Risperidone reverses the spatial object recognition impairment and hippocampal BDNF-TrkB signalling system alterations induced by acute MK-801 treatment

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Abstract. The aim of the present study was to investigate the effects of a commonly-used atypical antipsychotic, risperidone, on alterations in spatial learning and in the hippocampal brain-derived neurotrophic factor (BDNF)-tyrosine receptor kinase B (TrkB) signalling system caused by acute dizocilpine maleate (MK-801) treatment. In experiment 1, adult male Sprague-Dawley rats subjected to acute treatment of either low-dose MK801 (0.1 mg/kg) or normal saline (vehicle) were tested for spatial object recognition and hippocampal expression levels of BDNF, TrkB and the phophorylation of TrkB (p-TrkB). We found that compared to the vehicle, MK-801 treatment impaired spatial object recognition of animals and downregulated the expression levels of p-TrkB. In experiment 2, MK-801- or vehicle-treated animals were further injected with risperidone (0.1 mg/kg) or vehicle before behavioural testing and sacrifice. Of note, we found that risperidone successfully reversed the deleterious effects of MK-801 on spatial object recognition and upregulated the hippocampal BDNF-TrkB signalling system. Collectively, the findings suggest that cognitive deficits from acute *N*-methyl-D-aspartate receptor blockade may be associated with the hypofunction of hippocampal BDNF-TrkB signalling system and that risperidone was able to reverse these alterations.

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Introduction

The aetiologies and pathogenic mechanisms of schizophrenia are complicated and likely involve various neurotransmitter systems. Its clinical manifestations are also complicated and varied. Currently, its exact pathogenic mechanism has not been elucidated (1). As the major atypical antipsychotic drug, risperidone primarily exerts antipsychotic effects through the blocking of the serotonin 5-HT$_{2A}$ and dopamine D2 (DA$_2$) receptors (2). Although many clinical and pre-clinical studies (3-5) have confirmed that the improvements of the positive and negative symptoms of patients with schizophrenia via risperidone are associated with the blocking of the 5-HT$_{2A}$ and DA$_2$ receptors, the improvement of the pathogenic mechanism of patients' cognitive symptoms has not been elucidated (6).

As an important neurotropic factor in the brain, the brain-derived neurotrophic factor (BDNF) is involved in the maturation and survival of neurons as well as the growth and development of synapses. Furthermore, it plays important roles in synaptic plasticity as well as formation and consolidation of learning and memory (7). Both clinical and pre-clinical studies suggested that BDNF and tyrosine receptor kinase B (TrkB) is extensively involved in the development and treatment of mental illnesses, including schizophrenia (8). For example, one study (9) showed that risperidone may improve cognitive impairment in patients through the upregulation of the functions of the BNDF-TrkB signalling system.

Dizocilpine maleate (MK-801), a non-competitive *N*-methyl-D-aspartate (NMDA) receptor, has been applied extensively in recent animal models of schizophrenia with glutamate dysfunction (10). Acute treatment of different doses of MK-801 can induce schizophrenia-like behavioural changes in rodents, including increases in spontaneous activities, stereotyped behaviours, sensory gating function damage, and a variety of abnormal cognitive behaviours (10-12). Antipsychotics can reverse the above cognitive behavioural alterations to different degrees; however, the underlying mechanisms require additional investigation. A previous study showed that the continuous administration of MK-801

(0.1 mg/kg) for 4 days during the neonatal stage significantly downregulated the levels of BDNF, TrkB, and p-TrkB in the hippocampus of adult rats (13). Kim *et al* also showed that the continuous intraperitoneal administration of MK-801 (0.6 mg/kg) significantly downregulated BDNF expression in the hippocampi of mice (14). However, to the best of our knowledge, few studies have examined the effect of acute MK-801 injection on the BDNF-TrkB signalling system.

The aims of the current study are two-fold. Firstly, we investigated whether and how acute MK-801 treatment affected animals' cognitive performance in the hippocampus-dependent spatial object recognition task as well as the BDNF-TrkB signalling system in the hippocampus. Secondly, we examined whether risperidone could reverse MK-801-induced behavioural and neurobiological alterations.

