The Interaction of Nuclear Factor-Kappa B and Cytokines Is Associated with Schizophrenia

Xue-Qin Song, Lu-Xian Lv, Wen-Qiang Li, Yi-Hui Hao, and Jing-Ping Zhao

Background: Many reports suggest that schizophrenia is associated with the inflammatory response mediated by cytokines, and nuclear factor-kappa B (NF-κB) regulates the expression of cytokines. However, it remains unclear whether the interaction between NF-κB and cytokines is implicated in schizophrenia and whether the effect of neuroleptics treatment for 4 weeks is associated with the alteration of cytokines.

Methods: Sixty-five healthy subjects and 83 first-episode schizophrenic patients who met DSM-IV criteria and who were never treated with neuroleptics previously were included. Serum levels of cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) were examined by using sandwich enzyme immunoassay (EIA). Peripheral blood mononuclear cell (PBMC) mRNA expressions of cytokines (IL-1β, TNF-α) and NF-κB were detected by using semiquantitative reverse transcription polymerase chain reaction (RT-PCR). NF-κB activation was examined by using transcription factor assay kits.

Results: Schizophrenic patients showed significantly higher serum levels and PBMC mRNA expressions of IL-1β and TNF-α compared with healthy subjects. However, treatment with the neuroleptic risperidone for 4 weeks significantly decreased serum levels and PBMC mRNA expressions of IL-1β in schizophrenic patients. NF-κB activation and PBMC mRNA expression in patients were significantly higher than those in healthy subjects. Furthermore, PBMC mRNA expressions of IL-1β and TNF-α were positively correlated to NF-κB activation in both schizophrenic patients and healthy control subjects.

Conclusions: Schizophrenic patients showed activation of the cytokine system and immune disturbance. NF-κB activation may play a pivotal role in schizophrenia through interaction with cytokines.

Key Words: Interleukin-1, nuclear factor-kappa B, schizophrenia, tumor necrosis factor

Chronically activated macrophages and T-lymphocytes, along with excessive cytokine secretion, have been regarded as fundamental mediators of schizophrenia (1). Some reports suggest that abnormalities of striatal dopaminergic neurotransmission play a significant role in the pathophysiology of schizophrenia (2). Growing evidence suggests that the immune, endocrine, and nervous systems interact through cytokines, hormones, and neurotransmitters (3–5). Activation of the immune system, which is largely mediated by cytokines (6), and oxidative stress (OS) regulation of dopamine D2 receptor (DRD2) (2), may be involved in the neuropathologic changes in the central nervous system (CNS). Cytokines have diverse actions in the brain and modulate both systemic and CNS responses to injury, infection and inflammation (7). The striatum appears to be exposed to intrinsically high levels of OS in schizophrenia (2).

Cytokines are low-molecular-weight proteins, and their receptors are constitutively expressed on neurons and glial cells (5,8,9). It has been suggested that astrocyte- and microglia-derived cytokines strongly affect the function of neurons (10). Astrocyte and microglia express the receptors of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). Both neurons and glial cells produce TNF-α in the CNS, which affects the growth, differentiation, and apoptosis of nerve cells (10,11). It has been shown that TNF-α affects the formation of neurites and neuronal survival in the CNS (12,13).

Activation of neural cytokine receptors has a proved effect on neurotransmission (14). It seems that TNF-α and IL-1β can influence the release of neurotransmitters, especially in the catecholaminergic system. After intracerebral injection of IL-1, the dopamine turnover was increased (15,16). It is shown that TNF-α has cytotoxic effects on embryonic mesencephalic dopaminergic neurons and has a stimulatory effect on the catecholaminergic system, whereas chronic TNF-α release produces an inhibitory effect (17). The various effects of TNF-α suggest that disturbance of its concentration may affect the function of the brain.

Over the past decades, studies of abnormal cytokine levels in psychosis (18,19) have indicated that activation of the inflammatory response system mediated by cytokines may play a key role in the pathogenesis of schizophrenia (20,21). Studies have shown that schizophrenia is accompanied by various dysfunctions of immune system (22,23). The evidence supports that altered levels of cytokines, a class of proteins or peptides involved in signaling among cells during the immune response, may contribute to the development of schizophrenia. However, the molecular mechanism underlying the activation of cytokines in schizophrenia remains elusive.

