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Impacts of age on plasma monoamine metabolite concentrations in a large cohort of healthy individuals

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ABSTRACT

The measurement of plasma concentrations of monoamine metabolites is a useful method for inferring the dynamics of monoamine metabolites in the brain. To clarify effects of age and sex on plasma monoamine metabolites levels, we used high-performance liquid chromatography to measure plasma levels of homovanillic acid (HVA), free and total 3-methoxy-4-hydroxyphenylglycol (MHPG), and 5-hydroxyindoleacetic acid (5-HIAA) in healthy men and women of various ages ($n=214$). In all plasma monoamine metabolites, there were significant differences across the age groups, and multiple comparisons revealed that older subjects had higher levels than younger subjects. Moreover, significant positive correlations were found between age and plasma levels of HVA, free MHPG, total MHPG, and 5-HIAA. On the other hand, plasma concentrations of monoamine metabolites were not influenced by sex, except for total MHPG for which the plasma levels were significantly higher in men than in women. Age-related changes in monoamine oxidase and renal function might affect our results. This large cohort survey provides further evidence to be cautiously aware of age effects when regarding plasma monoamine metabolites levels as reflections of central activity.

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1. Introduction

Concentrations of monoamine metabolites have been studied (Beckmann and Goodwin, 1975; Asberg et al., 1976; Carlsson et al., 1985; Nagaoka et al., 1997; Kelly et al., 1999; Luykx et al., 2012) with relation to psychiatric disorders, such as schizophrenia or depression. Concentrations of homovanillic acid (HVA, a metabolite of dopamine), 3-methoxy-4-hydroxyphenylglycol (MHPG, a metabolite of noradrenaline) and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) have been measured in cerebrospinal fluid (CSF), urine, saliva, and plasma. Particularly, the measurement of plasma concentrations of monoamine metabolites is a relatively simple and useful method for inferring the dynamics of monoamine metabolites in the brain. Furthermore, plasma levels of monoamine metabolites are reported to be possible indicator of response to antipsychotics (Nagaoka et al., 1997; Kelly et al., 1999; Miura et al., 2012) in schizophrenia or antidepressants (Shinkai et al., 2004) in depression.

It is estimated that 30–50% of plasma HVA (Maas et al., 1980), and one third of plasma MHPG (Kopin et al., 1983), are derived from the brain, respectively. It is unclear whether plasma 5-HIAA levels are relevant from the central serotonergic activity, but a previous study suggested that platelet serotonin turnover is associated with the psychopathology in attention-deficit/hyperactivity disorder (Oades et al., 2002), and another study reported that plasma levels of 5-HIAA were associated with selective serotonin reuptake inhibitor (SSRI)-induced nausea (Ueda et al., 2003). However, there are some difficulties to regard plasma monoamine metabolites as reflections of central activity. Plasma concentrations of monoamine metabolites are thought to be influenced by peripheral factors including the autonomic nervous system and sex hormones, and it is estimated that there is an individual difference. Many studies (Ortiz et al., 1988; Blennow et al., 1993; Sumiyoshi et al., 1997) have stated that monoamine metabolite concentrations are affected by sex differences and age in healthy subjects, although caution is necessary when interpreting findings due to small sample sizes with age and sex biases. There are few studies systematically investigating plasma concentrations of monoamine metabolites in a large sample size of healthy subjects. In this study, we have measured plasma concentrations of monoamine metabolites in 214 healthy subjects of various age groups with the aim of defining age

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and sex difference on plasma concentrations of monoamine metabolites in healthy individuals.

