Journal of Psychiatric Research 47 (2013) 1049–1053

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Clinical symptoms and cognitive impairment associated with male schizophrenia relate to plasma manganese superoxide dismutase activity: A case-control study

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ARTICLE INFO

Article history:
Received 23 January 2013
Received in revised form
8 March 2013
Accepted 13 March 2013

Keywords:
Schizophrenia
Cognition
Oxidative stress
MnSOD
Psychopathology

ABSTRACT

Several lines of evidence suggest that excessive reactive oxygen species-induced oxidative damage may underlie cognitive impairment in psychiatric disorders. A growing body of evidence show that oxidative damage may relate to the range of cognitive deficits associated with schizophrenia. In this study we examine one of the primary antioxidant defense enzymes manganese superoxide dismutase (MnSOD), and whether it relates to cognitive deficits in schizophrenia. We recruited 185 chronic male schizophrenia patients and 132 male controls and compared results from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and plasma MnSOD activity between groups. Symptom severity in patients with schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS). Our results showed that MnSOD activities were significantly lower in patients than controls ($p < 0.05$). Cognitive scores on the RBANS and nearly all of its five subscales (all $p < 0.001$) except for the Visuospatial/Constructional index were significantly lower in schizophrenia patients than normal controls. MnSOD was negatively correlated with the general psychopathology subscale of PANSS, PANSS total score, positive symptoms and RBANS total score in patients with schizophrenia. Our findings add to growing evidence that oxidative stress may be involved in the psychopathology of male schizophrenia, and its associated cognitive impairment.

1. Introduction

Cognitive impairment is a core feature of schizophrenia, that can be severe and apparent long before overt signs of psychosis emerge (Allott et al., 2011; Condray and Yao, 2011; Dickerson et al., 2004; 2011; Harvey et al., 2004; Mesholam-Gately et al., 2009; Palmer et al., 2009; Sharma and Antonova, 2003). Often cognitive deficits may persist irrespective of a change in patients' symptom state (Hughes et al., 2003). Addressing persistent cognitive decline in schizophrenia is a primary concern in successful pharmacotherapy since these deficits are related to poor clinical and social functional outcomes (Bilder et al., 2000; Green et al., 2000; Granholm et al., 2008; Harvey, 2009; Kaneda et al., 2009). However, the pathophysiological mechanisms underlying these cognitive deficits are unclear (Lesh et al., 2011).

Numerous studies have explored the relationship between oxidative stress and cognitive function. It has been reported that compromised cellular energy metabolism and associated oxidative stress adversely affect cognitive processes (Kapogiannis and Mattson, 2011). Much of the work elucidating this relationship has focused on aging within the context of learning and memory (Kolosova et al., 2006). Evidence from preclinical studies that model aging implicate oxidative stress-induced damage within cortical and hippocampal brain areas contributes to impaired learning and memory (Fukui et al., 2001). Consistent with these findings, clinical studies also implicate oxidative damage produced by excessive reactive oxygen species (ROS) may underlie aging-related cognitive impairment and neurodegeneration (Nicolle et al., 2001; Hu et al., 2006). Although the specific mechanisms have yet to be fully elucidated, evidence suggests that cognitive decline can result

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http://dx.doi.org/10.1016/j.jpsychires.2013.03.014

from impaired antioxidative mechanisms needed to neutralize ROS within brain areas that mediate cognitive processes (Davies, 2000; Liu et al., 2003; Nagai et al., 2003; Ames, 2006; Corbetta et al., 2008). This has led to the general hypothesis that progressive cognitive impairments associated with a number of neurodegenerative disorders, including schizophrenia may be causally related to impaired antioxidant capacity resulting in increased oxidative stress. Superoxide dismutase (SOD) is a key enzyme involved in the inactivation of ROS and is abnormal in patients with schizophrenia (Mukherjee et al., 1996; Yao et al., 1998; Zhang et al., 2003), There are three isoforms of SOD: the manganese (Mn) isoform (SOD_2) located in mitochondria, and the copper and zinc (CuZn) isoforms present in the cytoplasm (SOD_1) and extracellular space (SOD_3). Of the three forms of SOD in humans, manganese SOD (MnSOD) may be particularly important for antioxidant defense since cellular metabolism, and thus, production of ROS occurs primarily in the mitochondria (Shimoda-Matsubayashi et al., 1997). Indeed, decreased plasma MnSOD activity has been found in patients with a chronic form of schizophrenia (Ranjekar et al., 2003). It is presently unknown however if low MnSOD plasma levels relate to any facets of cognitive impairment associated with schizophrenia. Therefore we conducted the present study to assess this possibility with the ongoing hypothesis that altered plasma MnSOD activity will be lower in patients with schizophrenia compared to controls and associated with cognitive deficits. In view of earlier reports that gender differences exist in cognitive domains (Halari et al., 2006; Wisner et al., 2011; Han et al., 2012), and in oxidative stress parameters (Zhang et al., 2006) in both schizophrenia and healthy controls, the present study included only male subjects.

