Journal of Psychiatric Research 96 (2018) 23–32

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Plasma amino acid profile in major depressive disorder: Analyses in two independent case-control sample sets

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ARTICLE INFO

Article history:
Received 19 May 2017
Received in revised form
27 August 2017
Accepted 13 September 2017

Keywords:
Amino acids
Blood plasma
Case-control study
Glutamate
Major depressive disorder
Methionine

ABSTRACT

Some amino acids act as neurotransmitters themselves, or are precursors of neurotransmitters. Previous studies reported inconsistent results regarding their changes in blood in major depressive disorder (MDD), which prompted us to examine plasma levels of amino acids and related molecules in two independent case-control sample sets. In total, 511 subjects were recruited. Sample set A consisted of 164 patients with MDD (147 currently depressed [dMDD]; 17 in remission, DSM-IV) and 217 healthy controls. Sample set B consisted of 65 patients (51 dMDD; 14 in remission) and 65 controls. Plasma amino acid levels were measured using high-performance liquid chromatography for set A and liquid chromatography/mass spectrometry for set B. We further analyzed the relationships between plasma amino acid levels and clinical variables. In sample set A, plasma asparagine, histidine+1-methylhistidine, methionine, phenylalanine, tryptophan, and tyrosine levels were decreased, while plasma glutamate and phosphoethanolamine were elevated in dMDD compared to controls (all $P < 0.0005$), even after correcting for multiple testing. Plasma leucine levels were associated with "psychic anxiety." In sample set B, glutamate and methionine levels were also altered in the same direction to that in sample set A (both $P < 0.05$). In the integrative analysis, plasma glutamate and methionine levels were found to be significantly associated with the diagnosis of MDD with small to medium effect sizes (both $P < 1.0E-6$). In conclusion, several amino acids and related molecules were altered in patients with MDD. Decreased methionine and increased glutamate levels were found consistently in the two sample sets, suggesting their involvement in MDD. Further investigations are warranted on the possible role of amino acids in the pathophysiology of MDD.

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1. Introduction

Major depressive disorder (MDD) is a common disease. Its adjusted global prevalence is estimated at 4.4% worldwide (Ferrari et al., 2013), and it is ranked as the third largest cause of years lived with disability (YLDs) (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Although several promising biological mechanisms have been proposed, such as the monoamine hypothesis, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and chronic inflammation, the pathophysiology of MDD remains elusive, and there are no established biomarkers (Kunugi et al., 2015).

Alterations in serotonergic (Charney and Manji, 2004), noradrenergic (Charney and Manji, 2004), dopaminergic (Ogawa and Kunugi, 2015), glutamatergic (Hashimoto, 2009), and γ-aminobutyric acid (GABAergic) (Pehrson and Sanchez, 2015) systems are implicated in psychiatric disorders (Hasler, 2010), and these neurotransmitters are themselves amino acids or are synthesized from amino acids. For example, tryptophan is a precursor of serotonin,

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https://doi.org/10.1016/j.jpsychires.2017.09.014
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and has well been investigated in MDD. Our meta-analysis demonstrated decreased plasma tryptophan levels in patients with MDD (Ogawa et al., 2014). However, other amino acids and related molecules are of interest also. Several previous studies focused on blood levels of amino acids that are precursors to monoamine neurotransmitters in patients with MDD and controls (DeMyer et al., 1981; Hoekstra et al., 2001; Lucca et al., 1992; Maes et al., 1990; Moller, 1993; Russ et al., 1990). Other studies investigated the profiles of plasma amino acids and related molecules in patients and controls (Altamura et al., 1995; Maes et al., 1998; Mauri et al., 1998, 2001; Mitani et al., 2006; Woo et al., 2015; Xu et al., 2012). However, the results are inconsistent. Some studies reported significantly increased alanine (Pinto et al., 2012; Woo et al., 2015), glutamate (Mauri et al., 1998; Mitani et al., 2006; Pinto et al., 2012; Woo et al., 2015), glutamine (Mitani et al., 2006; Xu et al., 2012), ornithine (Pinto et al., 2012), D-serine (Hashimoto et al., 2016), L-serine (Hashimoto et al., 2016; Pinto et al., 2012), taurine (Altamura et al., 1995; Mauri et al., 1998; Mitani et al., 2006; Pinto et al., 2012), and tyrosine (Pinto et al., 2012) levels, while others reported significantly decreased α-aminoadipic acid (Xu et al., 2012), β-aminoisobutyric acid (Woo et al., 2015), β-alanine (Woo et al., 2015), arginine (Pinto et al., 2012), aspartate (Pinto et al., 2012), cystathionine (Woo et al., 2015), GABA (Xu et al., 2012), homocysteine (Woo et al., 2015), isoleucine (Mauri et al., 2001), leucine (Xu et al., 2012), O-phospho-L-serine (Woo et al., 2015), sarcosine (Woo et al., 2015), and tryptophan (Xu et al., 2012) levels. The directions of change in blood ethanolamine (Woo et al., 2015; Xu et al., 2012), glycine (Altamura et al., 1995; Mitani et al., 2006), lysine (Mauri et al., 1998; Xu et al., 2012), methionine (Woo et al., 2015; Xu et al., 2012), and phenylalanine (Pinto et al., 2012; Xu et al., 2012) levels in patients with MDD were inconsistent. This may have arisen for several reasons. First, small sample sizes and low statistical power (Button et al., 2013) may have caused false-negative results (type II error). Second, not controlling for demographic factors, such as sex and age, may have yielded spurious results. Only a few studies (Altamura et al., 1995; Maes et al., 1998) controlled for these variables. Third, most studies did not correct for multiple testing, and so are subject to false-positive results (type I error).

