Article

Effects of Antipsychotic Treatment on S100B and Oxidative Stress in Patients with Schizophrenia

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ABSTRACT

Background: The study aimed to examine the antipsychotic treatment effect on the serum S100B and oxidative stress in patients with schizophrenia.

Methods: Subjects consisted of patients with schizophrenia of first-episode drug-naive and drug-free acute phases, and met the DSM-IV diagnostic criteria for schizophrenia. All patients were treated with risperidone for eight weeks. Positive and Negative Syndrome Scale (PANSS) was evaluated, and serum levels of S100B and parameters of oxidative stress including total oxidative status (TOS) and malondialdehyde (MDA) were measured before and after antipsychotic treatment. A general linear random-effect model was used for data analysis.

Results: Antipsychotic treatment with risperidone reduced the levels of S100B significantly in the first episode drug-naive patients with schizophrenia (Beta=24.89; p=0.0087) and marginally in the drug-free acute phase (Beta=15.65; p=0.093), no significant difference in the effect on S100B between patient groups (p=0.4785). In contrast, antipsychotic treatment increased the levels of MDA in drug-free acute phase schizophrenia (Beta=-6.55; p<0.0001) but not in the first episode drug-naive patients (beta=-0.57; p=0.6631); the effects on MDA were significantly different between two patient groups (p=0.0020). We found that the levels of S100B were only associated with the PANSS negative score in the drug-free acute phase patients who were treated with antipsychotics.

Conclusion: Antipsychotic treatment with risperidone reduced the levels of S100B in first-episode, drug-naive patients with schizophrenia, but may increase the levels of MDA in drug-free acute phase schizophrenia.

KEYWORDS

Antipsychotic treatment, Risperidone, S100B, Oxidative stress, Schizophrenia

INTRODUCTION

Schizophrenia is a chronic mental disorder characterized by delusions, hallucinations, disorganized speech and behavior, and other symptoms that cause social or occupational dysfunction (American Psychiatric Association, 2013). It has a lifetime prevalence of 0.6–1.9% across the world. (1). The etiology of schizophrenia is complex and believed to be multifactorial. Although several etiological hypotheses have been proposed, specific mechanisms are still not clearly understood. S100B is an attention-attracted pathophysiological factor that may be involved with schizophrenia(2), while the level of oxidative stress has also been a focus lately.

S100B is known to exert both paracrine and autocrine effects on neurons and glial cells(3) and has been postulated to either promote apoptotic phase or be released by astrocytes in an attempt to repair the neurodegenerative process(4). It has therefore been considered as a glial

marker protein(5-7), even a biomarker of pathophysiology in schizophrenia. Because a risk haplotype at this gene has been identified for the risk of schizophrenia, an increase in *S100B* expression (8) suggests that S100B may be a causal link to schizophrenia(9). Recently, studies have shown that blood S100B levels in schizophrenia patients are inconsistent. Exploring the association between S100B and schizophrenia may have clinical significance.

Oxidative stress may play an essential role in the processes of many diseases, including schizophrenia. In healthy individuals, reactive oxygen species (ROS) and antioxidant system maintained at constant levels and is controlled by enzymatic and non-enzymatic antioxidants. Imbalance resulted from the excess of ROS production or decline in antioxidant levels could lead to a specific condition of oxidative stress that will cause oxidative damage, in particular in the brain, the organ that has high energy demand, a high concentration of polyunsaturated fatty acids and relatively low level of antioxidant defenses(10). Besides, oxidative stress could exert detrimental effects on socio- and neurocognitive abilities in patients with schizophrenia. So antioxidative treatment could be beneficial for individuals with schizophrenia. Oxidative stress is known to be one of the factors that lead to schizophrenia and can be used as a biomarker for disease treatment. Elevated levels of oxidative stress have been found in cerebrospinal fluid (CSF) and prefrontal cortex, in vivo. Several studies have documented the changes in oxidative parameters and antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase), but the results were not consistent, or even opposite directions have been reported (10-13).