It has been shown that nuclear factor-kappa B (NF-κB), a prototypic transcription factor, is responsive to various genes, including those of cytokines, cell surface receptors, and antioxidant enzymes. It is known that NF-κB can transactivate promoters of genes involved in the regulation of cell differentiation and survival/apoptosis as well as immune and inflammatory responses (24). Moreover, NF-κB is present in synaptic terminals and serves as a regulator of neuronal plasticity, which is then
activated by the activity of neuronal circuits. NF-κB modulates the expression of genes that encode proteins involved in the regulation of neuronal excitability and plasticity (25). Larouche (2) reported that H2O2 can elicit a significant increase of DRD2 mRNA and protein levels and simultaneously increase NF-κB activation (as assessed by p65 nuclear translocation).

The intent of this study was to investigate further the interaction between cytokine expression and NF-κB activation in schizophrenia. Because T cells are promising candidates for the investigation of cellular function, including intracellular signaling and gene transcription, we identified serum levels of IL-1β and TNF-α; PBMC IL-1β, TNF-α, and NF-κB mRNA expressions; and NF-κB activation in schizophrenia. Cytokines may participate in the psychopathology through its influence on the release of neurotransmitters. NF-κB can be activated by pro-inflammatory cytokines and in turn plays a pivotal role in the regulation of pro-inflammatory cytokine gene expression. Both IL-1β and TNF-α are important inducing mediators of NF-κB and are transcriptionally regulated by a redox-sensitive NF-κB, which constitutes the positive feedback loop. We hypothesize that this feedback loop is associated with schizophrenia.

Methods and Materials

Participants

All the subjects gave written informed consent to participate in the study, which was approved by the Ethics Committee of Henan Mental Hospital. One hundred forty-eight subjects were invited to participate in the study, including 65 healthy control subjects (35 men and 30 women) and 83 patients (43 men and 40 women). Eligible patients were diagnosed according to DSM-IV criteria (27) with first-episode schizophrenia. The diagnosis of schizophrenia was determined by a psychiatrist using the Structured Clinical Interview for DSM-IV Axis I Disorders—Clinical Version (28) during the screening phase. Patients were aged between 16 and 45 years (mean 27.3 ± 6.7 years, mean ± SD), and control subjects were aged between 17 and 45 years (mean 28.4 ± 6.1 years, mean ± SD). There was no significant difference in age and the male-to-female ratio between the patients and healthy control subjects, who were also matched on smoking and body mass index (BMI) (Table 1). A complete medical history, physical examination, and laboratory tests were obtained from all subjects. Subjects with ongoing infections, allergies, or past history of alcohol or other substance abuse/dependence and autoimmune disorders were excluded. None of the schizophrenic patients or control subjects were taking immunosuppressive drugs. None of the patients had been treated with neuroleptics before recruitment, and the duration of disease was less than 2 years (median duration: 7 months). All patients were treated at the same center and underwent daily physical examinations and weekly routine blood work. Control subjects included hospital staff and undergraduate students at the medical college. Psychiatric disorders were ruled out among control subjects using a psychiatric review evaluation conducted by a psychiatrist. None of the patients suffered from an acute infection throughout the study.

Clinical Ratings and Treatment

The Positive and Negative Syndrome Scale (PANSS) was carried out by two clinical psychiatrists who had attended a training session for the proper use of PANSS to ensure the consistency and reliability of the ratings. A correlation coefficient above .8 was maintained for the PANSS total score after repeated assessments. The PANSS was assessed before and 4 weeks after the treatment. All the patients were treated with risperidone, and the medication dose ranged from 2 mg to 4 mg per day, on the basis of the physicians’ judgment. Concomitant medications were permitted throughout the trial, with the exception of additional neuroleptic agents.

