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Research paper

Global arginine bioavailability ratio is decreased in patients with major depressive disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is characterized by increased oxidative and nitrosative stress. We compared nitric oxide metabolism, i.e., the global arginine bioavailability ratio (GABR) and related serum amino acids, between MDD patients and non-depressed controls, and between remitted and non-remitted MDD patients.

Methods: Ninety-nine MDD patients and 253 non-depressed controls, aged 20–71 years, provided background data via questionnaires. Fasting serum samples were analyzed using ultra-performance liquid chromatography coupled to mass spectrometry to determine the serum levels of ornithine, arginine, citrulline, and symmetric and asymmetric dimethylarginine. GABR was calculated as arginine divided by the sum of ornithine plus citrulline. We compared the above measures between: 1) MDD patients and controls, 2) remitted (n = 33) and non-remitted (n = 45) MDD patients, and 3) baseline and follow-up within the remitted and non-remitted groups.

Results: Lower arginine levels (OR 0.98, 95% CI 0.97–0.99) and lower GABR (OR 0.13, 95% CI 0.03–0.50) were associated with the MDD vs. the non-depressed group after adjustments for potential confounders. The remitted group showed a decrease in GABR, arginine, and symmetric dimethylarginine, and an increase in ornithine after the follow-up compared with within-group baseline values. The non-remitted group displayed an increase in arginine and ornithine levels and a decrease in GABR. No significant differences were recorded between the remitted and non-remitted groups.

Limitations: The MDD group was not medication-free.

Conclusions: Arginine bioavailability may be decreased in MDD. This could impair the production of nitric oxide, and thus add to oxidative stress in the central nervous system.

1. Introduction

Major depression is the leading cause of disability and the global burden of disease, and is the most common psychiatric disorder in developed countries (WHO, 2014). However, the etiopathogenesis of major depressive disorder (MDD) remains poorly understood. Earlier studies have suggested aberrant nitric oxide (NO)-related pathways in MDD. In one earlier study, the bioavailability of arginine, a precursor of NO, was found to be decreased in inpatients with MDD (Baranyi et al., 2015). Furthermore, decreased activity of the endothelial isoform of nitric oxide synthase (eNOS) in platelets has been observed in MDD (Chrapko et al., 2006). However, first-episode MDD patients have been

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shown to have increased levels of plasma nitrate, indicating increased production of NO (Suzuki et al., 2001).

Nitric oxide (NO) is gaseous signaling molecule, which is formed from the semi-essential amino acid arginine by three isoforms of nitric oxide synthases (NOS) (Magariños and McEwen, 1995). These isoforms are called inducible NOS (iNOS), neuronal NOS (nNOS), and endothelial NOS (eNOS). NO modulates vasodilation and neuronal functions, and inhibits the aggregation of platelets, adhesion of monocytes and leucocytes, proliferation of smooth muscle cells, oxidation of low density lipoprotein cholesterol (LDL), and vascular inflammation by suppressing chemokines and adhesion molecules (Böger et al., 1998; Cooke et al., 1991; Förstermann and Sessa, 2012; Tsao et al., 1996; Wolf et al., 1997). Inducible NOS (iNOS) is mainly expressed by macrophages in response to inflammatory signals. However, virtually any cell is capable of expressing iNOS (Förstermann and Sessa, 2012). In addition, NO decreases NMDA receptor activity (Lei et al., 1992; Manzoni and Bockaert, 1993).

As the half-life of NO is short and NO is mostly synthesized on demand at the site of need, there are no methods to reliably measure the levels of NO. Therefore, the only possibility is to measure the bioavailability of its precursor, which is also the limiting factor for the synthesis of NO. Previously, the capacity to synthetize NO has been estimated using the l-arginine/ornithine ratio, which reflects the activity of arginase, an enzyme that competes with NOS for arginine. However, the global arginine bioavailability ratio (GABR) is novel and improved approach used to measure the capacity of a system to produce NO, and has also been used as biomarker for endothelial dysfunction and cardiovascular risk factors (Sourij et al., 2011). GABR is calculated as the serum levels of arginine divided by the sum of ornithine plus citrulline. The ratio gives a more precise estimation of the bioavailability of arginine and thus the ability to produce NO (Morris et al., 2005; Romero et al., 2008a, 2008b; Sourij et al., 2011).

Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of NOS (Vallance et al., 1992). Symmetric dimethylarginine (SDMA) has no NOS-inhibiting qualities, but has been thought to compete with the transportation of arginine through cell membranes (Leiper et al., 1999).

One recent study reported increased levels of ADMA and decreased levels of SDMA in patients with MDD (Baranyi et al., 2015).