Given the alterations in S100B and oxidative stress in patients with schizophrenia (14) as well as the intrinsic relationship between these parameters and psychopathology symptoms, it would be necessary to examine the antipsychotic effect on both S100B and Oxidant status and their association with psychopathology symptoms in patients with schizophrenia and to identify potential biomarkers for schizophrenia. The objective of the present study is to determine whether peripheral levels of S100B and oxidative stress parameters are different after treated with antipsychotics and whether the change in S100B and oxidative stress is associated with antipsychotic treatment response.

METHODS

Patients

All patients with schizophrenia were recruited from the inpatient units of Beijing HuiLongGuan Hospital, a Beijing-city owned psychiatric hospital and affiliated with Peking University. Patients comprised of first-episode drug-naive patients and drug-free acute phase patients, who met the DSM-IV criteria for schizophrenia. All patients had received dietetically balanced hospital meals. Exclusion criteria included the presence of any comorbid psychiatric dis-

order, severe systemic or neurologic illness, pregnancy, substance abuse or addiction, and structural brain changes apparent in magnetic resonance imaging (MRI) scan.

All subjects provided informed consents, and the study was approved by the Institutional Review Board of Beijing HuiLongGuan Hospital. All patients in both groups were treated with risperidone at the regular dose.

Clinical evaluation

Two psychiatrists, who had attended the same training session for PANSS evaluation, assessed the psycho-pathology symptoms in patients by using the Positive and Negative Syndrome Scale (PANSS). Repeated assessments of PANSS scores were performed at baseline and 8-week after antipsychotic treatment.

Measurement of oxidative stress and S100B

Venous blood was collected from the forearm vein of the patients before and 8-week after antipsychotic treatment. Plasma was separated, aliquoted, and stored at -70 °C before use. Biochemical analysis was performed by a technician who was blinded for the clinical status of the subjects. S100B and oxidative stress parameters including the total oxidants (TOS) and Malondialdehyde (MDA) were measured in the hospital laboratory center using commercially available ELISA kits from Leadman (Beijing Leadman Biotechnology Co. Ltd., Beijing, China) and an automatic biochemistry analyzer AU2700 (Olympus, Japan).

Statistical analysis

Demographic and clinical variables of patients were described by the first episode drug-naive and drug-free acute phase group. General linear regression analysis was performed to examine the effect of antipsychotic treatment on the levels of S100B and oxidative stress measured by TOS and MDA, and on the improvement of psychopathology, measured by the PANSS positive, negative and general psychopathology as well as the total score. The analysis was performed while adjusted for age, sex, education, duration of illness, and age of onset. SAS 9.4 was used for all statistical analysis. Two-tailed significance values were used, and the threshold level for significance was set at 0.05.

RESULTS

Demographics and baseline characterstics of patients with schizophrenia

Table 1 presents the demographics of the first episode drug-naive and drug-free acute phase patients with schizophrenia. The mean age was 27.83 (range from 19 to 52) and 26.34 (range from 18 to 48) years for the first episode drug-naive and drug-free acute phase groups, respectively, and 60% of the patients were males. The mean duration of illness was 28.16 months for the first episode drug-naive group and 48 months for drug-free acute phase patients. There was no significant difference in education, MCCB total score, or the age of onset (p>0.05).

Table 1. Demographics of the first episode drug-naive and drug-free acute phase patients with schizophrenia