Methods

Venous blood (7 mL) was collected between 7:00 and 8:00 AM to avoid circadian fluctuation of the parameters. Five milliliters of blood was put into a glass tube and allowed to clot at room temperature. Serum was obtained through centrifugation at 3000 rpm for 10 min and was then aliquoted and stored at −20°C until assayed for cytokine levels. Total RNA was extracted from 1 mL of whole blood with the SV Total RNA Isolation System (Promega Corporation, Madison, Wisconsin). cDNA was reversely transcribed with M-MLV (Moloney murine leukemia virus) reverse transcriptase (Promega) and was then stored at 20°C until used. Nuclear proteins were extracted using Nuclear Extract Kit (Active Motif, Carlsbad, California) according to the manufacturer’s instructions and were then stored at −80°C until assayed for the transcription factor NF-κB activation of PBMC.

Cytokine Assay

The serum levels of IL-1β and TNF-α were measured by sandwich enzyme immunoassay (EIA; BanDing Biological, Beijing, China). The assays were performed according to manufacturer’s instructions. The sensitivities of IL-1β and TNF-α were 1.0 and 1.6 pg/mL, with interassay coefficients of 6.3% and 6.7% and intraassay variation coefficients of 5.9% and 5.7%. Standard curve concentrations were calculated in triplicate for each plate. Absorbencies were measured by a microtiter plate reader (absorbency at 492 nm). All the assays were carried out at the same time by the same investigator and were conducted blinded to the subjects’ status.

NF-κB Activation Assay

Activation of the NF-κB p65 subunit was determined using an NF-κB p65 enzyme-linked immunosorbent assay (ELISA)-based transcription factor assay kit (TransAM assay; Active Motif) according to the manufacturer’s protocol. The NF-κB detecting antibody recognizes an epitope on p65 that is accessible only when NF-κB is activated. Active Motif offers a high-throughput

Table 1. Demographic Details of Patients and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n = 65)</th>
<th>Patients (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.4 ± 6.1 (17–45)</td>
<td>27.3 ± 6.7 (16–45)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (54)</td>
<td>43 (52)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (46)</td>
<td>40 (48)</td>
</tr>
<tr>
<td>Disease duration,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>months (median)</td>
<td>1–24 (7)</td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>14 (22)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>51 (78)</td>
<td>64 (77)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20.8 ± 2.1</td>
<td>20.9 ± 1.9</td>
</tr>
<tr>
<td>Female</td>
<td>20.6 ± 2.3</td>
<td>20.5 ± 2.4</td>
</tr>
</tbody>
</table>

BMI, body mass index.
assay to quantify NF-κB activation (29,30). Detection limit: < .5 ug nuclear extract per well.

**NF-κB and Cytokine mRNA Expression**

Semi-quantitative reverse transcription polymerase chain reaction (RT-PCR) was performed to measure mRNA expression. Glyceraldehyde phosphate dehydrogenase (GAPDH) was used as an internal control. PCR was performed with following PCR primers: GAPDH (forward: 5'-ACCAAGTTGCTAGCCATCAGC-3', reverse: 5'-TCCACCACCTGTGCTGTA-3'), IL-1β (forward: 5'-GGCTTATTACAGTGCCAATG-3', reverse: 5'-GGATCTCACTCTCAGCGT-3'), TNF-α (forward: 5'-CCGGTGACAGGCTGTAG-3', reverse: 5'-CAATGAACCAAGTAGCATCTC-3') and NF-κB (forward: 5'-CAGGGGACACACGGTAGTGA-3', reverse: 5'-CCTGTTAAACACAGGCTTA-3'). These combinations of the DNA primers produced single PCR products of 532 bp, 572 bp, 444 bp, and 299 bp in length, respectively. PCR was carried out in a DNA thermal cycler (Biometra, Goettingen, Germany) after the first denaturation at 95°C for 5 min, and each cycle consisted of denaturation at 94°C for 15 sec, annealing at 65°C (GAPDH at 62°C) for 30 sec, and extension at 72°C for 90 sec. The number of total PCR cycles was 35 for IL-1β, TNF-α, and NF-κB and 30 for GAPDH. For semiquantitative analysis, 25 μL of PCR products were examined by electrophoresis on 2.0% agarose gel containing 5 μg/mL of ethidium bromide. BIS-20M (Uvitec, Cambridge, United Kingdom) was used for photographing and analysis of optical densities. Optical densities of IL-1β, TNF-α, and NF-κB mRNA were normalized by that of GAPDH mRNA, and the ratios were analyzed.

**Statistical Analysis**

All data analysis was conducted using SPSS 13.0 for Windows. The values were presented as the means ± SD. For discrete variables, study groups were compared by chi-square test. Normality of the distribution was checked using the Kolmogorov-Smirnov one-sample test in schizophrenia and healthy subjects. The two study groups were compared for continuous variables by an independent t test. The pre- and posttreatment data were compared by the paired t test. Two-tailed p < .05 was considered significant. The correlation coefficients between NF-κB activation of PBMC and IL-1β and TNF-α mRNA expression of PBMC were evaluated using Bivariate correlation.

**Results**

**Demographic Data**

Demographic data from 148 examined subjects are listed in Table 1. Because of matching criteria, there was no difference in age, sex, smoking, and BMI between the schizophrenic patients and healthy subjects.

**Table 2. Serum Levels and PBMC mRNA Expressions of IL-1β and TNF-α, and NF-κB Activation and mRNA Expression in Both Schizophrenia and Control Group**

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Control Subjects</th>
<th>t</th>
<th>p</th>
<th>Effect Sizes</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IL-1β (pg/mL)</td>
<td>25.93 ± 13.30</td>
<td>14.19 ± 7.86</td>
<td>6.30</td>
<td>&lt;.05</td>
<td>1.49</td>
<td>8.058–15.420</td>
</tr>
<tr>
<td>Serum TNF-α (pg/mL)</td>
<td>31.01 ± 13.82</td>
<td>21.33 ± 8.90</td>
<td>4.90</td>
<td>&lt;.05</td>
<td>1.088</td>
<td>5.78–13.58</td>
</tr>
<tr>
<td>PBMC IL-1β mRNA</td>
<td>1.30 ± .30</td>
<td>.97 ± .27</td>
<td>6.86</td>
<td>&lt;.05</td>
<td>1.22</td>
<td>.23–42</td>
</tr>
<tr>
<td>PBMC TNF-α mRNA</td>
<td>1.34 ± .33</td>
<td>.84 ± .31</td>
<td>9.37</td>
<td>&lt;.05</td>
<td>1.61</td>
<td>.40–60</td>
</tr>
<tr>
<td>NF-κB activation (ng/mL)</td>
<td>.28 ± .21</td>
<td>.20 ± .17</td>
<td>2.33</td>
<td>&lt;.05</td>
<td>.47</td>
<td>.01–0.14</td>
</tr>
<tr>
<td>NF-κB mRNA expression</td>
<td>.842 ± .226</td>
<td>.723 ± .247</td>
<td>3.06</td>
<td>&lt;.05</td>
<td>.48</td>
<td>.04–20</td>
</tr>
</tbody>
</table>

CI, confidence interval; IL-β, interleukin-1β; NF-κB, nuclear factor-kappa B; PBMC, peripheral blood mononuclear cell; TNF-α, tumor necrosis factor-α.

**Discussion**

In this study, we found a significant increase in serum levels of IL-1β and TNF-α in schizophrenic patients. This is consistent with previous reports that IL-1 and TNF-α are increased in plasma and cerebrospinal fluid of schizophrenic patients (31–35). The alterations of cytokines in schizophrenia have been
extensively studied (36–39). Many reports have demonstrated that IL-2 receptors express on pyramidal cells of brain regions including the hippocampus, and IL-2 may modulate the release of dopamine, serotonin, and norepinephrine (40,41). Astrocytes and microglia also express the receptors of IL-1 and TNF-α. The activation of microglia receptors by IL-1 and TNF-α may ultimately cause neurons to release IL-2 that modulate the monoaminergic system, thereby contributing to the development of psychiatric disorders such as schizophrenia (42) and depression (43–47). In this study, schizophrenic patients were diag-

Table 3. Changes in Serum IL-1β and TNF-α Levels and PBMC IL-1β and TNF-α mRNA Expressions Before and After 4 Weeks of Treatment

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After 4 Weeks</th>
<th>t</th>
<th>p</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IL-1β (pg/mL)</td>
<td>25.93 ± 13.30</td>
<td>20.25 ± 12.73</td>
<td>3.25</td>
<td>&lt; .05</td>
<td>2.20–9.15</td>
</tr>
<tr>
<td>Serum TNF-α (pg/mL)</td>
<td>31.01 ± 13.82</td>
<td>29.77 ± 12.64</td>
<td>1.95</td>
<td>&gt; .05</td>
<td>−0.03–2.49</td>
</tr>
<tr>
<td>PBMC IL-1β</td>
<td>1.30 ± .30</td>
<td>1.13 ± .28</td>
<td>5.09</td>
<td>&lt; .05</td>
<td>.1–23</td>
</tr>
<tr>
<td>PBMC TNF-α</td>
<td>1.34 ± .33</td>
<td>1.28 ± .33</td>
<td>5.18</td>
<td>&gt; .05</td>
<td>−0.02–.14</td>
</tr>
</tbody>
</table>

CI, confidence interval; IL-1β, interleukin-1β; PBMC, peripheral blood mononuclear cell; TNF-α, tumor necrosis factor-α.
nosed according to DSM-IV criteria, and their demographic data were matched with those of healthy subjects. Because we did not examine depressive scales in patients, our findings that serum levels of IL-1 and TNF-α were increased in schizophrenia patients cannot exclude the contribution of possible comorbid depression. However, our data support the notion that the changes of cytokines may be involved in psychopathology. Furthermore, evidence shows that serum IL-1β and TNF-α is actively moved into CNS (48,49), whereas IL-1β is transported passively into CNS through circumventricular organs (50). Thus, it remains to be determined in the future study whether the increased serum levels of cytokines in schizophrenia patients come from the brain or periphery.

Consistent with our reports on serum levels of cytokines, PBMC mRNA expressions of IL-1β and TNF-α in schizophrenic patients are significantly higher than those in control subjects. This is consistent with Sirota et al. (51), who demonstrated that IL-1β release is increased in cell cultures of PBMC in schizophrenic patients, and with Katila et al. (52), who showed that serum IL-1β levels are increased in schizophrenia. Furthermore, PBMC is one of the main sources of serum cytokines. Thus, it is reasonable that PBMC mRNA expressions of IL-1β and TNF-α is decreased following the 4-week treatment of risperidone and is parallel with their serum levels. Exploration into the affecting

Table 4. Correlation of NF-κB Activation and mRNA Expression of IL-1β, TNF-α, and NF-κB in the Schizophrenia and Control Subjects (r)

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-1β</th>
<th>TNF-α</th>
<th>NF-κB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenics NF-κB Activation</td>
<td>.536&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.454&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.187</td>
</tr>
<tr>
<td>Control Subjects NF-κB Activation</td>
<td>.519&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.513&lt;sup&gt;a&lt;/sup&gt;</td>
<td>.217</td>
</tr>
</tbody>
</table>

IL-β, interleukin-1β; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor-α.

<sup>a</sup>p < .05.

Figure 2. Panels A, C, and E represent the correlation of NF-κB activation and mRNA expression of NF-κB, IL-1β, and TNF-α respectively in control subjects. Panels B, D, and F represent the correlation of NF-κB activation and mRNA expression of NF-κB, IL-1β, and TNF-α in schizophrenic patients, respectively. NF-κB, nuclear factor-kappa B; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α.
factors of PBMC cytokine mRNA expression may help us to realize the immune state of schizophrenia.