Materials and methods

Animals. A total of 52 adult male Sprague-Dawley rats, with a body weight of 300-350 g at the time of inclusion, were purchased from the animal laboratory of Jining Medical University (Shandong, China). The animals were randomly grouped using a random number table. The animals were housed in the same cage, 4 animals/cage, and had access to food and water *ad libitum*. The animals adapted to the feeding room for ≥7 days prior to the behavioural experiments. The room temperature was maintained at 23±2°C, humidity was maintained at 35-55%, and the circadian rhythm was 12 h (from 8:00 a.m. to 8:00 p.m.). Behavioural tests were completed from 9:00 a.m. to 1:00 p.m. The Ethics Committee of Jining Medical University approved the present study.

Drugs and pharmacological procedures. MK-801 and risperidone were purchased from Sigma (St. Louis, MO, USA). MK-801 was dissolved in normal saline, and risperidone was dissolved in 0.5% glacial acetic acid saline. Based on previous literature (15), 0.1 mg/kg MK-801 and risperidone were used. We chose a rather low dose of MK-801, because it has been established that low-dose MK-801 may induce cognitive deficits without affecting basic motor abilities, thus ruling out the potential influence of abnormal peripheral processes in cognitive performance. Drugs were administered through intraperitoneal injection, and the drug volumes were both 2 ml/kg. The control group received an equal volume of normal saline or 0.5 ml/kg glacial acetic acid saline.

Two animal cohorts were used in the present study. The first cohort included a total of 20 rats (10 animals per group), which were randomly assigned to the control group (vehicle) or the MK-801 (0.1 mg/kg) group, and received an intraperitoneal injection of MK-801 or vehicle 30 min before behavioural testing. After a one-week drug washout period, the animals received intraperitoneal injections of MK-801 or vehicle again and 30 min later they were sacrificed, with their brains removed for western blot analysis. The second cohort comprised 32 animals, which were randomly divided into four groups (8 animals per group): the control group (vehicle + vehicle), the MK-801 group (MK-801 + vehicle), the risperidone group (vehicle + risperidone), and the intervention group (MK-801 + risperidone). The interval between the drug administration times was 30 min. After

drug treatment, the animals were subjected to behavioural testing or sacrifice.

Spatial object recognition test. The task was performed as previously reported (16). Briefly, this task consisted of the habituation, familiarisation, and test phases. i) Habituation phase: Before the formal behavioural test, each animal was allowed to habituate to the test box for 10 min for 3 days to eliminate the effects of new environmental stimulation on their activity and exploration behaviours. ii) Familiarisation phase: Two solid aluminium cubes with a side length of 6 cm were placed in the two corners (A and B) of the test box. These objects were 9 cm from the two side walls, and the distance between these objects was 20 cm. The animals were placed inside, tracked and recorded for 10 min via video. iii) Recognition phase: After 60 min, the animals were placed inside the test box again to test for 10 min. During this phase, the object in corner A or B was moved to corner C. After each test, the odours were removed by wiping with 75% alcohol, and the box was dried for the next experimental group. The exploration time of the animals on each object was evaluated. Following the scoring criteria reported in previous studies (17), only when the animal's nose or forepaws were in contact with the object or directed to the object within 1 cm, was this scored as 'exploring' the object. Standing, sitting or leaning on the object was not scored as exploration. The preference index (PI) of the animals for the object in the new location was calculated as $PI = Tn/(Tn + To) \times 100\%$. In this formula, Tn represented the exploration time of the object in the new location, and To was the exploration time of the object in the old location. Animals with total exploration time of two objects <10 sec were not included in the data analysis.

Western blot analysis. Thirty minutes after the last drug injection, the animals were anesthetised using 20% chloral hydrate. After cervical dislocation, the hippocampal tissues were isolated on ice, quickly frozen using dry ice, and stored in a freezer at -70°C.

The tissues were removed prior to the experiments and thawed on ice, placed in a lysis buffer containing a variety of protease inhibitors, and mechanically lysed on ice. The total protein concentration was determined using a BCA protein analysis reagent kit (Pierce Biotechnology, Inc., Rockford, IL, USA). The amount of protein for loading was calculated. Proteins were denatured at 95°C for 10 min. Samples containing 30 μg of protein were subjected to 10% SDS-PAGE. After the electrophoresis was complete, the proteins on the gel were electro-transferred onto a PVDF membrane for 90 min. After the electro-transfer was complete, the membrane was washed with 10 ml of TBST for 2 min and blocked in a 10 ml TBST solution containing 5% non-fat milk powder for 60 min. The membrane was incubated with primary antibodies [BDNF: rabbit anti-BDNF, 1:1,000, Ab108319; Abcam (Cambridge, UK); TrkB: rabbit anti-TrkB, 1:1,000, sc-8316; Santa Cruz Biotechnology, Inc. (Dallas, TX, USA); p-TrkB: rabbit anti-phospho-TrkB, 1:2,000, ABN1381; Millipore Corp. (Billerica, MA, USA): β-actin: mouse anti-β-actin, 1:20,000, CS-3700; Cell Signaling Technology, Inc. (Danvers, MA, USA)] at 4°C on

Table I. Acute MK-801 injection altered the spatial object recognition ability of rats (means ± SD).

