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Increased serum levels of cysteine in patients with schizophrenia: A potential marker of cognitive function preservation

Wang Liang-Jen [a], Lin Pao-Yen [b,c], Lee Yu [b], Huang Yu-Chi [b], Wu Chih-Ching [d,e], Hsu Su-Ting [f], Chen Chien-Chih [b], Chong Mian-Yoon [b], Lin Chieh-Hsin [b], Hung Chi-Fa [b,*]

[a] Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[b] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan
[c] Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[d] Department of Otolaryngology-Head & Neck Surgery, Linkuo Chang Gung Memorial Hospital, Taoyuan, Taiwan
[e] Department of Medical Biotechnology and Laboratory Science, Chang Gung University, Tao-Yuan, Taiwan
[f] Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Taiwan

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ABSTRACT

Background: Oxidative stress has been implicated in the psychopathology of schizophrenia. Cysteine, a semi-essential amino acid, is the precursor of the antioxidant glutathione. The aim of this study was to investigate the differences in serum levels of cysteine between patients with schizophrenia and healthy controls. The relationships between levels of cysteine, psychopathology and cognitive function were also explored.
Methods: We recruited 65 patients with schizophrenia and 65 age- and gender-matched healthy controls. Blood samples were collected to determine the serum levels of cysteine and plasma levels of metabolic parameters. The cognitive function of participants was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS). The psychopathology of schizophrenic patients was evaluated using the Positive and Negative Syndrome Scale.
Results: Serum cysteine levels were significantly higher in schizophrenic patients than in controls ($P < 0.001$). In patients with schizophrenia, serum levels of cysteine were positively correlated with cognitive function in terms of verbal memory ($P = 0.013$), working memory ($P = 0.004$), verbal fluency ($P = 0.027$), attention and processing speed ($P = 0.025$), executive function ($P = 0.024$) and the composite score on the BACS ($P = 0.013$). In healthy controls, no significant correlation was observed between cysteine level and cognitive function.
Conclusions: These findings suggest that oxidative stress may be involved in the pathogenesis of schizophrenia, and compensatory elevated levels of cysteine may serve as an indicator of cognition preservation. Further prospective studies are warranted to investigate the dynamic alterations in cysteine and the underlying pathophysiology of schizophrenia.

1. Introduction

Schizophrenia is a serious mental disorder which affects approximate 1% of the global population (Chong et al., 2016; Owen et al., 2016). Patients with schizophrenia exhibit positive symptoms, negative symptoms, mood symptoms and a broad range of cognitive dysfunctions (Jaaskelainen et al., 2013). The underlying neurobiological etiology of schizophrenia may be multifactorial (Cannon, 2015; Koga et al., 2016). Currently, oxidative stress has been implicated in the pathophysiology of schizophrenia (Li et al., 2011; Pandya et al., 2013; Wu et al., 2013). Regulation of the reducing and oxidizing (redox) state is involved in cell viability, activation and proliferation (Birben et al., 2012). Dysfunction of antioxidant defense mechanisms could result in a free radical attack on neural cells, and is associated with abnormal neural growth, differentiation or neuro-degeneration (Uttara et al., 2009). Evidence has shown that an imbalance of reactive oxygen species (ROS) and the antioxidant system may be involved in the pathophysiology of schizophrenia (Wood et al., 2009).

As part of the antioxidant system, cysteine, a semi-essential amino acid, is an important structural and functional part of proteins (Yin et al., 2016). Cysteine is the limiting precursor of the major intracellular antioxidant glutathione (GSH) (Burgoyne and Morgan, 2015; Stipanuk et al., 2006). GSH is a redox regulator (Wu et al., 2004), and is essential

Abbreviations: AIMS, the Abnormal Involuntary Movement Scale; BARS, the Barnes Akathisia Rating Scale; BMI, body mass index; GSH, glutathione; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NAC, *N*-acetyl-L-cysteine; MINI, Mini International Neuropsychiatric Interview; PANSS, Positive and Negative Syndrome Scale; ROS, reactive oxygen species; SAS, the Simpson-Angus Scale; WHO, World Health Organization.

* Corresponding author at: Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital, No. 123, Ta-Pei Road, Kaohsiung City, Taiwan.
E-mail address: chifa@cgmh.org.tw (C.-F. Hung).

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for the cellular detoxification of ROS, and it has anti-inflammatory and neuroprotective properties in brain cells (Dringen and Hirrlinger, 2003). A decrease in cysteine is associated with dysfunction of the intracellular antioxidant GSH (Trivedi et al., 2014). Cystine, a rate-limiting substrate for GSH synthesis, is the oxidized form of cysteine stored in the extracellular space (serum). With oxidative stress, cystine is transported across plasma membranes to maintain intracellular GSH (McBean, 2002). A disturbance in cystine may therefore denote a compromised GSH system in the brain when there is additional oxidative stress in patients with neuropsychiatric disease (Gall et al., 2010).

N-acetyl-L-cysteine (NAC), an acetyl derivative of cysteine, is widely available as a nutritional supplement with antioxidant properties (Samuni et al., 2013). NAC is converted to cysteine, which is then converted to GSH (Berk et al., 2013). NAC has emerged as an effective augmentative strategy in the treatment of many neuropsychiatric disorders, including schizophrenia (Dean et al., 2011; Deepmala et al., 2015). Adjunctive NAC has been suggested as beneficial for the reduction of positive symptoms (Magalhaes et al., 2016; Rapado-Castro et al., 2015), as well as for alleviating negative symptoms in patients with schizophrenia (Berk et al., 2008; Carmeli et al., 2012; Farokhnia et al., 2013). NAC administration may result in EEG synchronization, which might serve as a biomarker for treatment efficacy in schizophrenic patients. Moreover, the gene for the key glutathione-synthesizing enzyme, the glutamate cysteine ligase modifier (GCLM) subunit, has been associated with schizophrenia in several Caucasian studies (Gysin et al., 2011; Gysin et al., 2007; Tosic et al., 2006); however, such a correlation was not replicated in the Japanese population (Hanzawa et al., 2011; Kishi et al., 2008) or in the Han Chinese population (Ma et al., 2010).

