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Baseline saliva level of 3-methoxy-4-hydroxyphenylglycole (MHPG) associates with a consequent cognitive decline in non-demented elderly subjects: Three-years follow-up study

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ABSTRACT

The aim of the study was to explore the relation between saliva level of 3-methoxy-4-hydroxy-phenylglycol (MHPG) and a later cognitive decline in non-demented elderly subjects. We have reported that sMHPG in 214 elderly subjects living in the community (age 74.5 ± 5.9 years) was associated with scores on the Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) in 2004 to 2006 (Time A). The same cohort underwent these cognitive tests again from 2007 to 2009 (Time B). The cognitive function of the 147 of 214 subjects could be reassessed by the same cognitive tests. The score on the FAB, but not the MMSE, was significantly reduced at Time B (14.6 ± 2.6) compared with that of Time A (15.2 ± 1.9). There was a significant negative correlation between the baseline sMHPG and the changes in the FAB score subtracted from Time B to Time A or the scores on the FAB at Time B in men, but not at Time A. These correlations were not found in women. These data indicate that high sMHPG might be associated with subsequent cognitive decline assessed by the FAB in non-demented elderly men living in the community.

1. Introduction

Dementia is a growing health-economic issue worldwide. Therefore, the identification of modifiable factors associated with cognitive decline in later life is a major public health priority. The aim of the study was to explore the relation between saliva level of 3-methoxy-4-hydroxy-phenylglycol (sMHPG), a norepinephrine (NE) metabolite, and a later cognitive decline in non-demented elderly subjects. Many studies on the monoamine systems in Alzheimer's disease (AD) have found abnormalities in the noradrenergic system in the brain (Nazarali and Reynolds, 1992; Hoogendijk et al., 1999; Raskind et al., 1999). Except for a few studies (Molchan et al., 1991; Parnetti et al., 1992), several lines of evidence support that cerebrospinal fluid (CSF) levels of MHPG are higher in patients with AD than in normal controls (Brane et al., 1989; Liu et al., 1991; Martignoni et al., 1992; Tohgi et al., 1992). Significant negative correlations were found between the Mini-Mental State Examination (MMSE) score and NE or MHPG concentrations in CSF (Oishi et al., 1996; Sheline et al., 1998). MHPG concentrations in several brain regions were significantly increased in subjects with AD versus controls (Palmer et al., 1987).

MHPG is a major metabolite of noradrenaline in the human brain that readily diffuses into the CSF or general circulation. The plasma level of MHPG is thought to reflect the activity of noradrenergic neurons in the brain, and it is reported to reflect noradrenergic neuronal tone in humans (Leckman et al., 1980). The saliva level of MHPG (sMHPG) has been reported to correlate significantly with plasma and CSF levels of MHPG (Yang et al., 1997; Reuster et al., 2002). We have reported that sMHPG was higher in patients with anxiety disorders than in normal volunteers (Yamada et al., 2000) and was negatively associated with scores on the General Health Questionnaire-28 in female volunteers (Li et al., 2006). We also showed that baseline sMHPG levels predicted the performance on a continuous task requiring effortful attention in young male subjects (Li et al., 2004). These data indicate that sMHPG may be a useful marker for detecting changes in central and peripheral catecholamine metabolism associated with some mental conditions. In a cross-sectional observational study from 2004 to 2006 (Time A), we reported that sMHPG levels were negatively correlated with scores on the MMSE and the Frontal Assessment Battery (FAB) in 214 elderly people living in a local community (Li et al., 2008). To assess sMHPG as a risk factor for later cognitive decline in non-demented elderly

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subjects living in the community, a second assessment of cognitive function in the same cohort group was performed from 2007 to 2009 (Time B).

2. Methods

2.1. Subjects

At Time A, 226 healthy elderly people (68 men, mean age 74.26 ± 6.09 years; 158 women, mean age 75.27 ± 6.44 years) living in the community were recruited to this study. Their medical status in terms of hypertension, diabetes mellitus, alcohol consumption, education, and smoking was recorded on their own statement. Subjects suffering from cardiovascular disease, alcohol abuse, or any apparent cognitive deficit who resided in a nursing home were excluded. Informed consent was obtained from all participants. Data from 12 subjects were omitted from the analysis due to sampling failure. At Time B, all participants who received the first assessment were invited to take part in the follow-up assessment of cognitive function. One hundred forty-seven of 214 subjects underwent the second assessment. The entry rate to the second assessment was higher in men (75%) than in women (61%). This study was approved by the Institutional Review Board of Saga University Faculty of Medicine.

2.2. Cognitive tests

The Japanese versions of the MMSE and the FAB were administered according to standard structions after saliva sampling.

2.3. Saliva level of MHPG

Saliva was collected using a Salivette (Sarstedt, Nümbrecht, Netherlands) between 13:00 and 16:00 h at Time A, when there is no diurnal change in sMHPG (Yajima et al., 2001). sMHPG was determined by gas chromatography-mass spectrometry (QP-5000, Shimazu Scientific Construction, Kyoto, Japan), according to the method of Maas et al. (1976) with a slight modification. In short, 10 ng of $^{13}C_6$-MHPG as an internal standard (IS) was added to 0.5 ml of saliva. Then free MHPG and IS were extracted with 4 ml of ethylacetate. The organic layer was removed and evaporated to dryness with a centrifugal concentrator (CC-105, Tomy, Tokyo, Japan); then the residue was derivatized with 60 μl of trifluoroacetate (TFA, Tokyo Kasei, Tokyo, Japan) at 120 °C for 20 min. For the selected ion monitoring assay, m/z 472 (M^+ for MHPG-TFA) and m/z 478 (M^+ for $^{13}C_6$-MHPG-TFA) were monitored. The ratio of the peak areas was used for the estimation of the amount of MHPG. Intra-assay and inter-assay coefficients of variation (CV) were 4.6% and 6.6%, respectively. sMHPG was expressed as ng/ml.

