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Fluoxetine attenuates prepulse inhibition deficit induced by neonatal administration of MK-801 in mice

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Increasing evidence supports schizophrenia may be a neurodevelopmental and neurodegenerative disorder. Fluoxetine, a selective serotonin reuptake inhibitor, has been reported to have neuroprotective effects and be effective in treating neurodegenerative disorders including schizophrenia. The objective of the present study was to evaluate the effect and underlying neuroprotective mechanism of fluoxetine on the sensorimotor gating deficit, a schizophrenia-like behavior in a neurodevelopmental schizophrenic mouse model induced by MK-801, an *N*-methyl-D-aspartate glutamate receptor antagonist. On postnatal day 7, mouse pups were treated with a total seven subcutaneous daily injections of MK-801 (1 mg/kg/day), followed by intraperitoneal injection of fluoxetine (5 or 10 mg/kg/day) starting on postnatal day 14 in the MK-801-injected mice for 4 weeks. The sensorimotor gating deficit in mice was measured by prepulse inhibition (PPI) behavioral test on postnatal day 43. After the behavioral test, the protein expression of brain-derived neurotrophic factor (BDNF) was measured by western blot or ELISA in the frontal cortex of mice. Our results showed fluoxetine attenuated PPI deficit and the decrease of cerebral BDNF expression in the MK-801-injected mice. These results suggest that fluoxetine can be used to treat sensorimotor gating deficit in a neurodevelopmental mouse model of schizophrenia, and the attenuating effect of fluoxetine on sensorimotor gating deficit may be related to fluoxetine's neuroprotective effect targeting on the modulation of cerebral BDNF.

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Introduction

Schizophrenia may be a neurodevelopmental and neurodegenerative disorder, neonatal administration of *N*-methyl-D-aspartate (NMDA) receptor antagonists such as MK-801 or phencyclidine during brain neurodevelopmental stage induces cerebral neurodegeneration and the symptoms including sensory gating impairment of schizophrenia in rodents [1,2]. Sensory gating can be measured by prepulse inhibition (PPI) which refers to the inhibition of a startle reflex produced by a preceding weak prepulse stimulus [3]. Schizophrenia is characterized by positive and negative symptoms which are often accompanied by depression and cognitive deficits. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, has been used to treat depression in schizophrenia, and has shown to be effective in augmenting therapeutic effects of second-generation antipsychotics in schizophrenia [4]. Our previous study has shown fluoxetine improved learning and emotional disturbances in a transgenic mouse model of Alzheimer's disease, another common neurodegenerative disorder of the central nervous system [5]. Fluoxetine may exert its anti-depressive and neuroprotective effects through increasing the level of brain-derived neurotrophic factor (BDNF) in the brain of animals [6], and reduced expression of BDNF has been implicated in the sensory gating impairment and the pathophysiology of schizophrenia [7].

Therefore, we hypothesize that fluoxetine is neuroprotective and may be able to attenuate sensorimotor gating deficit in schizophrenia in the present study. To test this hypothesis, the effects of fluoxetine on the possible PPI deficit and the expression change of BDNF, a well-known neuroprotective protein, in the frontal cortex were evaluated in a neurodevelopmental schizophrenic mouse model induced by MK-801.

Materials and methods

Animals

All animal experimental procedures were reviewed and approved by the Care and Use of Laboratory Animal

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Ethics Committee of Xiamen Xian Yue Hospital. The experimental mice were obtained from timed pregnant ICR (CD1) mice (Xiamen University Laboratory Animal Center, Xiamen, Fujian Province, China). Female mice were housed three to five per cage, with free access to food and water under controlled laboratory conditions (a 12:12 h light/dark cycle with room temperature 20°C ± 1°C). Behavioral testing was performed in the light phase.

