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Kynurenine pathway changes in late-life depression with memory deficit

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ABSTRACT

Kynurenine pathway (KP) activation is associated with many neuropsychiatric diseases, such as major depressive disorder (MDD) and Alzheimer's disease (AD). Investigations conducted on MDD seldom shed light on KP changes in late-life depression (LLD), though memory deficit (MD) in patients with LLD is a predictable sign of AD. Thus, we aimed to investigate whether tryptophan (TRP) metabolism and kynurenine (KYN) metabolism were imbalanced in patients with LLD with MD and in patients with LLD without MD. We explored KP characteristics between LLD with MD and LLD without MD groups. We investigated 85 patients with LLD and MD, 71 patients with LLD without MD, and 129 healthy controls (HCs). Serum concentrations of TRP, KYN, and kynurenic acid (KYNA) were detected by liquid chromatography-tandem mass spectrometry. Cognition performance was assessed by the Mini-Mental State Examination (MMSE). Language ability was assessed by the Boston Naming Test (BNT). Depressive symptoms were assessed by the 17-item Hamilton Depression Scale (HAMD-17). Lower TRP and KYNA levels, a lower KYNA/KYN ratio and a higher KYN/TRP ratio were found in patients with LLD and MD compared to those in HC. Low levels of TRP and KYN, in the absence of a changed KYN/TRP ratio, were found in patients with LLD without MD. The KYNA/TRP ratio and MMSE, BNT, and HAMD-17 scores were associated with the presence of LLD. MMSE scores and a trend for the KYN/TRP ratio were associated with the presence of MD in patients with LLD. Aside from MMSE scores, there was a trend toward an association between the KYN/TRP ratio and the presence of MD in patients with LLD. In conclusion, profound shifts in TRP metabolism and KYN metabolism were found in patients with LLD and MD but not in patients with LLD without MD.

1. Introduction

Late-life depression (LLD) is the most common mental illness in old age, with a diagnosis in 0.04% to 13.4% of elderly individuals (Guerra et al., 2016) and is associated with a high cost of medical expenses and nursing (Donohue and Pincus, 2007). In addition, patients with LLD have a higher risk of developing cognitive deficit than those without depression (Yeh et al., 2011). Some authors have also proposed that LLD with cognitive deficit is a preclinical stage of Alzheimer's disease (AD) (Heser et al., 2016). However, LLD with cognitive deficit is part of the last stage of disease development and therefore almost beyond benefit of intervention. Memory deficit (MD) has been acknowledged to be the most predictable sign of AD development (Rushing et al., 2014). Studies on patients with LLD and MD could provide more information to clinical practice. Therefore, it is imperative that the underlying factors of LLD in patients with MD be determined.

Kynurenine pathway (KP) activation is associated with many neuropsychiatric diseases, such as major depressive disorder (MDD), schizophrenia, and AD. Tryptophan (TRP) is an essential amino acid in humans and is the precursor of kynurenine (KYN). Both TRP and KYN can also pass through the blood-brain barrier. The activity of indoleamine 2,3-dioxygenase (IDO), the major rate-limiting enzyme, plays an essential role in accelerating TRP breakdown. The activation of IDO can enhance the shift in TRP conversion to the KYN arm and result in an increase in KYN concentration and a depletion of serotonin (Oxenkrug, 2010). Thus, a higher kynurenine to tryptophan (KYN/TRP) ratio represents a shift in TRP transformation to the KYN arm. Then, during the KYN metabolism stage, the enzyme kynurenine-3-monooxygenase (KMO) can accelerate 3-hydroxykynurenine (OHK) production. The formation of OHK occurs faster than kynurenic acid (KYNA) formation; therefore, KYN metabolism shifts to the OHK arm causes a lower kynurenic acid to kynurenine (KYNA/KYN) ratio. Quinolinic acid (QUIN) is synthesized from OHK. QUIN is an N-methyl-D-aspartate receptor (NMDA-R) agonist, and accumulation of QUIN can result in excitotoxicity (Schwarz et al., 2013), whereas KYNA is a protective

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metabolite against QUIN (Myint, 2012). Thus, lower KYNA/KYN means a shift in KYN to the QUIN arm and might result in neuro-damage. In MMD, the ratio of KYN/TRP is increased (Gabbay et al., 2010) and associated with suicidality (Brundin et al., 2016). Furthermore, KYNA (Wichers et al., 2005) and TRP (Gabbay et al., 2010) are also found to be lower in patients with MDD. Based on previous literature, the KP shift is also found to be disrupted in both AD (Majláth et al., 2013) and MDD (Gabbay et al., 2010), which indicates that AD and LLD may share the common change in KP. Therefore, we supposed that in patients with LLD and MD, the KP shift would appear more significant in comparison with patients with LLD without MD and healthy subjects. Therefore, we designed this study to test our hypotheses.

Among those disrupted cognitive domains in LLD, working memory, executive function, and language are the common dysfunctions (Sheline et al., 2006). In the previous literature, both working memory and executive function have been fully investigated in patients with LLD (Baba et al., 2010; Liao et al., 2017). However, language problems as one of the earliest and most common symptoms in AD (Kempler and Goral, 2008) has not yet been fully clarified. Problems finding words might induce AD patients to revert to childhood language (Liu et al., 2017). Furthermore, language problems can also become a barrier between patients with LLD and caregivers (Potkins et al., 2003). Therefore, we have examined language ability to enhance the practical significance of our study.

