Tropical Journal of Pharmaceutical Research June 2021; 20 (6): 1251-1259
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i6.22

Original Research Article

Dysfunctional oxidative stress response in first-episode of schizophrenia

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Sent for review: 22 February 2021 *Revised accepted: 18 May 2021*

Abstract

Purpose: *To investigate the probable effect of oxidative stress on cognitive deficits in schizophrenia.*
Methods: *A total of 149 first-episode schizophrenia (FES) patients and 65 healthy controls were enrolled in this study. Psychiatric symptoms were evaluated using Positive and Negative Syndrome Scale, while cognitive function was assessed using MATRICS Consensus Cognitive Battery. Oxidative parameters, including glutathione (GSH), thioredoxin (TRX), nitric oxide (NO), homocysteine (Hcy) and superoxide dismutase (SOD)]; hypersensitive C-reactive protein (Hs-CRP, an inflammation marker); lipopolysaccharide (LPS) and CD4+T cell sub-sets (Th1, Th2, Th17 and Treg cells) were measured in all subjects, while PANSS was evaluated in FES patients only.*
Results: *Levels of the oxidants, NO, Hcy and inflammatory parameters (Hs-CRP, LPS, Th1, Th2 and Th17) were higher in FES patients than in controls ($p < 0.05$). In contrast, levels of antioxidants (GSH and SOD) in FES patents were lower than those in controls ($p < 0.05$). Moreover, TRX was higher in schizophrenia patients than in controls ($p < 0.05$). The changes in levels of these biomarker indicated oxidative stress responses. There were statistically significant differences in hemogram and T cell subtype between FES and control ($p < 0.05$). Results from fMRI analysis revealed schizophrenia-induced lesions in the encephalic region associated with cognition function.*
Conclusion: *Oxidative stress (OS) induces immune response which eventually leads to impairment of cognition.*

Keywords: *Schizophrenia, Oxidative stress, Inflammation, Cognitive function*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Schizophrenia is a severe mental illness often accompanied with cognitive impairment [1]. The neurodevelopmental hypothesis of schizophrenia postulates that abnormality in brain development is due to combination of genetic susceptibility and environmental factors [2]. During adolescence or early adulthood, hidden problems exposed by stress under the condition of

synaptic pruning, rectification and regulation of neurogenesis, lead to neuronal damage, apoptosis and abnormal neurodevelopment. Brain-derived neurotropic factor (BDNF) enhances synaptic efficiency which is closely related to neurocognitive ability. Oxidative stress-induced dysfunction in BDNF may contribute to impaired brain development and abnormal synaptic connectivity, thereby leading to schizophrenia [3].

Several studies showed that oxidative stress is associated with brain neuronal injury which may be related to many diseases, especially mental illnesses such as post-traumatic stress disorder, schizophrenia, and depression [4-6]. Studies have demonstrated an imbalance between oxidants and antioxidants in schizophrenia, which is manifested in obvious increase in lipid peroxides and protein oxides in blood, cerebrospinal fluid and postmortem tissues [7,8]. The serum levels of antioxidants such as vitamin C, vitamin E, GSH, GPx and SOD are lower in schizophrenia patients than in healthy controls [3].

A study has shown that levels of TRX, an ubiquitous thiol protein normally released from cells in the presence of oxidative stress to scavenge reactive oxygen radicals, are increased in schizophrenia patients [9]. In addition, oxidative stress is closely related to cognitive function. Studies in patients with FEP found that the concentrations of Hcy and NO were negatively correlated with cognitive function [10,11]. Another study using a GSH synthesis inhibitor revealed that GSH defects led to behavioral abnormalities in mice [19]. However, the specific mechanism associated with oxidative stress response, inflammation and immune system remains unclear.

Previous research showed significant association between oxidative stress response and the cause of schizophrenia. Oxidative stress reflects an imbalance between the systemic manifestations of reactive oxygen species (ROS) and the ability of biological systems to readily detoxify them. Disorders in normal redox state of cells may produce toxic effects due to production of peroxides and free radicals, which lead to neuronal damage and BDNF dysfunction. Heterozygous deletion of BDNF decreases spine density and dendrite length of hippocampal and PFC neurons, decreases hippocampal volume, and occludes the effects of chronic stress [13].