Drug treatment

MK-801 [(+)-MK-801 hydrogen maleate] purchased from Sigma-Aldrich (St. Louis, Missouri, USA) and fluoxetine obtained from National Institutes for Food and Drug Control (Beijing, China, CAS number:59333-67-4) were both freshly dissolved in saline. The total experimental period was 38 days, from postnatal day 7–44. On postnatal day 7, the mouse pups were treated with a total seven subcutaneous daily injections of MK-801 (0 or 1 mg/kg/day), followed by intraperitoneal injection of fluoxetine (0, 5 or 10 mg/kg/day) starting on postnatal day 14 in the MK-801-injected mice for 4 weeks. The volume of all injected solutions was 10 mL/kg. Totally 40 female mice were randomly assigned into four groups ($n = 10$ in each group): saline + saline (CON), MK-801 + saline (MK), MK-801 + fluoxetine 5 mg/kg/day (MK + F5), MK-801 + fluoxetine 10 mg/kg/day (MK + F10). In order to evaluate the effects of fluoxetine without MK-801 on PPI and cerebral BDNF in mice, the experiment of measuring the effects of fluoxetine in the Con mice was also included: on postnatal day 7, the mouse pups were treated with a total seven subcutaneous daily injections of saline, followed by intraperitoneal injection of fluoxetine (0 or 10 mg/kg/day) starting on postnatal day 14 in the saline-injected mice for 4 weeks; totally 12 female mice were randomly assigned into two groups ($n = 6$ in each group): saline + saline (CON), saline + fluoxetine 10 mg/kg/day (F10).

Prepulse inhibition of the startle response test

On postnatal day 43, the sensorimotor gating in mice was evaluated in a PPI test [8]. PPI of the startle response provides an operational measure of sensorimotor gating, a putative neural mechanism that inhibits the processing of extraneous sensory, cognitive, and motor information [9]. PPI refers to the normal reduction in startle magnitude that occurs when an abrupt startling stimulus is preceded 30–500 ms by a weak prestimulus [9]. Disruption of PPI has been well documented in schizophrenia patients [10,11].

Each mouse was placed into a small Plexiglas cylinder connecting motion sensors within a large sound-attenuating chamber (San Diego Instruments, San Diego, California, USA). The motion sensors recorded voltage changes in arbitrary units (mV) that were digitized and stored by the computer controlling the delivery of acoustic stimuli through loudspeakers mounted 21 cm above the plastic cylinders. Motion sensors were calibrated daily with the SR-LAB Standardization Unit (San Diego Instruments). The background sound level (70 dB) and calibration of the acoustic stimuli were confirmed daily with a digital sound level meter. Startle pulse was set to 120 dB and prepulse intensities were set to 3 dB (PP3), 6 dB (PP6), and 12 dB (PP12) above background noise level. The test session consisted of 64 trials and included five trial types (startle pulse-alone, PP3, PP6, PP12, and no-stimulus) in four blocks. Blocks 1 and 4 included six startle pulse-alone trials in each block, and blocks 2 and 3 included six startle pulse-alone trials, five PP3, five PP6, five PP12, and five no-stimulus in each block. Duration of acoustic stimuli was set to 20 ms for prepulses and 40 ms for startle pulses, and interstimulus interval between prepulse and startle pulse was set to 100 ms (from onset to onset).

After a 5-min habituation period, PPI-test sessions were conducted. The intertrial intervals with an average of 15 s were varied from 5 to 23 s in pseudo-random order in the session, and a total PPI test time for each mouse was approximately 23 min. The maximum response in the 65-ms recording window was used as the startle amplitude for each trial. Levels of PPI at each prepulse sound level were calculated in blocks 2 and 3 as (1-averaged response amplitude in trials with a prepulse stimulus and startle stimulus/averaged response amplitude in trials with the startle stimulus alone) × 100%. The averaged response amplitude in trials with the startle stimulus alone and the averaged response amplitude in trials with no-stimulus in blocks 2 and 3 were also calculated.

Western blot analysis

One day after the behavioral test on postnatal day 44, the mice were sacrificed and perfused with 0.1 M PBS (pH 7.4), and the frontal cortex from right hemisphere was dissected, frozen in dry-ice powder and stored at –70°C until used [12]. The frontal cortex samples from each mouse were homogenized at 4°C in a lysis buffer [50 mM Tris-HCl, 150 mM NaCl, 10 mM EDTA, 10 mM NaF, 1 mM sodium orthovanadate, 1% NP-40, 10 mM sodium pyrophosphate decahydrate, 0.5 mM dithiothreitol, 0.2 mM phenylmethanesulfonyl fluoride, and Complete Mini Protease Inhibitor Cocktail (Roche Diagnostics, Laval, Qc, Canada); pH 7.4]. The lysates were centrifuged twice at 10 000*g* for 10 min. The protein concentration of the supernatant was determined using a bicinchoninic acid protein assay kit (Pierce, Rockford, Illinois, USA). An aliquot of each sample containing equal amounts of total protein (50 μg/8–9 μL) was denatured in a protein loading buffer, separated on a 12% polyacylamide gel, and subsequently transferred to a polyvinylidene difluoride membrane (Bio-Rad, Hercules, California, USA). After being blocked by 5% skim milk powder in TBST (10 mM Tris-HCl, 150 mM NaCl, 0.05% Tween 20; pH 7.4), the membranes were incubated overnight at 4°C with an