Groups	No. of rats	Activity distance during the habituation phase (m)	Exploration time during the familiarisation phase (s)	Exploration time for the objects in new locations (s)	Exploration time for the objects in old locations (s)	PI of the objects in new locations (%)
Control	10	42.26±2.54	65.05±7.78	44.27±6.31	20.65±3.97[b]	69.20±3.35
MK-801 (0.1 mg/kg)	10	44.07±2.64	78.83±8.52	43.84±4.70	35.12±3.75	54.89±3.13[a]

Independent sample t-test compared with the control group, [a]P<0.01. Paired sample t-test between the new and old locations of objects with regard to exploration time, [b]P<0.01. SD, standard deviation; MK-801, dizocilpine maleate; PI, preference index.

a shaker overnight. After washing 3 times with TBST, the membrane was incubated with HRP-labelled goat anti-rabbit or anti-mouse secondary antibody (Santa Cruz Biotechnology, Inc.) at 1:5,000 or 1:20,000, respectively. After incubation at room temperature for 2 h, the membrane was washed with TBST 3 times. The proteins were exposed in a dark room using ECL. The exposure time was adjusted according to the fluorescence intensity, and the images were developed and fixed. The optic density values of the bands were analysed using Quantity One software. The optic density values of all the target bands were normalised based on the optic density values of the corresponding β-actin bands. All of the data were compared with those in the control group and presented as percentages (the control group was set at 100%).

Statistical analysis. The experimental results are presented as means ± SD. Statistical analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). The comparison between the two groups was performed using an independent samples t-test. The comparison between the time exploring objects in the novel and familiar locations was carried out using paired samples t-tests. The one sample t-test was used to examine whether the PI index in each group was significantly higher than the chance level, i.e., 50%. The risperidone intervention experiment analysis was performed using two-factor analysis of variance (ANOVA). MK-801 (vehicle vs. MK-801) and risperidone (vehicle vs. risperidone) were used as between group factors. If the interaction was significant, then the simple effect analysis was performed. Homogeneity of variance was examined using Levene's test. If the variance was homogenous, then the least significant difference (LSD) method was performed for subsequent tests; if the variance was heterogeneous, then the Games-Howell method was performed for subsequent tests. P<0.05 was considered to indicate a statistically significant difference.

Results

Acute MK-801 injection decreases the spatial object recognition ability of rats. The differences in the activity during the habituation phase and the total time to explore objects in the familiarisation phase between MK-801-treated and vehicle-treated animals were not significant (P>0.05), indicating that acute injection of MK-801 (0.1 mg/kg) did not significantly affect the movement ability or the animals'

natural exploration of objects. The variance of all the data were homogeneity (Table I).

During the test phase, a paired samples t-test showed that the time used to explore objects at new locations by the animals in the control group was significantly longer than that used to explore objects at old locations (t_9=4.333, P<0.001). However, the times used to explore the objects at the new and old locations by the animals in the MK-801 group did not significantly differ (t_9=1.904, P=0.089). One sample t-test by comparing PI to 50% further demonstrated that animals in the control group showed clear preference to the object in the novel location (t_9=5.732, P<0.001), whereas animals receiving MK-801 treatment failed to discriminate the novel from the familiar object location (t_9=1.566, P=0.152). The PI for the objects at the new locations between these two groups was also compared using an independent samples t-test. The results showed that the PI of the control animals was significantly higher than that of the MK-801 group (t_{18}=3.122, P<0.001). The above results indicated that rats in the MK-801 group did not accurately recognize the new or old locations of the objects and that their spatial object recognition ability was significantly lower than that of the control group.