2.4. Data analysis

Data were analyzed using a commercially available statistical package (Stat View 4.5, Abacus Concepts, Inc., USA). Paired *t*-tests were used to compare the score of the MMSE, FAB, and BDI at Time A and Time B. The relationship between sMHPG and age, MMSE score, FAB score, BDI score, or the changes in the scores on the MMSE, FAB, or BDI, which were determined by subtracting scores at Time B from scores at Time A, were examined using Pearson's correlation coefficient. The cut-off point of the FAB for cognitive impairment was 14/15. The Student's *t*-tests was used to compare the sMHPG level in the group with cognitive impairment on the FAB with that in the group without cognitive impairment on the FAB. A logistic regression analysis used the existence of cognitive impairment (FAB ≤ 14) at Time B as the dependent variable and sMHPG at Time A, sex (0 women; 1 men), age (years), education (years), smoking (0 no; 1 yes), alcohol drink (0, none; 1, occasional drink; 2, more than one drink per day), hypertension (0 no; 1 yes) and diabetes mellitus (0 no; yes 1) as independent variables. Spearman's rank correlation was used to assess the relationship between sMHPG and each subscale of the FAB. A *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Subject demographics

As shown in Table 1, the education period for men was significantly longer than for women ($t = 3.88$, $P = 0.0001$). The sMHPG was higher in women (13.5 ± 4.6 ng/ml) than in men (12.4 ± 4.9 ng/ml), but differences did not reach statistical significance. As shown in Table 2, scores on the cognitive tests were comparable to those of previous reports (Goldberg et al., 2003). The MMSE score at Time B was comparable with that at Time A. However, the FAB score at Time B was significantly lower than at Time A (15.2 ± 1.9 for Time A; 14.6 ± 2.6 for Time B, $t = -3.0$, $P = 0.003$). There was a small but significant correlation between age and sMHPG level ($r = 0.18$, $P = 0.017$), which was more prominent in women ($r = 0.20$, $P < 0.05$) than in men ($r = 0.19$, $P = 0.22$).

3.2. Relationship between sMHPG and cognitive test scores

As shown in Table 3, the baseline sMHPG was negatively associated with the FAB score at Time B ($r = -0.46$, $P = 0.002$) in men. Changes in the FAB score from Time A to Time B were negatively associated with the baseline sMHPG in men ($n = 44$, $r = -0.42$, $P = 0.004$, Fig. 1). The baseline sMHPG in the cognitively impaired group (FAB score ≤14 at Time B) was 14.9 ± 5.2 ng/ml, which was significantly higher than that in the non-cognitively impaired group (12.2 ± 4.0 ng/ml, $t = 3.4$, $P = 0.0009$), especially in men (16.0 ± 5.8 ng/ml for cognitively impaired group, 10.7 ± 3.4 ng/ml for non-cognitively impaired group, $t = 3.8$, $P = 0.0004$, Table 4). The logistic regression analysis revealed that this significant difference was still found after controlling for the effects of age, sex, education, smoking, alcohol, diabetes and hypertension (Table 5). There was a significant negative correlation between sMHPG and similarities of FAB test results at Time B in men ($P = 0.004$, Table 6). All the others were not significant. Thus, there was a significant negative association between baseline sMHPG and later cognitive decline, especially in men.

4. Discussion

sMHPG levels were higher among elderly subjects in the present study than among a previously studied younger generation (Li et al., 2004; Li et al., 2006). This difference could be explained by age-associated increase in sMHPG (Yamada et al., 2000). We previously reported that sMHPG levels in 214 elderly subjects living in a community were negatively correlated with MMSE or FAB scores (Li et al., 2008). The present 3-year follow-up study in the same cohort group revealed that baseline sMHPG levels were not associated with the MMSE score nor with the FAB score at Time A, but were negatively associated with a consequent cognitive decline, as assessed with the FAB at Time B, in elderly subjects living in a Japanese rural community. There was no association between sMHPG levels and MMSE score at Time B. This discrepancy could be due to the absence of 67 subjects who rejected the follow-up cognitive assessment or died during the 3 years between our assessments. There was no reduction in the MMSE score over 3 years. It is possible that a time interval of 3 years may be too short to detect cognitive reduction as assessed by the MMSE. It has been reported that there is a small but significant decline in scores on the MMSE with increasing population age (Unger et al., 1999). However, the effect can be masked in longitudinal cohorts by a learning effect (especially early in follow-up) and other factors associated with repeated testing (Unger et al., 1999). The learning effect of the MMSE may have masked the cognitive decline in the present study. In contrast, the FAB score at Time B was significantly lower than at Time A. It has been reported that after 6 months of

Table 1
Subjects' demographics.

	Men	Women	Statistical significance
N	43	104	
Age (years, Time A)	74.1 ± 6.5	74.7 ± 5.6	ns
Education (years)	10.0 ± 2.2	8.8 ± 1.6	$t = 3.88$, $P = 0.0001$
sMHPG (ng/ml)	12.4 ± 4.9	13.5 ± 4.6	ns

Student's *t* test. Values represent mean ± standard deviation. ns, not significant.

Table 2
Changes in cognitive function during 3 years.

	Time A	Time B	
MMSE	27.0 ± 2.9	26.9 ± 2.5	ns
FAB	15.2 ± 1.9	14.6 ± 2.6**	$t = -3.0$, $P = 0.003$

Paired *t* test; **$P < 0.01$. Data represent mean ± SD; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery.