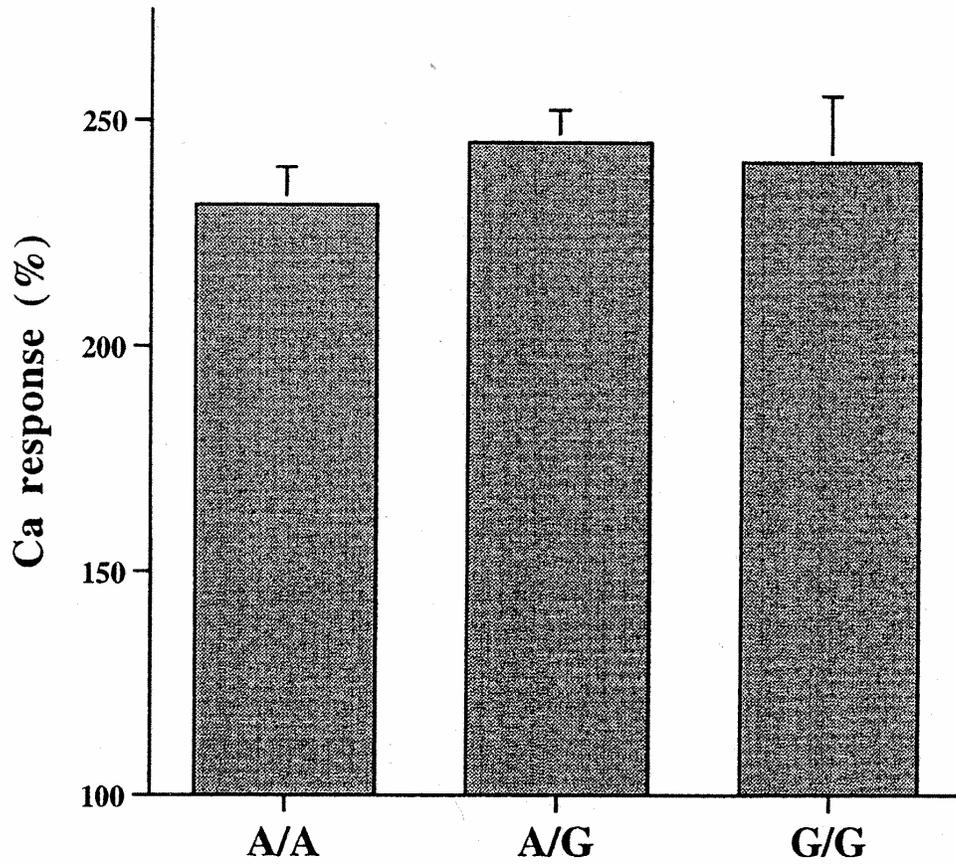


Fig. 1. 5-HT(10 uM)-induced intraplatelet Ca response in healthy subjects sorted by 5-HT_{2A} receptor A-1438G genotypes. Results are the means \pm S.E..