	First episode drug-naive group (N=29)					Drug-free acute phase (N=29)				
	Mean	Med	SD	Min	Max	Mean	Med	SD	Min	Max
Age (year)	27.83	27	7.53	190	52	26.34	24	7.61	18	48
Sex (male=1)	0.59	1	0.50	0	1	0.62	1	0.49	0	1
Duration of illness(month)	28.16	20	27.87	1	98	48.00	36	49.11	3	193
Education (years)	12.66	12	2.92	4	19	12.48	12	2.31	8	16
Age of onset (years)	25.37	24	7.09	17	51.61	22.67	22	5.51	14	34..5
PANSS Positive	24.86	24	5.15	17	34	21.52	20	6.25	12	34
PANSS Negative	21.76	22	5.44	9	37	22.55	21	4.88	15	32
PANSS General	40.97	40	5.77	30	52	35.76	35	6.32	26	50
PANSS total score	87.59	87	11.70	68	117	79.83	79	13.00	59	106
MCCB total score	45.56	46	11.26	25	71	44.65	44	11.07	26	66
S100B	234.91	239.1	79.33	136.9	406.4	210.2	203	72.53	97.08	373.6
Total Oxidant status	8.83	7.69	2.89	5.51	15.96	10.08	9.94	2.02	6.46	14.58
Malondialdehyde	8.35	5.74	5.69	3.64	25.62	8.06	7.04	4.48	4.05	24.81

Antipsychotic effect on psychopathology symptoms

Psychopathology symptoms improved significantly after eight weeks of antipsychotic treatment (Table 2). In the first episode, drug-naive patients, PANSS positive symptoms decreased most significantly from 24.86 to 12.26 (*p*<0.01), with an improvement by more than 50%. We also noted that the PANSS negative score decreased from 21.76 to 15.56, PANSS general score from 40.97 to 26.04, PANSS total score from 87.59 to 53.85. All changes were statistically significant (*p*<0.001). Comparatively, the symptom improvements were less in the drug-free acute phase patients, likely due to the relatively lower levels of symptom score at the baseline, but they were still significant (*p*<0.01).

Table 2. Summary of psychopathology symptoms before and after treatment in both first-episode drug-naive and drug-free acute phase patients with schizophrenia

	Before treatment					After treatment					
	Mean	Med	SD	Min	Max	Mean	Med	SD	Min	Max	P
First episode drug-naive											
PANSS positive	24.86	24	5.15	17	34	12.26	11	4.83	7	23	<0.001
PANSS negative	21.76	22	5.44	9	37	15.56	16	5.04	8	25	<0.001
PANSS general	40.97	40	5.77	30	52	26.04	27	5.28	17	36	<0.001
PANSS total score	87.59	87	11.70	68	117	53.85	56	12.78	33	77	<0.001
Drug-free acute phase											
PANSS positive	21.52	20	6.25	12	34	11.97	11	4.25	7	21	<0.001
PANSS negative	22.55	21	4.88	15	32	17.41	17	5.76	7	30	<0.001
PANSS general	35.76	35	6.32	26	50	26.24	26	5.79	19	39	<0.001
PANSS total score	79.83	79	13.00	59	106	55.62	55	14.04	35	86	<0.001

P, P-value for testing the difference while adjusting for age, sex, education, duration of illness, and age of onset.

Antipsychotic effect on protein S100B and oxidative stress

Table 3 shows the effect of antipsychotic treatment on the levels of protein S100B and oxidative stress. As a result, antipsychotic treatment for eight weeks significantly reduced the level of S100B (Beta=24.89; p=0.0087) in the first episode drug-naive patients with schizophrenia and exhibited a marginal effect on the levels of S100B (Beta= 15.65; p=0.0929) in the drug-free acute phase patients with schizophrenia. While the later was at a marginal signi-ficance, there was no difference in the effect between patient groups (*p*=0.4785). When combining two groups, the antipsychotic treatment had a more significant effect on the S100B (Beta=20.27; *p*=0.0026).

Interestingly, we observed a slightly different pattern of antipsychotic treatment effect on two parameters of oxidative stress between two different groups of patients. The treatment showed no significant effect on TOS in either of the two groups (*p*>0.1). However, antipsychotic treatment slightly increased the level of TOS in the first episode, drug-naive patients (Beta=-1.08; *p*=0.1055) but not in the drug-free acute phase patients (Beta=-0.73;*p*=0.2683). Conversely, the antipsychotic treatment significantly increased the levels of MDA in the drug-free acute phase patients (Beta=-6.55; *p*<0.0001). The mean of MDA increased by more than 80% after antipsychotic treatment (LS mean =14.38) compared to the mean of 7.83 before treat-ment in the first episode drug-naive group. However, there had little influence on MDA in the first episode drug-naive patients with schizophrenia (Beta=-0.57*; p*=0.6631).