Both total PANSS scores and serum levels of IL-1β in schizophrenic patients were significantly decreased after risperidone treatment for 4 weeks. Remarkably, the decrease of total PANSS scores and serum levels of IL-1β was significantly correlated. It has been suggested that typical or atypical neuroleptic drugs may partially restore abnormal immune alterations in schizophrenia. Compared with haloperidol, risperidone can inhibit the production of inflammatory cytokines, for example, IL-1β and TNF-α, which are produced by the activation of microglia. Neuroleptics, especially risperidone, may produce anti-inflammatory effects by inhibiting microglial activation, which not only is directly toxic to neurons but also has an inhibitory effect on neurogenesis and oligodendrogenesis, both of which are suggested to be critical in the pathology of schizophrenia (53). Some immune parameters at baseline may be useful for the prediction of the neuroleptic response in schizophrenic patients (54). Here we found that the decrease rate of serum levels of IL-1β were positively correlated to that of total PANSS scores following risperidone treatment within 4 weeks, indicating that alteration of serum IL-1β levels may serve as a sensitive parameter for illness recovery with neuroleptic treatment.

NF-κB is sensitive to many factors such as illness, cytokines, and other factors. We found that NF-κB activation was moderate in control subjects. However, NF-κB activation and its mRNA expression were excessively increased in schizophrenia patients compared with healthy subjects, which may be attributed to the increased cytokines. However, we did not find a correlation between NF-κB activation and its mRNA expression in either group. When inactivated, the NF-κB complex, consisting of three subunits, is located in cytosol (25), and its mRNA expression can be increased by various stressors. NF-κB has many target genes, and its activation can be regulated through positive or negative feedbacks, for example, positively by cytokines (55), negatively by the IkBα gene (56), and so on. However, the predominant form of regulation is NF-κB state (57,58). In this study, we found that it was activated NF-κB that played the transcription roles (Figure 3), and NF-κB activation was positively correlated with PBMC mRNA expressions of IL-1β and TNF-α in both schizophrenic patients and control subjects. IL-1 contains κB binding sites, and its expression can lead to IkBβ degeneration and then NF-κB activation, which in turn regulates IL-1β gene transcription (59). The key factor inducing monocyte-macrophage cells to secrete TNF-α lies in TNF-α gene transcription is involved in the regulation of NF-κB (60). One report has shown that lipopoly-saccharide (LPS)-induced upregulation of cytokine expression can be inhibited by suppression of ERK1/2 and p38 kinase-mediated NF-κB activation (61). In addition, suppressing the activation of NF-κB (62,63) and activator protein-1 (AP-1) can reduce the levels of TNF-α, IL-1β, IL-6, IL-8, and their corresponding mRNAs (64). NF-κB in cells is activated in the acute state of schizophrenia, and activated NF-κB moves to the nucleus and binds to κB sites in target genes that rapidly induce transcription and contribute to the release of IL-1β and TNF-α.

Thus, cytokines can activate NF-κB and in turn are increased by NF-κB. It could be a positive feedback with amplification effects (65). In this study, we cannot verify which occurs in the first, cytokine increase or NF-κB activation. However, it is known that NF-κB activation is the final step of the surface-to-nucleus signal transduction pathway, which amplifies the inflammation signal of cytokines and maintains a regulating function of inflammation. Because of its responsiveness to neuronal activity and injury of the nervous system, NF-κB is likely to play an important role in various physiologic and pathologic processes. In the treatment of schizophrenia, we believe that multiple activating processes of NF-κB and NF-κB signal transduction pathway should be prevented as early as possible and an NF-κB inhibitor should be administered to break the positive feedback chain of cytokines-NF-κB. This may be helpful to improve the treatment and prognosis of schizophrenia. Therefore, our finding that the interaction between cytokines and NF-κB is associated with schizophrenia may lead to novel approaches in preventing and treating various neuropsychiatric disorders.

We thank Dr. Lin Xu for the critical comments on this article. This study was supported by National Key Technologies R&D Program in the 10th five-year-plan grant from the Ministry of Science and Technology of the People’s Republic of China (Grant No. 2004BA720A22 to J-FZ), the National Natural Science Foundation of China (Grant No. 30870892 to L-XL), and the Ministry of Public Health Foundation of China (Grant No. 200801009 to L-XL).

Financial disclosures: Professor Zhao has received grant support from and served as a consultant to Johnson & Johnson, Pfizer, Eli Lilly, AstraZeneca, and GlaxoSmithKline. The other authors report no biomedical financial interests or potential conflicts of interest.


www.sobp.org/journal