In this study, it was hypothesized that neuronal damage and abnormal brain network connectivity caused by oxidative stress may play a pivotal role in the pathophysiology of schizophrenia. Neurotrophins produced by neurons are decreased, which may lead to synaptic contraction and changes in white matter in the brain. The abnormality of connection network between brain regions and abnormal signal transmission may result in the impairment of cognitive function. The present study measured typical oxidative parameters (NO, GSH and TRX) and BDNFs in FES patients. In addition, inflammatory cytokines (LPS and Hs-CRP) and Hcy (which enhances ROS production in hosts) were assayed. The connections of brain networks were presented using fMRI to investigate the pathogenesis of cognitive impairments in schizophrenia. Multi-dimensional schizophrenia patient data were used to comprehensively analyze the effect of OS response in schizophrenia, and the clinical characteristics of patients were used to provide comprehensive evidence.

METHODS

Subjects

From January 2017 to March 2018, drug-free, FES patients from the psychiatric ward of the First Affiliated Hospital of Zhengzhou University were enrolled in the study. Healthy control subjects were recruited through advertisement. This research was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. in accordance with The Code of Ethics of the World Medical Association for experiments involving humans [14]. All subjects who participated in the study were informed about the objectives of the study, and they signed informed consent forms.

The diagnosis of schizophrenia was done by an experienced psychiatrist using the Structured Clinical Interview for DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR). The recruitment criteria for patients were : age from 16 to 40 years, non-use of antipsychotic medication, and PANSS total score > 70 points. The following categories of patients were excluded: those diagnosed with autoimmune diseases, heart diseases, hepatobiliary and gastrointestinal diseases, blood diseases, diabetes, neurological diseases, or psychiatric diseases other than schizophrenia; patients with a history of alcohol or other substance use/abuse; pregnant or lactating women, and patients who used any antiviral or anti-inflammatory agent in the previous one month. Healthy controls had the same exclusion criteria as patients. Complete medical history, and results of physical examination and routine

laboratory tests were obtained from all subjects, to rule out possible medical conditions.

Clinical assessments

Symptoms of schizophrenia were assessed for all patients using the Positive and Negative Syndrome Scale (PANSS), including positive and negative symptoms and general psychopathology. The PANSS was administered by the same rater (J.G.) throughout the study. Cognitive functions were evaluated using MATRICS Consensus Cognitive Battery (MCCB) in Chinese language [15]. The MCCB included speed of processing (SOP): Trail Making Test (TMT), part B: Brief Assessment of Cognition in Schizophrenia: Symbol Coding [BACS-SC] and Category Fluency: Animal Naming (Fluency); attention/vigilance (AV): Continuous Performance Test—Identical Pairs [CPT-IP]; working memory (WM): Wechsler Memory Scale-III Spatial Span (WMS-III SS); verbal learning: Hopkins Verbal Learning Test—Revised [HVLT-R]; visual learning: Brief Visual Memory Test—Revised [BVMT-R]; reasoning and problem solving (RPS): Neuropsychological Assessment Battery [NAB] Mazes, and social cognition (SC): Mayer-Salovey-Caruso Emotional Intelligence Test {MSCEIT^{TM}} (Managing Emotions). The raw scores were entered into the professional software which transformed them to seven domains of cognitive function, and all T-scores were corrected for age and education.

Identification and determination of biomarkers

Venous blood (10 mL: 5 mL for serum indicators, and 5 mL for immunological indicators) was collected from schizophrenia patients and healthy controls in EDTA tubes between 6:30 and 7:00 am to avoid circadian fluctuations in parameters to be measured. The blood (5 mL) was centrifuged at 1500 rpm for 10 min and used for flow assay. The other 5 mL was centrifuged at 3000 rpm for 10 min, and then aliquoted and stored at −80 °C for other parameters. Micro-enzyme method (Nanjing Jiancheng Bioengineering Institute, China) was used to measure GSH and NO. Serum levels of BDNF, TRX, HPT, FABP2, LPS and IL-1β were measured using enzyme-linked immunosorbent assay (ELISA) (Elabscience Biotechnology Co. Ltd, China). Serum levels of Hcy were determined using immune turbidimetric test (Roche Cobas c501, Switzerland). All assays were performed according to the kit manufacturer's instructions. Serum levels of homocysteine were measured with the enzymatic Cycling method (Kangte Bio-Tech, China).