In the present study, we analyzed the serum levels of arginine, citrulline, and ornithine, and calculated GABR for a longitudinal sample of MDD patients and for a non-depressed control group. Additionally, we analyzed the levels of asymmetric and symmetric dimethylarginine to assess the possible NOS-inhibiting role of these metabolites. These metabolites and GABR were compared 1) between the MDD and non-depressed groups and 2) within the MDD group between those who recovered and did not recover during the follow-up of eight months. Furthermore, we examined 3) changes in the metabolite levels during the follow-up period within the groups of a) remitted MDD patients and b) non-remitted MDD patients.

2. Methods

2.1. Study samples

The present study utilized two sample sets: 1) a naturalistic follow-up study sample of patients with MDD and 2) a general population-based sample of non-depressed individuals (Ali-Sisto et al., 2016). The age distribution of the participants was 20–71 years. Both studies were approved by the Ethics Committee of Kuopio University Hospital. All participants provided written informed consent before entering the study. Both study samples geographically represent the same population.

The patient sample initially consisted of 100 outpatients with MDD, and was recruited from the Department of Psychiatry at Kuopio University Hospital. Due to a technical error during blood sample handling, one sample was unusable, and thus the final sample set consisted of 99 MDD patients. Due to the insignificant amount of missing data, no attrition analyses were performed. At baseline, the diagnosis of MDD was confirmed by using the Structured Clinical Interview for DSM-IV (SCID) (DSM-IV American Psychiatric Association, 1994). At the follow-up, the same criteria were used to confirm clinical depression or the remission status. Of the initial 99 patients, 78 participated in the follow-up study (mean follow-up time 8 months; range 5–13 months). We observed no differences in age ($p = 0.152$), sex ($p = 0.663$), marital status ($p = 0.575$), alcohol use ($p = 0.324$), smoking ($p = 0.964$), regular exercise ($p = 0.964$), or BDI scores ($p = 0.493$) between the depressed patients who participated in the follow-up and those who did not. All participants gave venous blood samples at baseline and on follow-up. The exclusion criteria for the study were a history of epilepsy, bipolar disorder, psychotic disorders, mental symptomology due to substance abuse, and current somatic conditions preventing participation in the study.

At baseline, 84 (84.8%) of the patients used antidepressant medication and 48 (48.5%) used antipsychotic medication. Antidepressant use was distributed as follows: 1) selective serotonin reuptake inhibitors (SSRI), n = 42 (42.4%); 2) venlafaxine, n = 21 (21.2%); 3) mirtazapine, n = 13 (13.1%); 4) duloxetine, n = 12 (12.1%); 5) moclobemide, n = 8 (8.9%); 6) bupropion, n = 6 (6.1%), and 7) trazodone, n = 1 (1.0%).

The non-depressed control sample was a population-based longitudinal cohort of 480 individuals living in the municipality of Lapinlahti, Finland. The sample included in this study was collected as part of the 5-year follow-up of the Lapinlahti Study in 2010. Altogether, 257 non-depressed controls were derived from the population-based Lapinlahti study sample. The exclusion criteria were an elevated level of depressive symptoms, i.e., Beck Depression Inventory (BDI) scores ≥ 10 (Beck et al., 1961) at baseline or the 5-year follow-up of the Lapinlahti Study, or the reported use of antidepressants. Participants underwent a complete health examination and completed a background questionnaire (Savolainen et al., 2014).

2.2. Background data

The following variables were extracted from questionnaires completed by the participants in both study samples: the frequency of weekly physical exercise (≥ 1 times vs. < 1 time), regular smoking (yes vs. no), weekly alcohol use (0–5 portions vs. ≥ 6 portions; 1 portion corresponds to 1 bottle of beer, 1 glass of wine, or 4 cl of spirits), marital status (married or living with a partner vs. living alone), educational level (university, polytechnic, or college education vs. lower than university, polytechnic, or college education), and a physician-determined diagnosis of hypertension (yes vs. no). Depressive symptoms were assessed with the 21-item BDI (range 0–63; Beck et al., 1961). The use of prescription and over-the-counter medications was also recorded with a questionnaire, and double-checked from the prescription documents the patients provided at the study visit.

2.3. Laboratory analyses

Before venipuncture, the participants in both study populations were instructed to fast for 12 h. All samples were stored at −70 °C until analyzed. The blood samples were used to quantify the concentrations of a batch of metabolites related to different aspects of the patient study and the population-based Lapinlahti Study, from which the non-depressed control sample was derived. Based on previous literature indicating a role of NO in MDD, this study focused on the precursor of NO, arginine, two closely related amino acids (i.e., ornithine and citrulline), and two metabolites know to regulate NOS enzymes (symmetric and asymmetric dimethylarginine).

Metabolites were extracted from the serum samples using acetonitrile (1:4, sample:solvent) and analyzed using a WATERS XEVO-TQ-S