2. Methods

2.1. Subjects

A total of 214 subjects, without mental disorders, were recruited from each of the following six age groups spanning 13–69 years: Group 10 (10–19 years; 20 males and 25 females); Group 20 (20–29 years; 19 males and 22 females); Group 30 (30–39 years; 14 males and 20 females); Group 40 (40–49 years; 15 males and 15 females); Group 50 (50–59 years; 20 males and 21 females); Group 6 (60–69 years; 7 males and 16 females). Subjects were recruited through advertisement posted at Fukushima Medical University and Fukushima Medical University Hospital (Fukushima, Japan). All subjects were physically healthy, and we excluded subjects with cancer, heart diseases, renal diseases, liver diseases, collagen diseases, and neurological diseases, as well as subjects taking steroids. The number of total male subjects was 95 with mean age $\pm$S.D. of 37.0$\pm$15.2 (age range, 13–67 years), and those of female subjects were 119, 37.5$\pm$16.0, and 18–69 years, respectively. All participants were examined by psychiatrists (E.S. and Q.Y.) using unstructured interviews to confirm the absence of mental and major somatic disorders. After application of all exclusion criteria, blood samples were collected in 214 subjects to measure monoamine metabolite concentration. This study was approved by the Ethics Committee of Fukushima Medical University, and written informed consent was obtained from all subjects.

2.2. Sampling

Subjects were asked to avoid excessive exercise and not to consume any foods with high monoamine levels the night before their examination (consumption of food not containing high monoamine levels was permitted). Foods with high monoamine levels include octopus, squid, cheese, bananas, and chocolate (Amin et al., 1992). After confirmation that the subjects met inclusion criteria, 21-mL blood samples were collected. Samples were coded prior to preservation, and were placed into test tubes and centrifuged (3000 rpm, 5 min). The supernatant (plasma) was cryopreserved at $-80\,^{\circ}$C until measurements were performed. The measurement of plasma monoamine metabolite levels were performed without knowledge of age and gender of the participating subjects.

2.3. Measurements of concentrations of plasma monoamine metabolites

Concentrations of plasma monoamine metabolites were analyzed with high-performance liquid chromatography (HPLC) with electrochemical detection using modified methods of Gerhardt et al. (1986). All chromatographic separations were performed on octadecyl-silica gel (3 μm particles, 4.5 mm × 150 mm) reversed-phase column. To measure HVA, 5.5 mL of 0.018 M- ethylenediaminetetraacetic acid (EDTA)-2Na, 1 mL of 10% $ZnSO_4$, and 0.5 mL of 1 M NaOH were added to 1 mL plasma sample. After shaking for 5 min, the sample was deproteinized using a centrifuge (3500 rpm, 20 min), sodium chloride (1500 mg) was then added to the fractionated supernatant and, the mixture was shaken vigorously. After adding 3 mL of ethyl acetate, the sample was shaken for 5 min and centrifuged (3500 rpm, 20 min), and the ethyl acetate layer was fractionated twice. After fractionation, the sample was dried using centrifuged evaporator, and 0.5 mL of ultrapure water was added to the residue. After shaking for 3 min, dissolved sample was injected into an HPLC device.

For MHPG, we measured both free and total (free and conjugated) MHPG. To measure free MHPG, standard MHPG mixed with 1 mL of 0.5 M acetate buffer (pH 5.5) containing 0.1 M EDTA-2Na and 0.5 mL of plasma sample was mixed 0.5 mL of 0.5 M acetate buffer (pH 5.5) containing 0.1 M EDTA-2Na, and 500 mg of sodium chloride was added to each tube. Both test tubes were then shaken and 3 mL ethyl acetate was added. After shaking for 5 min and centrifuging (2000 rpm, 3 min), the ethyl acetate layer was fractionated twice. Next, 1 mL of Na_2CO_3 was added to the ethyl acetate layer, which was then shaken for 10 min and centrifuged (2000 rpm, 3 min). After fractionating the ethyl acetate layer once more, the sample was dried using centrifuged evaporator, 1 mL of ultrapure water was added to the residue. Finally after shaking for 3 min, dissolved sample was injected into an HPLC device. To measure total MHPG, sulfatase and 0.5 mL of 0.5 M acetate buffer (pH 5.5) containing 0.1 M EDTA-2Na were added to 0.5 ml of plasma sample. After shaking vigorously, the sample was incubated at $37\,^{\circ}$C for 18 h. The same extraction procedure used for free MHPG was then performed, and the sample was injected into an HPLC device.