Acute MK-801 injection downregulates the function of the hippocampal BDNF-TrkB signalling system. Although the acute intraperitoneal injection of MK-801 did not significantly affect the concentration of BNDF or the expression of the TrkB receptor in the rat hippocampus (P>0.05), MK-801 significantly downregulated the expression level of p-TrkB in the hippocampus (t_{18}=3.385, P<0.001). p-TrkB is the active form of the TrkB receptor; its levels can represent the strength of the function of the BDNF-TrkB signalling system. Thus, these results showed that acute MK-801 injection downregulated the function of the hippocampal BDNF-TrkB signalling system (Fig. 1).

Risperidone reverses the role that MK-801 plays in the change in the spatial object recognition ability of rats. As shown in Table II, there were no significant differences among the four groups regarding the distance travelled during the habituation phase and the total time used to explore the objects during the familiarisation phase (Ps>0.05), indicating that both MK-801 (0.1 mg/kg) and risperidone (0.1 mg/kg) did not significantly affect the movement ability or the object preferences of the animals.

Table II. Risperidone reversed the role that MK-801 plays regarding the spatial object recognition ability changes in rats (means ± SD).

Group	Number of rats	Activity distance during the habituation phase (m)	Exploration time during the familiarisation phase (s)	Exploration time for the objects in new locations (s)	Exploration time for objects in old locations (s)	PI of the objects in new locations (%)
Control	8	37.54±1.84	62.20±6.79	42.78±5.23	18.43±2.24[d]	68.53±4.28[c]
MK-801	8	37.21±3.13	71.33±6.63	34.99±4.58	33.83±4.47	50.78±3.99[a]
Risperidone	8	33.97±3.58	54.65±4.15	40.23±4.85	19.68±2.05[d]	66.19±3.46[c]
Intervention	8	36.17±2.38	64.21±7.95	41.24±6.69	21.23±2.52[d]	64.95±3.31[b]

A two-factor analysis of variance and the LSD test compared with the control group, [a]$P<0.01$, and compared with the model group, [b]$P<0.05$ and [c]$P<0.01$. A paired samples t-test regarding the exploration time for objects in new and old locations, [d]$P<0.01$. SD, standard deviation; MK-801, dizocilpine maleate; PI, preference index; LSD, least significant difference.
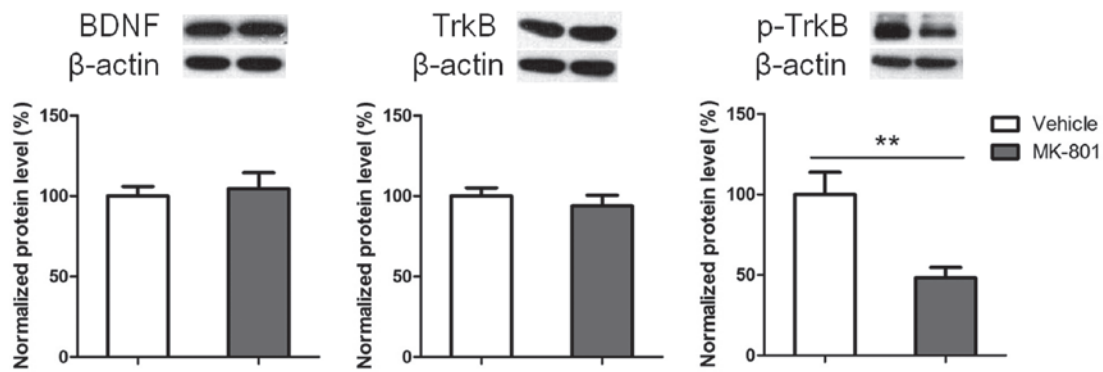

