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L-ARGININE-NITRIC OXIDE PATHWAY AND NEURAL NETWORKS IN MAJOR DEPRESSION

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Dear editor,

Nitric oxide (NO) modulates norepinephrine, serotonin, dopamine, and glutamate, which are major neurotransmitters involved in the pathophysiology of major depression (MD) (Lesperance et al. 2004). NO is a signaling molecule that plays a pivotal role in regulating vascular tone. Further, NO has been shown to benefit vasculature. NO is synthesized by a family of nitric oxide synthases (NOS) via the conversion of L-arginine (Arg) to L-citrulline. Further, the availability and transport of Arg modulates the rate of NO biosynthesis in circulating blood cells and the vasculature, which protects against cardiovascular diseases. By contrast, dimethylarginines are endogenous Arg analogs that inhibit NO synthesis. Asymmetric dimethylarginine (ADMA) competes with the substrate at the NOS catalytic site, while symmetric dimethyllarginine (SDMA) competitively interacts with Arg transport into the cells, and the enzyme arginase competes with NOS and metabolizes Arg to ornithine (Orn). Arginase activity is upregulated in several diseases, such as diabetes mellitus and inflammation. The Arg/Orn ratio reflects arginase activity (Barth et al. 2004). Thus, the Arg-NO pathway may be impairred in MD and play an important role in the pathophysiology of the disease (Baranyi et al. 2015). These structural networks arise from neural plasticity; that is, regions that fire and wire together may be coupled due to mutual trophic- and plasticity-related changes at synaptic and cellular levels (Hess et al. 2017). We investigated the brain's salience network (SN), central executive (CE) network, and default mode (DM) network, and their relationship with the Arg-NO pathway in patients with MD. Twenty Patients (M/F: 8/12, age: 43±15 yr.) were recruited from the University Hospital of the University of Occupational and Environmental Health, Kitakyushu, Japan, from March 2009 to January 2017. All patients met the diagnostic criteria of MD as per a structured clinical interview specified in the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision, Research Version. The 17-item Hamilton Rating Scale for Depression (HAMD) was used to evaluate the severity of MD, and patients with an HAMD score ≥ 14 points were enrolled in the study (mean±SD: 21±7). Patients with a history of neurological diseases, substance use, and/or the presence of any other psychiatric disorder were excluded. In total, 20 right-handed, drug-naïve patients with MD were included in this study. Magnetic resonance imaging (MRI) scanning, HAMD scoring, and serum sampling were performed prior to the initiation of pharmacological treatment. There were no significant differences in age, HAMD scores, serum levels of Arg, ADMA, SDMA, and Orn levels between male and female patients. Multiple regression analysis was performed with the Z-score as the objective variable to determine whether serum levels of Arg, ADMA, SDMA, or Orn affected the three brain structural networks considered (SN, CE, and DM) (Okamoto et al. 2020). Age was included in the analysis The assessment revealed that Arg, ADMA, SDMA, and Orn were not associated with any of the three brain networks considered. No correlations between Arg/ADMA ratio and any of the brain networks considered were found. Furthermore, no correlations between Arg/ADMA and HAMD scores were identified. Multiple regression analysis was performed to examine the relationship between the serum Arg/Orn ratio and the three brain networks. To remove age as a confounding factor, we included it in the analysis as an explanatory variable. No correlations between Arg/Orn ratio and any brain networks were identified. Furthermore, no correlations between Arg/Orn ratio and HAMD scores were found. A correlation was observed between serum Arg and SDMA ($r=0.62$, $p=0.0032$), but not between Arg and ADMA ($r=0.334$, $p=0.15$). A correlation between serum SDMA and ADMA was also noted ($r=0.567$, $p=0.0091$). No correlations between Arg, ADMA, or SDMA levels and brain networks (SN, CE, DM) in first-episode, drug-naïve patients with MD were identified. In this study, we did not observe any correlation between Arg, ADMA, and SDMA levels and the three brain networks assessed. We found that in patients with MD, Arg was associated with SDMA, but not with ADMA. Although interpretation of present results is difficult, it remains plausible that an imbalance among Arg, ADMA, and SDMA levels may exist in patients with MD. Furthermore, we found no correlation between the Arg/Orn ratio and brain networks, indicating that arginase activity has little influence on brain networks considered in patients with MD. Thus, the Arg/ADMA and Arg/Orn ratios were independent of the severity of the depressive state. In conclusion, no correlations were observed between the Arg-NO pathway and three neural networks in the MD patients considered. Although the main result was negative, this is the first preliminary study to assess the relationship between Arg and its metabolites and neural networks in first-episode, drug-naïve patients with MD.

Statement of Ethics:

The study protocol was approved by the Ethics Committee of the University of Occupational and Environmental Health, Kitakyushu, Japan (approval number: H25-13; May 8, 2013), and was conducted while upholding its ethical standards. It conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All participants who entered the study signed an informed consent document that explained the study protocol and potential risks associated with study participation.

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Conflict of interest: None to declare.

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