The effects were significant between two groups as there was a significant interaction (*p*=0.0020) between two groups on the increase in the levels of MDA. The analysis of log-transformed TOS and MDA showed mostly consistent results.

Table 3. The effect of antipsychotic treatment on the levels of S100B and oxidative stress in first-episode drug-naive and drug-free acute phase patients with schizophrenia

Patient group	LS Mean Before	After	Beta	SE	DF	t Value	P	P_int
S100B								
First episode drug-naive	239.05	214.16	24.89	9.16	56	2.72	0.0087	0.4785
Drug-free acute phase	207.56	191.91	15.65	9.16	56	1.71	0.0929	
Total oxidants (TOS)								
First episode drug-naive	8.66	9.73	-1.08	0.65	56	-1.65	0.1055	0.7107
Drug-free acute phase	10.11	10.84	-0.73	0.65	56	-1.12	0.2683	
Malondialdehyde (MDA)								
First episode drug-naive	8.53	9.10	-0.57	1.30	56	-0.44	0.6631	0.0020
Drug-free acute phase	7.83	14.38	-6.55	1.30	56	-5.02	<.0001	

P_int, the interaction between the patient group and treatment.

Association between serum parameters and psychopathology symptoms

We also performed an analysis to examine whether the levels of S100B and oxidative stress would affect the psychopathology symptoms in the patients treated with antipsychotics (**Table 4**). Although the level of protein S100B significantly reduced after antipsychotic treatment in the first episode drug-naive patients, as shown above, no significant association of S100B with psychopathology symptoms of all three sub-clusters or total PANSS scores (*p*>0.1). Instead, the levels of S100B were associated with the improvement of PANSS negative (Beta=0.0397; *p*=0.0039) in the drug-free acute phase patients with schizophrenia.

While the antipsychotic treatment had no significant effect on TOS in either of the groups, as shown above, the TOS was associated with PANSS positive (Beta=0.535;*p*=0.0283) and PANSS total (Beta=1.434; *p*=0.0238) in the first episode drug-naive patient. However, no clear association appeared between changes in MDA and PANSS symptom (*p*>0.05).

Table 4. Association of S100B and oxidative stress with psychopathology symptoms in both groups of schizophrenia patients

	S100B Beta	SE	P	TOS Beta	SE	P	MDA Beta	SE	P
Drug naïve first episode									
PANSS positive	0.0115	0.0099	0.2554	0.5352	0.2299	0.0283	0.1228	0.1112	0.2797
PANSS negative	0.0048	0.0119	0.6934	0.3059	0.2487	0.2301	0.1324	0.1247	0.2984
PANSS general	0.0105	0.0123	0.4026	0.5316	0.2709	0.061	0.2279	0.1299	0.0917
PANSS total	0.0259	0.0259	0.3258	1.4338	0.5958	0.0238	0.5418	0.2776	0.0622
Drug-free acute phase									
PANSS positive	0.0095	0.0144	0.5121	0.2801	0.2613	0.2933	0.0346	0.1091	0.7535
PANSS negative	0.0397	0.0126	0.0039	0.1429	0.2633	0.5918	0.0445	0.1088	0.6859
PANSS general	0.0105	0.0123	0.4026	0.5316	0.2709	0.061	0.2002	0.1253	0.1216
PANSS total	0.0575	0.035	0.1117	0.1431	0.6811	0.8351	0.205	0.2797	0.47

DISCUSSION

In this study, we found that antipsychotic treatment reduced the levels of S100B in serum significantly in the first-episode drug-naive but marginally significantly in drug-free acute phase patients with schizophrenia. The antipsychotic treatment had no significant effect on total oxidant status in either of two groups, but it significantly increased the serum level of MDA in the drug-free acute phase only. We noted that S100B was positively associated with the antipsychotic response of PANSS negative in the drug-free acute phase, but TOS had a positive association with PANSS

positive and total score in first-episode drug-naive patients.