To the best of our knowledge, only one case-control study has investigated differential cystine levels between patients with schizophrenia and healthy controls (Yang et al., 2013). Compared to healthy controls, an elevated level of cystine was observed in the urine of patients with schizophrenia; however, an opposite trend appeared in the serum levels of cystine. Moreover, it has been suggested that oxidative stress plays a role in cognition dysfunction in schizophrenia (Gonzalez-Liencres et al., 2014; Wu et al., 2014). Nevertheless, it remains unclear whether cysteine is associated with the clinical characteristics or neurocognitive functions in schizophrenic patients. To fill this research gap, this study investigated the difference in serum levels of cysteine between patients with schizophrenia and healthy control subjects. Additionally, the relationships between levels of cysteine, psychopathology and cognitive function were explored. We hypothesized that cysteine was associated with the psychopathology of schizophrenia involving the antioxidant system.

2. Methods

2.1. Participants

This cross-sectional, case-control study was approved by the institutional review board (IRB) of the Chang Gung Memorial Hospital (IRB No: 102-3977A3). Written informed consent was obtained from all participants.

Eligible patients with schizophrenia in an out-patient department in the Kaohsiung Chang Gung Memorial Hospital were selected for this study if they (1) were 18–65 years of age; (2) were assessed with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and diagnosed with schizophrenia as defined by the DSM-IV-TR (American Psychiatric Association, 2000); (3) had been treated with an antipsychotic drug at a stable dose for at least one month before the study started and their psychotic symptoms were relatively stable; (4) had no history of major physical illnesses (such as genetic, infectious conditions, cardiovascular diseases or cancer), and (5) were of ethnic Han Chinese origin.

The control group consisted of healthy individuals recruited from the Kaohsiung Chang Gung Memorial Hospital staff and from community volunteers in Kaohsiung City. The recruitment criteria were (1) 18–65 years of age; (2) no history of illicit drug use or major psychiatric disorders (e.g., psychosis, bipolar disorder, major depressive disorder, substance use disorders, or organic mental disorders) or major physical illnesses (such as genetic, infectious conditions, cardiovascular diseases or cancer); (3) of ethnic Han Chinese origin, and (4) age and gender matched with patients with schizophrenia.

2.2. Biochemical measurements

This cross-sectional study assessed the difference in serum cysteine level between patients with schizophrenia and healthy controls. Blood samples were drawn in the morning when participants were in a fasting state. Serum cysteine was detected using the MicroMolar Cysteine Assay Kit (Catalog no. CYS200, ProFoldin, Hudson, MA, USA) that was developed for determining cysteine in a micromolar range. Assay is based on the generation of fluorescence at 535 nm of the dye R53 in the presence of reduced cysteine. Assay is highly sensitive and specific, and other thiol-based amino acids do not interfere with assay.

The metabolic parameters including plasma levels of fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), were determined by Laboratory Medicine, Chang Gung Memorial Hospital.

2.3. Clinical assessments

Psychiatric diagnoses of both the patients with schizophrenia and the healthy control subjects were conducted using the Mini International Neuropsychiatric Interview (MINI), which is a short structured diagnostic interview for psychiatric disorders (Sheehan et al., 1998). The Mandarin MINI has good reliability, and has been widely adopted in international clinical trials and epidemiological studies (Chou et al., 2004; Kuo et al., 2003). The psychopathology of patients with schizophrenia was evaluated with the Positive and Negative Syndrome Scale (PANSS) score (Kay et al., 1987). The PANSS contains three subscales representing three dimensions of psychotic symptoms: positive, negative, and general psychiatric symptoms (Kay et al., 1988). Adverse effects of antipsychotics were assessed using the Abnormal Involuntary Movement Scale (Lane et al., 1985), the Simpson-Angus Scale (Simpson and Angus, 1970), and the Barnes Akathisia Rating Scale (Barnes, 2003).

The patients' ages at onset, the duration of the illness, times of admission to psychiatric wards, use of antipsychotics, the average daily dose (D) and duration of their current antipsychotic treatments were determined through interviews and review of medical records. The antipsychotic drugs prescribed to these 65 schizophrenic patients were: Risperidone (n = 11, D = 3.7 mg); Olanzapine (n = 12, D = 10.8 mg); Quetiapine (n = 5, D = 375 mg); Amisulpride (n = 5, D = 660 mg); Sulpiride (n = 2, D = 600 mg); Aripiprazole (n = 8, D = 10.6 mg); Zotepine (n = 1, D = 100 mg); Ziprasidone (n = 2, D = 60 mg); Paliperidone (n = 2, D = 6 mg); Clozapine (n = 16, D = 242.2 mg); Trifluoperazine (n = 1, D = 25 mg). The dose of antipsychotic drugs was re-calculated according to the defined daily dose (DDD) recommended by the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2016).

2.4. Cognitive assessments

The cognitive functions of all participants were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). BACS is a battery of tests that measures the aspects of cognition that are most impaired and it is strongly correlated with the real-world functioning of patients with schizophrenia (Keefe et al., 2006). BACS requires approximately 30 min, generates a high completion rate in patients, and has high test–retest reliability. The validity of the Chinese version of BACS has been proven (Wang et al., 2016b).

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