Flow cytometry (FCM)

Blood samples of schizophrenia patients and healthy controls were collected into EDTA tubes and used for determination of the concentrations of Th1, Th2, Th17 and Treg. In the determination of T effector cells, lymphocytes extracted from peripheral blood were stimulated with 20 ng/ml phorbol myristate acetate (Solarbio Life Science, China); 1ug/ml ionomycin calcium salt (Solarbio Life Science, China) and 10 ug/ml brefeldin A solution (Biolegend, China), followed by culturing in an incubator at 37 °C for 4 h in a 5 % CO_2 environment. Erythrocytes were depleted using cell Lysis buffer (Biolegend, US), and hemameba were washed twice in stain buffer before surface marker staining with fluorochrome-conjugated anti-human antibody i.e., CD4-fluorescein isothiocyanate (FITC) (Biolegend, US). After surface staining at 4 ℃ for 20 min, the lymphocytes were fixed and permeabilized using Fix & Perm buffer according to the manufacturer's instructions (Biolegend, US). The cells were incubated with anti-human IFN-γ-PerCP-Cy5.5 Reagent, anti-human IL-17A-allophycocyanin (APC), IL-22-phycoerythrin (PE), and anti-human IL-4- PerCP for determination of levels of Th1, Th17 and Th2, respectively, or isotype control to confirm antibody specificity. The lymphocytes were fixed and permeabilized using Foxp3 Fix and Perm buffer according to the manufacturer's instructions (Biolegend, US) following surface maker CD25-APC. After permeabilization, FoxP3-PE was added to the tube to detect Treg or its isotype control in order to confirm antibody specificity. All antibodies were purchased from Biolegend. After staining, the cells were washed and subjected to flow cytometric analysis using BD FACSAria™ III flow cytometer and FACScalibur system (http://www.bdbiosciences.com/cn/home) for determination of the proportions of Th1, Th2, Th17 and Treg cells among the $CD4^+$ T cells. At least 10,000 lymphocytes were counted for each sample. Flowjo was used for comparison of $CD3^+$, $CD4^+$, FOXP3, IL-4, CD25 between two groups.

fMRI analysis

Each participant underwent three resting state scanning sessions, each of which lasted for 8 min. First, an EC resting state session was scanned (data for this session was acquired for other different resting-state Modulate Local Brain Dynamics purpose, but was not analyzed in the present study), followed by two sessions counter-balanced across subjects: one EO resting state session, and one EC resting state session. During all sessions, participants were instructed

to lie quietly in the scanner, and not to fall asleep or think about anything in particular. The MR images were acquired using a SIEMENS TRIO 3-Tesla scanner.

Functional images were obtained using an echo-planar imaging sequence under the following conditions: 33 axial slices, 3.5mm slice thickness, 20% gap, in-plane resolution = 64 × 64, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 200 × 200 mm^2. Each condition consisted of 240 functional volumes. In addition, a 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) image was acquired with the following parameters: 128 sagittal slices, 1.33 mm slice thickness, 0 % gap, in-plane resolution = 256 × 192, TR = 2530 ms, TE = 3.39 ms, inversion time (TI) = 1100 ms, flip angle = 7°, and FOV = 256 × 256 mm^2.

Image pre-processing

Image analysis was done with SPM8 (http://www.fil.ion.ucl.ac. uk/spm). The first 10 time points were removed to eliminate non-equilibrium effects of magnetization. The remaining 230 volumes of functional BOLD images were corrected for slice timing effects, motion-corrected and spatially normalized to the Montreal Neurological Institute (MNI) template using the standard EPI template, resulting in functional image series of 61×73×61 voxels (voxel size of 3 × 3 × 3 mm^3). No translation or rotation parameters in any given data set exceeded ± 2 mm or ± 2 degree. Motion parameters, linear trend, and signals from the ventricles and white matter, were regressed out from the time course of each voxel, to correct for co-fluctuations in BOLD signal due to noise.

KEGG pathway analysis

The effect of BDNF on physiological process was determined with KEGG pathway analysis [16,17]. The chosen pathway code was ko04722 (Neurotrophin signaling pathway). The relationship between BDNF and other signal molecules (TrkA, GDNF *etc.*) which could cause damage of cognition was found.