Thus, we aimed to determine plasma levels of amino acids and related molecules in two independent case-control sample sets ($N = 511$) taking demographic, clinical variables, and multiple comparisons into account. We also examined whether plasma amino acids levels were related to clinical variables, such as psychotropic drug doses and MDD symptoms.

1.1. Subjects and methods

1.1.1. Subjects

We examined two independent sample sets, A and B. Set A consisted of 164 patients with MDD (147 currently depressed [dMDD] and 17 remitted [rMDD]) and 217 healthy controls (Table 1), and was obtained from our bio-resource repository for biomarker research projects, collected between October 2003 and October 2015. Set B consisted of 65 patients with MDD (51 dMDD and 14 remitted) and 65 controls (Supplemental Table S1) who participated in a nutrition study between March 2011 and July 2012. Subjects were recruited through advertisements in free local magazines, our website, and the National Center of Neurology and Psychiatry hospital (Tokyo, Japan). Thirty-four participants who were included in both sets A and B were omitted from set B. Trained psychologists/psychiatrists screened all subjects using the structured interview M.I.N.I. (Mini International Neuropsychiatric Interview) (Sheehan et al., 1998), Japanese edition (Otsubo et al., 2005). A consensus diagnosis was made by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (American Psychiatric Association, 1994) and information from medical records, if available. Individuals with prior medical history of central nervous system disease, severe head injury, or substance abuse/dependence were excluded. Individuals who had a history of past or current regular contact with psychiatric services, or a history of psychotropic drug use were excluded from the healthy controls. Depressive symptoms were assessed using the Japanese version of the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960; Tabuse et al., 2007) and the cut-off score for remission was ≤ 7 (Zimmerman et al., 2013). Daily doses of benzodiazepine derivatives and antidepressants were converted to equivalent diazepam and imipramine doses, respectively, using published guidelines (Inagaki et al., 2013).

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee at NCNP (No. 305). All subjects provided written informed consent.

1.1.2. Blood collection and determination of plasma levels of amino acids and related molecules

Blood collection was performed in a "real world setting" without fasting. Venous blood was drawn into ethylenediamine tetra-acetic acid sodium (EDTA-2Na) vacutainer tubes (Terumo, Tokyo, Japan). The blood was immediately placed on ice and then centrifuged at 4 °C at 3000 rpm for 15 min, and the supernatant was aliquoted into microtubes and stored at −80 °C.

Researchers who handled the blood samples were blind to clinical information. For set A, samples were analyzed using high-performance liquid chromatography (HPLC) as described previously (Ogawa et al., 2015). We prepared 40 standards for the absolute calibration curve using the Amino Acids Mixture Standard Solution, Type B and Type AN-2 (Wako Pure Chemical Industries, Ltd. Osaka, Japan), and an additional standard solution mixture for tryptophan, glutamine, theanine, proline, and asparagine (all purchased from Wako). Since histidine and 1-methylhistidine cannot be separated by their peak in our system, we used combined plasma histidine+1-methylhistidine values. For set B, samples were analyzed using liquid chromatography/mass spectrometry (LC/MS) (SRL Co. Inc. Tokyo, Japan). Briefly, plasma samples deproteinized using acetonitrile were centrifuged twice at 4 °C at 12,000 rpm for 10 min and the supernatant was aliquoted. The prepared samples were separated on an octadecyl-silica (ODS) column (Inertsil ODS-3, 2.1 mm ID × 100 mm, GL Sciences Inc. Tokyo, Japan) during the HPLC analysis and amino acid levels were determined via the LC-MS2020 system (Shimadzu Corp., Kyoto, Japan) at SRL.

1.1.3. Statistical analysis

We assigned several dummy variables to each batch for HPLC in set A (three batches) to control for batch effects. Continuous variables are reported as means ± standard deviation (SD). We compared demographic and clinical data using a *t*-test or analysis of variance (ANOVA), and categorical distributions using a chi-squared test. An analysis of covariance (ANCOVA) was used to compare plasma amino acid and related molecule levels between dMDD and controls, controlling for age, sex, and batch effects. Plasma amino acid levels of the rMDD group were not used in the comparison of patients and controls. However, they were used in the multiple regression analyses to examine the association between plasma amino acid levels and depression severity. To estimate the association of plasma amino acids with diagnosis, a logistic regression was performed using diagnosis as the dependent variable, age, sex, and batch numbers as the explanatory variables with forced entry, and plasma amino acid levels as explanatory variables with forward stepwise selection. The relationships

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