S100B, a calcium-binding protein, is mainly synthesized by and released from astrocytes and oligodendrocytes(15, 16), and can pass the blood-brain barrier(17, 18). Reportedly, its peripheral levels correlate well with those in the central nervous system extensively investigated in psychotic disorders (4, 19). This protein has been considered as a surrogate marker for brain and astrocyte-specific damage or dysfunction in neurologic disorders such as stroke and traumatic brain injury (15, 16, 20). Reports on S100B levels in schizophrenia patients have been inconsistent. Accurately, some reported no diff-erences in S100B bet-

ween schizophrenia patients and healthy controls (21, 22), while others reported an increased (23) or decreased S100B (16) in patients with schizophrenia compared with healthy controls. Both the first-generation antipsychotic drug (haloperidol) and the second-generation drug (risperidone) are shown to inhibit interleukin-6-induced S100B secretion in C6 glioma cells (24). Another study also supports that S100B levels reduced during convalescence from acute paranoid schizophrenia that is regulated by its scavenger, a soluble receptor for advanced glycation end products (RAGE)(25). Previous studies of patients with the negative symptom or deficit schizophrenia find that the reduced levels of S100B are associated with negative symptom in patients treated with antipsychotics for six weeks (26). These are mostly consistent with our findings that the levels of S100B positively associated with PANSS negative score after antipsychotic treatment for eight weeks.

However, there are inconsistent reports that antipsychotic treatment leads to an increased level of serum S100B in early treatment(20), medicated and unmedicated patients (27), and older patients (>50 years) with long-term treatment of clozapine and typical antipsychotics. There was no association between S100B and PANSS, which was similar between atypical and typical drugs (28). These contradictory seemed to have some underlying explanation. Most antipsychotics such as clozapine and olanzapine have a side effect such as weight gain and impaired glucose tolerance, which may contribute to the elevated level of S100B (29, 30). While the treatment with anti-psychotics may reduce the psychotic symptoms and S100B levels simultaneously, the improvement of psychotic symptoms could not be determined by the level change of S100B, and no correlations have been detected for S100B levels with PANSS total, positive, negative, or general scores (21, 25, 28). This suggests that antipsychotic drugs could improve symptoms in patients with schizophrenia through other mechanisms rather than S100B, although the level of S100B was also affected by antipsychotic treatment. Moreover, two recent meta-analyses found no differences in S100B concentrations between medicated and non-medicated patients (31, 32). These inconsistencies could be due to the relatively small sample size or clinical heterogeneity of the patients with schizophrenia.

Recent data suggest a convergence of redox dysregulation and oxidative stress in promoting the emergence of psychosis. Many studies have identified that patients with schizophrenia increase in oxidative stress in the blood plasma, cerebrospinal fluid (CSF) and postmortem samples, including increased lipid and protein oxidation and alterations in antioxidant defense systems, such as catalase and superoxide dismutase (33-37). In contrast, a study showed that antipsychotic treatment reduced the index of oxidative stress, including the total level of peroxides in the first episode drug-naive patients treated with olanzapine and risperidone for three months (38). Anti-psychotics do not have a significant effect on the oxidative and anti-oxidative system parameter after treatment for six weeks (39). We noted limited evidence that risperidone antipsychotic treatment affects oxidative stress and their associations with PANSS symptoms. In this study, the levels of

TOS had no significant change before and after antipsychotic treatment in both groups of patients but were associated with PANSS positive and total scores only in the first episode drug-naive patients with schizophrenia.