Statistical analysis

Demographic and clinical characteristics were reported using descriptive statistics method. Student's *t*-test was used for comparisons between control group and patients' group. Mean and standard deviation values for age, education level, and age at illness onset between two groups were calculated using SPSS20.0. Chi-square test was used to compare differences in gender and smoking status between the two groups. Statistical significance level was set at $p \leq 0.05$.

The mean and standard deviation of each stress biomarkers (GSH, NO, LPS, TRX, HPT, FABP2 and IL-1β) were calculated, and the corresponding histograms were plotted using Origin 8.0. Minor quartile, median and the larger quartile of various blood cells in patents were calculated, and a box plot of hemogram was prepared using R software. The hemogram of control group was obtained with current clinical test specification. Pearson correlation test was used to analyze stress biomarkers and the MCCB. The corresponding heat map was plotted with R, and cluster analysis was done based on Pearson correlation coefficients between two variables.

RESULTS

Demographic and clinical characteristics of the study sample

The original study subjects comprised 149 patients with schizophrenia (P) and 65 healthy controls (C). The results revealed that there were no significant differences between the schizophrenia group and the control group with respect to gender, educational background, age and smoking status ($p > 0.05$; Table 1).

Relationship between schizophrenia and oxidative stress response

The biomarkers of oxidative stress were GSH, NO, LPS and TRX. To find out whether the schizophrenia patients suffered oxidative stress, the concentration of each biomarker was compared between the patients and controls (Figure 1). Comparison of the concentration of each biomarkers between the patients' group and controls showed that except for FABP2, there were statistically significant differences in all biomarkers between the two groups, indicating that the schizophrenia patients did suffer oxidative stress. These results are shown in Figure 1. Thus, there might be other consequences of oxidative stress in these schizophrenia patients, such as impairment of cognition.

Relationship between schizophrenia and immunology

Deficiency of T cells leads to cognitive dysfunction. It was found that there were more mono cells and less lymph cells in schizophrenia

patients than in controls (Figure 2), implying that the immune system in patients was slightly abnormal. Thus, there might be some inflammation response in schizophrenia patients.

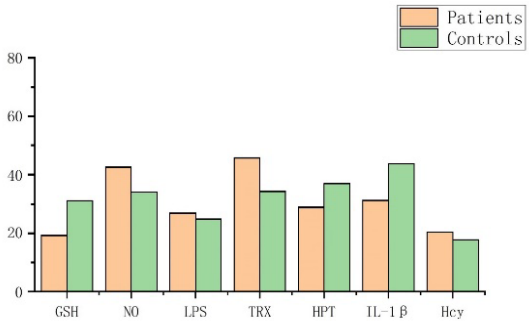

Figure 1: Levels of stress biomarkers in controls and schizophrenia patients. The mean concentrations of each biomarker (GSH, NO, LPS, Trx, HPT, IL-1β and Hcy) in controls and patients are shown. Bars indicate standard deviation of each biomarker.

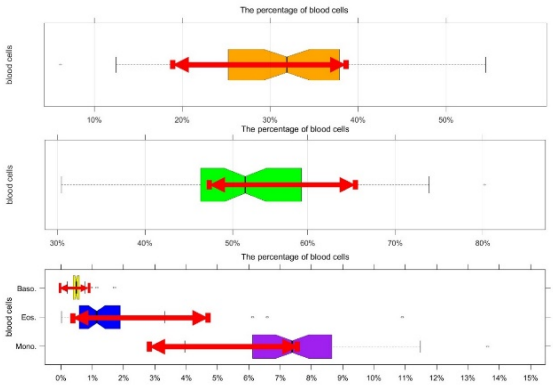

Figure 2: Hemogram index for control and schizophrenia patients. The red arrow shows the range of changes in the blood image of healthy control. The Figure shows the range of neutrophils in schizophrenia patients. The middle Figure shows the range of lymphocytes. The last Figure shows the range of basophils (yellow), eosinophils (blue) and monocytes (purple).