Figure 1. Effects of acute MK-801 injection on the BDNF-TrkB signalling system in the rat hippocampus. An independent samples t-test compared MK-801 injection with the control group. ([**]$P<0.01$). MK-801, dizocilpine maleate; BDNF, brain-derived neurotrophic factor; TrkB, tyrosine receptor kinase B.
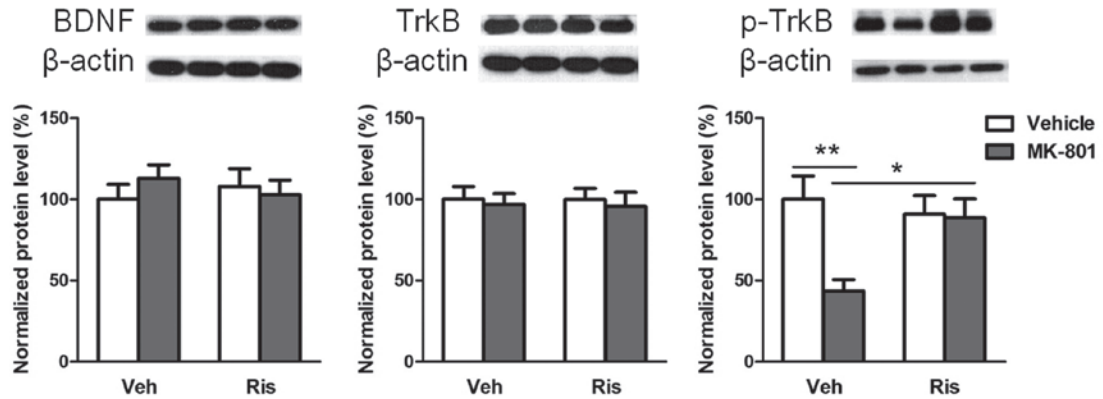

Figure 2. The intervention functions of risperidone regarding the changes in the function of the BDNF-TrkB signalling system in the rat hippocampus caused by MK-801. Two-factor analysis of variance and an LSD test were performed; compared with the control group, [**]$P<0.01$; compared with the model group ([*]$P<0.05$). BDNF, brain-derived neurotrophic factor; TrkB, tyrosine receptor kinase B; MK-801, dizocilpine maleate; LSD, least significant difference.

The results of the two-factor ANOVA regarding the PI among the groups of animals showed that the main effect of MK-801 ($F_{(1,28)}=6.303$, $P=0.018$) and the interaction between MK-801 and risperidone ($F_{(1,28)}=4.762$, $P=0.038$) were significant, whereas the main effect of risperidone was not significant ($F_{(1,28)}=2.448$, $P=0.129$). An additional simple main effect analysis showed that the PI of the animals in the MK-801 group for objects at new locations significantly decreased compared with that of the control group ($P<0.001$). The PI value of the intervention group did not significantly differ from that of the control group ($P>0.05$) but was significantly higher than that of the MK-801 group ($P<0.001$). One sample t-test by comparing PI to 50% further demonstrated that animals received MK-801 treatment only spent comparable time exploring novel and familiar object positions ($P>0.05$); nevertheless, the other three groups showed clear preference to the object in the novel

location (P<0.001). This was confirmed by a paired samples t-test showing that except for the MK-801 group (P>0.05), all of the animals in the other groups spent significantly more time exploring the object in the novel location (Ps<0.001). The above results indicate that risperidone reversed the role that MK-801 plays in the spatial object recognition ability changes of rats.

Intervention of risperidone on the functional changes to the BDNF-TrkB signalling system in the rat hippocampus caused by MK-801. A two-factor ANOVA showed that the main effects of MK-801 and risperidone as well as their interaction were not significant with regard to the expression levels of BDNF and TrkB (Ps>0.05). However, the main effect of MK-801 ($F_{(1,28)}$=6.552, P=0.016) as well as the interaction between MK-801 and risperidone ($F_{(1,28)}$=5.550, P=0.026) were significant with regard to the p-TrkB expression level, whereas the main effect of risperidone was not significant ($F_{(1,28)}$=2.423, P=0.131). An additional simple main effect analysis showed that the hippocampal p-TrkB level of the MK-801 group was significantly decreased compared with that of the control group (P<0.01). The p-TrkB level of the intervention group did not significantly differ from that of the control group (P>0.05), but it was significantly higher than that of the MK-801 group (P=0.010). The above results indicate that risperidone reversed the role that MK-801 plays in the downregulation of p-TrkB in the rat hippocampus and repaired the function of the BDNF-TrkB signalling system (Fig. 2).

Discussion

The present study used acute intraperitoneal injection of the NMDA receptor antagonist MK-801 to establish an animal model of schizophrenia. First, the results showed that an injection at 0.1 mg/kg deteriorated the spatial object recognition ability of adult male rats and modelled the reduction of spatial learning and memory abilities in patients with schizophrenia. These results have excellent face validity. Additionally, the acute intraperitoneal injection of MK-801 downregulated the function of the BNDF-TrkB signalling system in rat hippocampus. This finding is consistent with the reduction of BDNF levels in the cerebrospinal fluid of patients with schizophrenia and the reduction of the BDNF protein and mRNA levels in cognition-related brain areas such as the prefrontal cortex and hippocampus. These results support the neurotrophic factor hypothesis of schizophrenia and showed good construct validity. Finally, the atypical antipsychotic drug risperidone (0.1 mg/kg) significantly reversed the aforementioned behavioural and molecular changes caused by MK-801 and showed good predictive validity. These results provide a basic theoretical basis for the improvement of cognitive impairment in patients with schizophrenia via the atypical antipsychotic drug, risperidone.