In the current study, we aimed to (1) detect the serum concentrations of TPR, KYN, and KYNA in all participants, (2) compare the differences in KP changes between the patients with LLD and MD and those with LLD without MD, and 3) investigate the predictable signs in patients with LLD and MD by logistic regression.

2. Materials and methods

2.1. Participants and control subjects

We fully explained the study and obtained written informed consent from each participant. All patients were recruited from the outpatient Department of Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital, Guangzhou, Guangdong, China) and healthy elderly people as healthy controls (HCs) were from community. This study was approved by the ethics committee of the Affiliated Brain Hospital of Guangzhou Medical University.

To meet the inclusion and exclusion criteria, all participants were evaluated by structural clinical interviews. Depression was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria. MD was defined by the Auditory Verbal Learning Test delayed recall score (AVLT-N5), and patients with age- and education-adjusted scores ≤ 1.5 standard deviation (the cutoff was AVLT-N5 ≤ 4 for ages 50 to 59 years) were identified as having MD. Cognition performance was evaluated by Mini-Mental State Examination (MMSE). Language ability was evaluated by the Boston Naming Test (BNT). The presence of depressive symptoms was evaluated by the 17-item Hamilton Rating Scale for Depression (HAMD-17). Exclusion criteria were as follows: (1) serious suicidal behavior; (2) medical conditions or concomitant medications likely to influence the central nervous system or immunological function, including cardiovascular, respiratory, endocrine and neurological diseases; and (3) a history of drug or alcohol abuse within 6 months or a history of drug or alcohol dependence within 1 year (Savitz et al., 2015). HCs had no first-degree relative with a psychiatric disorder.

Following the inclusion and exclusion criteria, we recruited 170 patients with LLD and 135 HC, but 14 patients with LLD and 6 HC had hearing problems or special accents, such as those from the eastern area of Guangdong province, which would influence their understanding and completions of the cognition tests. Finally, we investigated 156 LLD patients (85 with LLD and MD, 71 with LLD without MD) and 129 HCs.

2.2. Laboratory analyses

Peripheral blood samples were collected between 8:00 and 9:00 AM after an overnight fast. Blood samples were collected in vacutainers without further additives. After 0.5 h of coagulation, samples were centrifuged at 3000 r/min for 10 min and the supernatant was aliquoted into Eppendorf tubes (Eppendorf, Hamburg, Germany) and immediately frozen at −80 °C until assay.

We used a rapid and highly reproducible liquid chromatography-tandem mass spectrometry (LC-MS/MS) method to detect TRP, KYN, and KYNA serum concentrations as described (Hu et al., 2017). The details of material suppliers were followed: L-TRP, L-KYN, KYNA, and activated charcoal (Sigma-Aldrich); Kyna-d5 (Toronto Research Chemicals Inc. [Toronto, Canada]); ammonium formate (Sigma-Aldrich Corporation [Bangalore, India]); methanol was obtained from Merck KGaA (Darmstadt, Germany); purified water was processed by the Milli-Q water purification system (Millipore Corporation, Billerica, MA, USA). A serial dilution of stock solution with methanol was applied to establish calibrator standards. Final calibration curve concentrations were: TRP: 1, 2, 5, 10, 20, 40, and 50 μg/mL of TRP; 0.1, 0.2, 0.5, 1, 2, 4, and 5 μg/mL of KYN; 1, 2, 5, 10, 30, 50 and 60 ng/mL of KYNA. Finally, concentrations of QC in serum were 2, 8, and 40 μg/mL of TRP; 0.2, 0.8, and 4 μg/mL of KYN; 2, 8, and 50 ng/mL of KYNA. Prior to the date of sample analysis, each concentration level of calibration curve and QC was duplicated.

2.3. Statistical analyses

Statistical analysis was performed using Statistical Package for Social Sciences Software version 22.0 (SPSS IBM, Chicago, Illinois, USA). Demographic and clinical variables were analyzed using the χ^2 test for the categorical variables and one-way analysis of variance for the continuous variables; post hoc analysis was performed using the LSD method. Further, to control significant between-group effects for difference in HAMD-17 score, sex, age and education years, we used a general linear model with diagnosis as an independent factor and HAMD-17 score, sex, age and education years as covariates. Binary logistic regression was conducted to confirm the associations between depression, cognitive performance, language ability, and potential KP changes. Thus, HAMD-17 scores, MMSE scores, BNT scores, KYN/TRP ratio, KYNA/KYN ratio, sex, and age were added to logistic regression. Adjusted odds ratios (OR) with 95% confidence intervals (CIs) were provided.

We set the level of significance as two-tailed values of $P = 0.05$. False Discovery Rate (FDR) correlation was used to adjust the P-value of multiple comparisons.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical variables of patients in the LLD with MD, LLD without MD, and HC groups are shown in Table 1. The group with LLD and MD had significantly different AVLT-N5 scores than the LLD without MD and HC groups (both $P < 0.001$). The LLD with MD group had fewer education years than the LLD without MD and HC groups ($P = 0.007$, $P < 0.001$). LLD with MD patients had significant differences in MMSE scores (both $P < 0.001$), BNT scores (both $P < 0.001$), and HAMD-17 scores ($P = 0.006$, $P < 0.001$) compared to the LLD without MD and HC groups. The LLD without MD group showed lower BNT scores ($P = 0.006$) and higher HAMD-17 scores than the HC group ($P < 0.001$). No difference in sex or age was found among these three groups (all $P > 0.05$).

Among the LLD with MD group, 17 patients received a serotonin noradrenaline re-uptake inhibitor (SNRI), 56 patients received selective serotonin reuptake inhibitors (SSRI), 5 patients received tricyclic

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