To obtain detailed information about the immunological changes in schizophrenia, flow cytometry test was carried out on randomly picked patients and normal controls. The levels of CD3, CD4 and FOXP3 were statistically different between the patients and controls (Figure 3), indicating changes in Th1, Th2 and Treg cells in schizophrenia patients due to the existence of immune response. The immune response induced OS response, while OS response contributed to more severe immune response. There was a positive feedback regulation mechanism between immune response and OS response at some period of schizophrenia, which was a vicious circle in these patients.

Recognition damage

Cognition functions were evaluated using MATRICS Consensus Cognitive Battery (MCCB). The results were validated with functional MRI test. For all MCCB parameters (SOP, AV, WM, HLVT, BVMT, RPS and SC), the patients' scores were significantly lower than the corresponding control scores (Figure 4). The fMRI analysis showed slight alterations in the craniocerebral region in patients, when compared with healthy controls. Further outcomes indicated that the connection between the occipital lobe and craniocerebral region was jammed up due to damage to the brain (Figure 5 – Figure 7).

Table 1: Demographic and clinical characteristics of the study population

Characteristic	Patients (n=149)	Control (n=65)	*t*	*P*-value
	Mean ± SD	Mean ± SD		
Age (years)	23.3±7.5	24.7±3.2	-1.456	0.147
Education level (years)	12.4±2.2	12.7±1.3	-1.086	0.279
Age at illness onset (years)	21.7±6.1			
Disease duration (months)	15.4±9.2			
PANSS-positive	22.5±6.1			
PANSS-negative	22.9±6.5			
PANSS-general	40.2±8.1			
PANSS-total	85.7±13.3			
	n (%)	*n (%)*	χ^2	*p*
Gender				
Male	84(56)	29(45)	2.512	0.137
Female	65(44)	36(55)		
Smoking status				
Yes	8(5)	4(6)	0.053	0.758
No	141(95)	61(94)		

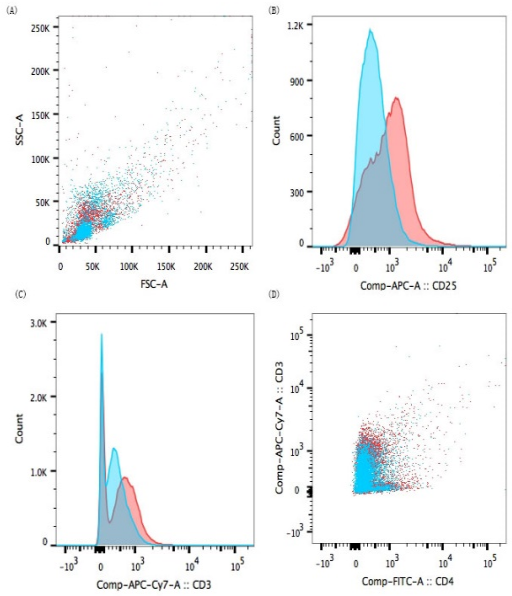

Figure 3: Flow cytometry data for T-cell for control and test patients. The control group is depicted in red, while the patient group is depicted in blue. (A) Scatter plot of FSC and SSC in the two groups. (B) Distribution plot of CD25 fluorescence intensity. (C) Distribution plot of CD3 fluorescence intensity. (D) Scatter plot of CD3 and CD4

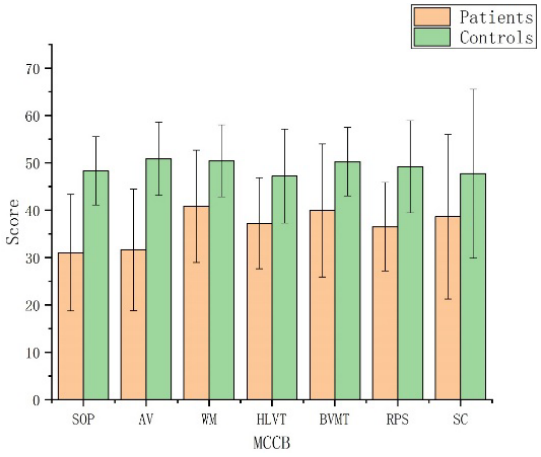

Figure 4: Cognition function in control and schizophrenia patients. This figure shows the mean cognition scores in MCCB (SOP, AV, WM, HVLT, BVMT, RPS and SC) for control and test patients (the bars indicate standard deviation)

DISCUSSION

Oxidative stress has been shown to play a significant role in the pathogenesis of psychosomatic diseases such as schizophrenia, depression and anxiety [4,18]. There is comprehensive mutual communication between oxidative stress and the immune system, both of which exert important effect on neurodevelopment. Studies have shown that dysfunctions in these systems play critical roles in the pathogenesis of psychiatric disorders, including schizophrenia [19,20].