It has been previously confirmed that the acute and chronic administration of NMDA receptor antagonists damages the learning and memory ability of rodents (10,12,18-20). Consistent with results of the present study, Nilsson *et al* (19) and Rogóź and Kamińska (20) showed that the intraperitoneal administration of MK-801 (at 0.1 and 0.2 mg/kg) 30 min prior to the test during the familiarisation phase deteriorated the recognition abilities of rats regarding novel objects. However,

to the best of our knowledge, no report has examined the effect of the acute intraperitoneal injection of MK-801 on the spatial object recognition ability of rats. To the best of our knowledge, this study was the first to show that the acute peritoneal injection of MK-801 deteriorates the spatial object recognition ability of rats. This finding adds to the behavioural phenotype of this model.

The function of risperidone regarding the improvement of the cognitive symptoms of patients with schizophrenia remains controversial (21). Takekita *et al* performed a 6-month randomised, controlled, and double-blinded trial and found that risperidone significantly improved cognitive skills such as attention and verbal fluency (6). A pre-clinical study also showed that the continuous intraperitoneal administration of risperidone (0.2 mg/kg) for 14 days reversed the spatial learning, memory, and attention deficits caused by MK-801 in rats (5). Rogóź and Kamińska found that a low dose of risperidone (0.01 mg/kg) did not reverse the changes in object recognition ability caused by MK-801; however, a higher dose of risperidone (0.1 mg/kg) successfully reversed the cognitive deterioration caused by MK-801 (20). The present study showed that risperidone (0.1 mg/kg) reversed the role that MK-801 played in the deterioration of the spatial objective recognition ability of rats, providing pre-clinical evidence for cognitive function improvement in patients with schizophrenia via the atypical antipsychotic drug risperidone.

How acute MK-801 treatment may affect hippocampal BDNF-TrkB signalling system is currently unclear. Hill *et al* (22) showed that the acute intraperitoneal injection of MK-801 (0.05 mg/kg) significantly downregulated the expression of BDNF protein in the hippocampus after 24 or 48 h. The results of the present study showed that after 30 min of acute MK-801 injection, the expression levels of BDNF and TrkB receptor were not significantly changed in the hippocampus. This finding may be associated with the different time points of detection (i.e., immediate vs. long-term effects). However, the current findings have shown that an acute MK-801 injection significantly downregulated the phosphorylation level of TrkB after 30 min. As the active form of the TrkB receptor, the expression level of p-TrkB likely reflects the activity of the BNDF-TrkB signalling system. Therefore, the acute MK-801 injection downregulated the function of the BNDF-TrkB signalling system and partially simulated the pathogenic mechanism of patients with schizophrenia.

The mechanism that underlies the improvement of cognitive symptoms in patients with schizophrenia via risperidone has not been elucidated. However, one study showed that risperidone may improve cognitive impairment in patients through the upregulation of the functions of the BNDF-TrkB signalling system (9). The present study showed that acute MK-801 injection upregulated the functions of the BNDF-TrkB signalling system to improve the spatial learning and memory abilities of rats. However, this study found that risperidone did not affect the BNDF-TrkB signalling system. A study in China showed that risperidone upregulated the BNDF-TrkB signalling pathway in the left and right prefrontal cortex, left and right temporal cortex, and hippocampus (23). The differences between these results may be associated with inconsistent drug doses (0.1 vs. 0.25 mg/kg) and the length of

drug administration (one-time acute administration vs. continuous drug administration for 14 days).

The present study showed that the atypical antipsychotic drug risperidone reversed the cognitive behavioural damage and changes in the hippocampal BDNF-TrkB signalling system caused by MK-801, suggesting that the insufficiency of the function of the hippocampal BDNF-TrkB signalling system may be involved in the development of schizophrenia. However, the mechanism through which risperidone regulates the BDNF-TrkB signalling system to improve the cognitive function of patients with schizophrenia as well as how the BDNF-TrkB signalling system participates in the development of schizophrenia require additional investigation.

Acknowledgements

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