In healthy individuals, oxidant and antioxidant systems are maintained at constant levels and balanced, and such a balance could be disturbed in patients with schizophrenia. A significant association between antioxidant enzyme levels and clinical features of schizophrenia has been previously reported in several studies (26, 40-48). For instance, abnormalities in the antioxidant system lipid peroxidation have been associated with negative(43)and positive symptoms(47). However, most studies did not identify a significant association between oxidative stress biomarkers and clinical severity among chronic schizophrenia patients or first-episode psychosis (49-52). For drug-free acute phase patients with schizophrenia, there was no change in TOS levels before and after treatment or no correlation between TOS levels and PANSS scores, which perhaps is confounded by medication history in the non-acute phase.

Malondialdehyde (MDA) is deemed as another parameter of oxidative stress, representing the level of Lipid peroxidation (LPO). So LPO on erythrocyte membranes was assessed through determining the levels of reactive alde-hyde MDA, an end product of lipid peroxidation cascade(53). In the current study, MDA levels increased in the drug-free acute phase patients but did not in the first episode drug-naive ones; MDA has no medication effect on psychopathology symptoms in all patients after treatment. Such a phenomenon might be explained by the fact that antipsychotics leads to stress, although the previous study based on small patients showed that treatment with typi-cal antipsychotics increased the level of MDA(54). While LPO levels seemed to be lower in patients showing higher severity of negative symptoms, according to both PANSS and BNSS scales(55), the majority of relevant studies failed to replicate any correlation between MDA and clinical features(36).

Lacking association of antipsychotics treatment with the oxidative stress parameters and oxidative stress parameters with PANSS symptoms could be caused by complicated reasons. *First*, the therapeutic actions of antipsychotic drugs are heterogeneous. For example, antipsychotics may have different antioxidant and oxidant properties. Typical antipsychotics were likely to have a higher level of the neurotoxicity, which may be through the lipid peroxidation which induced oxidative injury in the brain and led to the development of extrapyramidal symptoms including tardive dyskinesia(56). Even among the atypical drugs, there were marked differences in the induced oxidative stress. Clozapine was shown to have higher antioxidant properties than risperidone and perphenazine, especially increasing the levels of antioxidants (e.g., superoxide dismutase, SOD; glutathione, GSH) and reducing levels of lipid peroxidation in patients with schizophrenia (57); olanzapine and clozapine may increase antioxidant activities, which may contribute to therapeutic actions (58). Unfortunately, we did not measure the antioxidants in this study.

Also, the alteration of a single oxidative stress parameter maybe not representtative for the anti-psychotic effect, which may be determined by the balance of oxidant and antioxidant systems at a constant level.

Given that, an increase in oxidative stress may be detrimental to cognition (59), which, in the long run, may affect the prognosis of patients with schizophrenia. Therefore, it is crucial to keep oxidative stress under control for patients treated with antipsychotics. It will be an interesting topic to see if antipsychotics plus antioxidant supplement would increase the therapeutic efficacy in patients with schizophrenia.

Limitation and strength

Several limitations of this study should be noted. The number of enrolled patients may not provide enough power for this type of study. In addition, we only measured two parameters of oxidative stress, which may not be able to assess the ultimately oxidative stress system. Oxidative and anti-oxidative parameters should be included simul-taneously in the analysis. Despite those limitations, some strength in the current study was noteworthy. The patients were from inpatient units and stayed in the hospital throughout the treatment. Despite a relatively short period of patients' hospitalization, they acquired good clinical improvement.

In summary, after antipsychotic treatment, while the levels of S100B decreased in both groups. S100B had no significant meditational effect on psychopathology symptoms in the first episode drug-naive patients, but on PANSS negative symptoms in the drug-free acute phase patients with schizophrenia. However, the level of MDA increased in drug-free acute phase schizophrenia patients but not associated with psychopathology symptoms. These findings warrant a further study in a larger sample size.

CONFLICT OF INTEREST

The authors reported no biomedical financial interests or potential conflicts of interest regarding the publication of this paper.

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