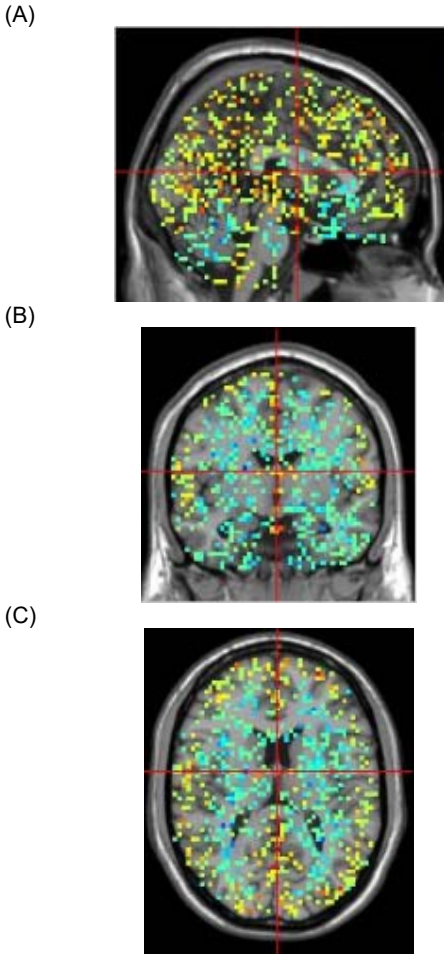

Figure 5: Three views of human brain using fMRI analysis. (A) Front view. (B) Side view. (C) Top view. The points in each figure show the ratio of patient to healthy control. The yellow points indicate that the signals in patients were stronger than those in controls, while blue points indicate that the patients signals were weaker than those in controls.

The blood-brain barrier (BBB) is damaged by changes in oxidative parameters and cytokines in peripheral system due to the ability of some receptors expressed on the epithelial cells of BBB to cross damaged blood-brain barrier into brain, thereby activating microglia. Lots of inflammatory factors and oxygen free radicals are produced by activated microglia, thereby impairing neurons and white matter, in addition to abnormal levels of microglia-derived neurotrophic factors, all of which justifiably lead to psychopathological changes and cognitive impairment.

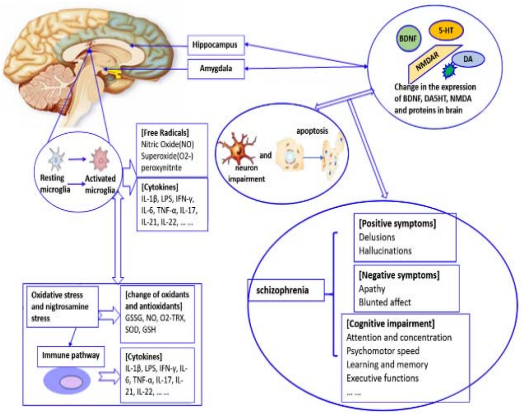

Figure 6: Relationship amongst oxidative stress response, inflammation response and pathology of schizophrenia

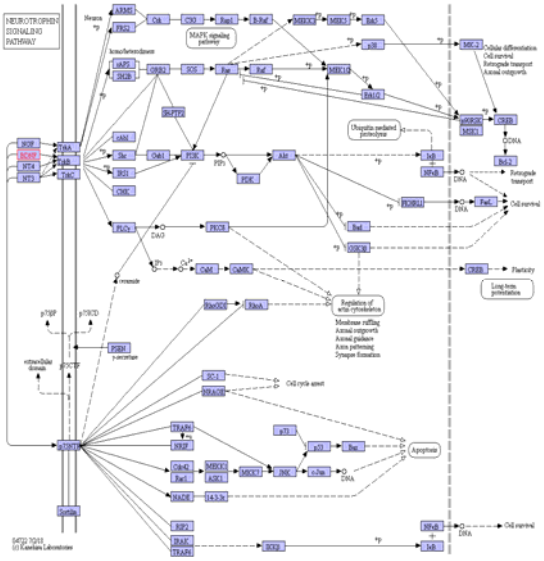

Figure 7: KEGG signal pathway of BDNF in schizophrenia patients. This neurotrophin signaling pathway shows how BDNF participate in physiological processes