2. Methods

2.1. Subjects

One hundred eighty-five male inpatients were recruited from the Beijing Hui-Long-Guan Hospital, a Beijing city owned psychiatric hospital. All patients met DSM-IV criteria for schizophrenia as diagnosed by two clinical psychiatrists on the basis of the Structured Clinical Interview for DSM-IV (SCID). Patients were of the chronic type, aged 25–60 years (mean 44.9 ± 7.1), with a mean duration of illness of 22.8 years (SD = 7.3), and a mean education of 8.3 years (SD = 2.1). All patients had been receiving stable doses of oral neuroleptic medications for at least 6 months. Antipsychotic drug treatment consisted mainly of monotherapy with clozapine ($n = 81$), risperidone ($n = 47$), sulpiride ($n = 20$), perphenazine ($n = 13$), chlorpromazine ($n = 12$), haloperidol ($n = 5$) and others ($n = 7$). Mean antipsychotic dose (in chlorpromazine equivalents) was 480 ± 475 mg/day. The patients had been on their respective medication for 4.3 ± 4.4 years at the time of the investigation.

One hundred and thirty-two male healthy controls were recruited from the local community, with an average age of 43.8 ± 13.2 years (range from 20 to 60 years), and 10.5 ± 7.7 years of education. All subjects were Han Chinese and were recruited at the same period from the Beijing area. Both patients and control subjects had similar socioeconomic status and dietary patterns.

A complete medical history and physical examination, laboratory tests, and electrocardiogram were obtained from all subjects. All participants were healthy and did not reach criteria for substance abuse/dependence. All subjects gave written, informed consent to participate in the study, which was approved by the Institutional Review Board of Beijing Hui-Long-Guan hospital.

2.1.1. Plasma MnSOD activity measurement

Venous blood was obtained from each subject between 0700 and 0900 AM following an overnight fast. MnSOD activity was analyzed using established procedures. Our previous report gives a full description of the assays (Zhang et al., 2006). Plasma MnSOD activity is expressed as units per milliliter plasma (U/ml). The inter- and intra-assay coefficients of variation for SOD were 8% and 6%. A research assistant blind to the clinical situation assayed all samples. A code number maintained by the primary investigator indicated the identity of subjects.

2.2. Cognitive tests

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) was used to measure cognitive function. The 12 subtests included in the RBANS were used to calculate 5 age-adjusted index scores and a total score. Test indices are Immediate Memory (comprised of List Learning and Story Memory tasks); Visuospatial/Constructional (comprised of Figure Copy and Line Orientation tasks); Language (comprised of Picture Naming and Semantic Fluency tasks); Attention (comprised of Digit Span and Coding tasks); and Delayed Memory (comprised of List Recall, Story Recall, Figure Recall, and List Recognition tasks). Our group previously translated RBANS into Chinese and established its clinical validity and its test–retest reliability among controls and schizophrenic patients (Zhang et al., 2009). A higher RBANS score is associated with better cognitive functioning.

2.3. Statistical analysis

Demographic and clinical variables of the patient and healthy control groups were compared using *t*-test or analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables. We also compared RBANS scores among the patient and control groups using ANOVA. When ANOVA was significant, we tested the effects of age, education, and smoking by adding these variables to the analysis model as covariates. We assessed relationships between variables with Pearson's product moment correlation coefficients. Bonferroni corrections were applied to adjust for multiple testing. Multivariate regression analyses (stepwise regression model) were employed to assess possible associations of MnSOD with RBANS while adjusting for various potentially confounding variables of age, education, and smoking in both patient and control groups, and clinical variables in the patient group, such as PANSS, years of education, age of onset, hospitalization, and antipsychotic treatment. SPSS version 15.0 was used to do all statistical analysis. Two-tailed significance values were used and significance levels were set at 0.05.

3. Results

Clinical and demographic characteristics for the schizophrenic patients and healthy controls are presented in Table 1. Patients and control groups showed no differences in age, education and body mass index (BMI) but differed in smoking ($p < 0.001$), which was adjusted in the following analyses.

Age, education, BMI and smoking status were not associated with MnSOD activity in the combined groups, or when the association was examined in patient and control groups separately (all $p > 0.05$).

3.1. Plasma MnSOD activity in schizophrenia and healthy controls

Plasma MnSOD activity was lower in patients than in controls ($p < 0.05$) and not attenuated after covariance for smoking ($F = 4.85$, df = 2, 312, $p < 0.05$).

In patient group, MnSOD activity also showed a significant association with the duration of antipsychotic treatment ($r = 0.21$,