To measure 5-HIAA, 15 ng of the internal standard 5-HICA (5-hydroxyindole-3-carboxylic acid), 1000 mg of sodium chloride, and 1 mL of 0.5 M acetate buffer (pH 5.5) containing 0.1 M EDTA-2Na were added to 1 mL of plasma sample and, the mixture was vigorously shaken. After adding 3 mL ethyl acetate, the solution was shaken for 5 min and centrifuged (2000 rpm, 3 min) and the ethyl acetate layer was fractionated twice. After fractionation, the sample was dried using centrifuged evaporator, and 1 mL of ultrapure water was added to the residue. After shaking for 3 min, dissolved sample was injected into an HPLC device. The units of plasma monoamine metabolite concentrations were ng/mL. The intra-assay coefficients of variation for HVA, free MHPG, total MHPG, and 5-HIAA in our laboratory were 3.9%, 3.6%, 2.9%, and 17% respectively. The inter-assay coefficients of variation for HVA, free MHPG, total MHPG, and 5-HIAA were 5.6%, 5.7%, 5.3%, and 14%, respectively.

2.4. Data analysis

Analyses were conducted using chi-squared tests to confirm a relationship between the number of men and women and age. Shapiro–Wilk tests were then performed to confirm the normality of the monoamine metabolite data. In addition, differences in monoamine metabolite levels according to sex were examined using Mann–Whitney U test. Kruskal–Wallis test was performed to examine whether there were differences in metabolite levels among age groups. In addition, Steel–Dwass test was used to analyze the age groups that differed in metabolite levels. Finally, we determined Spearman's correlation coefficient to examine the correlation between age and metabolites. The above tests were conducted with SPSS, Microsoft Excel 2010 (Microsoft Co., Redmond, WA, USA), and the add-in software Statcel 3 (OMS add-in application software).

3. Results

3.1. Results of samples

To examine whether sex differences were present in age distribution among the 214 subjects, chi-squared tests were performed between age groups and sex regarding numbers of men and women in each 10-year age group, as mentioned in Section 2.1. It was confirmed that no relationship was present between the age distributions of men and women (χ^2 [5]=2.723, P=0.743). Next, we excluded deviated outliers using a box plot. There were 2 outliers for HVA, no outliers for free and total MHPG, and 7 outliers for 5-HIAA, respectively. To examine whether HVA, free and total MHPG, and 5-HIAA values formed normal distributions, frequency distributions were plotted for each monoamine metabolite concentration. In addition, analyses were performed using Shapiro–Wilk tests to examine the normality of the distributions. Shapiro–Wilk test revealed that monoamine metabolites did not form normal distributions. For HVA (n=205), Shapiro–Wilk's W (205) was 0.923($P<0.01$), and its max, min, median values were 37.1, 6.7, and 13.7, respectively (Supplementary Fig. 1, Table 1). The corresponding values for free MHPG (n=211) were W (211)=0.917($P<0.01$), max=10.4, min=3.0, and median=5.0 (Supplementary Fig. 2, Table 1) and for total MHPG (n=210), W (210)=0.916 ($P<0.01$), max=32.9, min=5.7, and median=18.4 (Supplementary Fig. 3, Table 1). The values for 5-HIAA (n=207) were as follows; W (207), 0.918($P<0.01$); max, 16.2; min, 1.9, and median, 5.5 (Supplementary Fig. 4, Table 1).

3.2. Age and monoamine metabolites concentrations

Median, maximum, and minimum were calculated for all monoamine metabolite concentrations in each age group, and Kruskal–Wallis test was used in order to compare these values between age groups. Kruskal–Wallis test revealed that HVA concentrations significantly differed across age groups [H(5)=11.85, $P<0.05$] (Fig. 1). However, when using the Steel–Dwass method to compare the different age groups with regard to HVA concentrations, no significant differences emerged. Free MHPG tended to differ across age groups [Kruskal–Wallis, H(5)=10.46, $P<0.1$]. Statistically significant differences in free MHPG were found between group 10 and group 50 (Steel–Dwass, $t=-2.99$, $P<0.05$) (Fig. 2). Total MHPG significantly differ across age groups [Kruskal–Wallis, H(5)=24.51, $P<0.01$]. Statistically significant differences were observed in total MHPG between group 10 and group 50 (Steel–Dwass, $t=-3.69$, $P<0.01$), and between group 20 and group 50 (Steel–Dwass, $t=-3.81$, $P<0.01$) with total MHPG concentrations for subjects in group 50 being significantly higher

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