Oxidative stress and inflammatory cytokines that cause neuronal damage have been associated with the pathogenesis of schizophrenia. The present study was designed to compare the levels of oxidative stress markers (inflammatory cytokines and oxidants) and neurotrophins between patients with schizophrenia and healthy controls, in order to find out the possible etiology of cognitive impairments in patients with schizophrenia. Moreover, the correlation amongst neurocognitive impairments and construction and brain network connection was analyzed using fMRI analysis. There were higher levels of oxidative stress in schizophrenia patients than in controls, and oxidative stress, neurotrophins and cognitive function were correlated in schizophrenia patients but not in controls. This finding demonstrated that oxidative stress and neurotrophins may be involved, at least to some extent, in the cognitive impairments of schizophrenia.

Previous results from animal studies and clinical trials have demonstrated an excess oxidative stress in patients with schizophrenia due to increased levels of pro-oxidants and decreased levels of antioxidants [4,11,21,22]. This is consistent with the results obtained in this study which showed significantly higher levels of NO, TRX, LPS, IL-1β, and Hcy, but lower levels of GSH and SOD, as well as severe neurocognitive impairments in schizophrenia patients [9,11,23-25]. In addition, there were significant correlations amongst GSH and NO levels and BDNF, as well as correlations between these markers and cognitive function.

Schizophrenia patients are characterized by impairments in neurocognitive function, as well as neuron and microglia damage marked by lower levels of neutrophins, including BDNF produced by these cells in the brain. The possible pathological mechanism involved in the association between oxidative stress-induced schizophrenia and inflammation response has been put forward, as shown in Figure 6. The down-regulation of BDNF could activate membrane receptor Tr-κβ and activate the phosphorylation of Shc (Figure 7). Then, Shc, Gab1 and PI3k may form a complex which activates the expression of Akt with the help of PIP3, with Akt being an essential factor which could contribute to the phosphorylation-induced activation of Ikb, eventually leading to the suppression of NF-κB. Activated NF-κB pathway in microglia enhances the downstream production of oxidants and cytokines that can damage neurons and lead to cognitive impairments. In the peripheral region, an imbalance between oxidative system and anti-oxidative system is symbolized by high levels of oxidants such as NO, Hcy and inflammatory cytokines (LPS and IL-1β). This promotes the production of oxygen free radicals, and lower levels anti-oxidants including GSH, SOD and HPT. In addition, as a compensatory mechanism, TRX is increased to eliminate oxygen free radicals that impose oxidative stress.

The main limitation of our hypothesis is that it is mainly data-oriented, and lacks sufficient experiments. For example, it was assumed that variations in oxidative stress biomarkers would lead to damaged cognition through the effect of oxidative stress response. Therefore, there is need for further experiments to determine the

correctness of the current assertion. The concentration of oxidative stress biomarkers should be reduced using miRNA gene knock-out technique in mice, to assess its effect on cognition. Moreover, the oxidative stress response in mice should be relieved to ascertain whether the cognition damage could be reversed. With more validation of experimental results, the hypothesis would become more solid and convincing, and the mechanism put forward could be discussed more deeply. Therefore, further studies are required to validate the proposed hypothesis.

CONCLUSION

A hypothesis can be advanced proposing that oxidative stress is the biochemical trigger for activating the immune system. Oxidative stress and immune activation lead to increased permeability of the BBB which may enable ROS or neurotoxic cytokines to enter the CNS and trigger psychopathological changes.

DECLARATIONS

Acknowledgement

Thanks to Dr. Xiangyan for his suggestions and for helping us improve the quality of expressions in this manuscript.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this manuscript, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. XY and YW collect the clinical data of schizophrenia patients. YK and SL analyzed the data and performed the fMRI analysis. YK and ZL designed the experiment and revised the manuscript. All authors participated in the discussion of the original version of the manuscript.

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