anti-BDNF (14 kDa, 1:1000, rabbit polyclonal; Santa Cruz Biotechnology, Santa Cruz, California, USA) antibody or anti-β-actin (42 kDa, 1:5000, monoclonal; Sigma-Aldrich) antibody. The membranes were then washed with TBST and probed with horseradish peroxidase-conjugated anti-rabbit or anti-mouse secondary antibody for 2 h at room temperature. The immune complexes were detected by an electrochemiluminescence chemiluminescence system (Amersham Biosciences, Buckinghamshire, UK) and exposed to high-performance chemiluminescence film (Amersham, Buckinghamshire, UK). The BDNF or β-actin band in the film was scanned using Vista Scan software. Then the band intensities (optical density) of BDNF or β-actin were analyzed by densitometry (density × area) using an Image-Pro Plus image analysis system (Media Cybernetics, Silver Spring, Maryland, USA), and the BDNF/β-actin ratio was calculated. The results of BDNF/β-actin ratio in each group were standardized to the measurement results of the CON group (as 100%).

ELISA measurement

For the experiment of measuring the effect of fluoxetine on cerebral BDNF in the Con mice, one day after the behavioral test on postnatal day 44, the mice were sacrificed and perfused with 0.1 M PBS (pH 7.4). The frontal cortex from right hemisphere was dissected on the back surface of an iced tissue culture dish covered by a PBS-wetted filter paper and was kept for BDNF ELISA measurement. The level of BDNF was quantified using a commercial Mouse BDNF ELISA kit (Fitzgerald Industries International, North Acton, Massachusetts, USA) according to the manufacturer's protocol. All measurements were done in duplicate. The level of BDNF was corrected for total protein of brain tissue and dilution factor and was standardized to that in the Con group (as 100%).

Statistical analysis

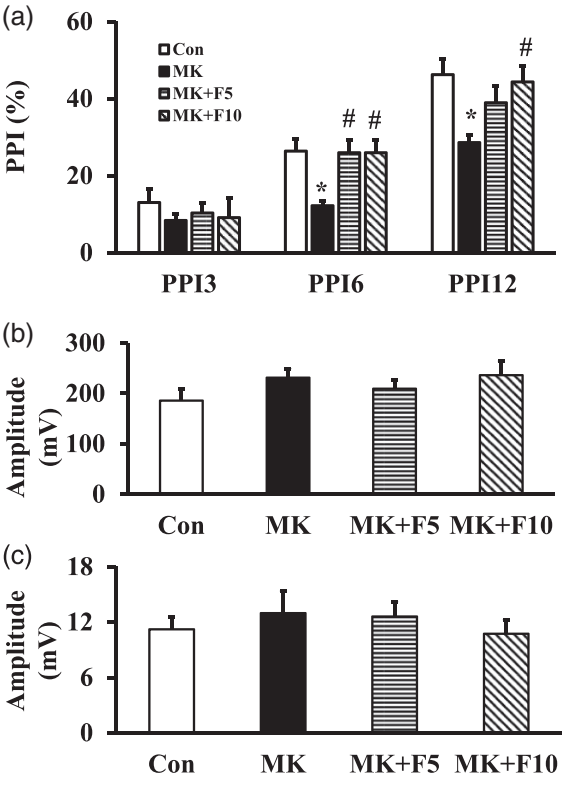
All results were expressed as means ± SEM. The significance of differences was determined by one-way analysis of variance (ANOVA), followed by a Newman–Keuls post-hoc test for multiple comparisons. A two-tailed *t*-test for independent samples was used for two-group comparisons between Con group and F10 group. A *P* value of less than 0.05 was regarded as statistically significant.

Results

Fluoxetine attenuated prepulse inhibition deficit in the MK-801-treated mice

To investigate the sensorimotor gating in mice after MK-801 or (and) fluoxetine treatment, a PPI test was performed. As shown in Fig. 1a, one-way ANOVA showed that MK-801 and fluoxetine produced a significant change in the PPI (%) at PPI6 [F (3,36) = 5.88, $P < 0.01$] and PPI12 [F (3,36) = 4.52, $P < 0.01$] in mice. A post-hoc analysis revealed that PPI (%) at PPI6 and PPI12 in the MK-801 mice was less than that in the control mice and that fluoxetine significantly attenuated the decrease of PPI (%) in the MK-801 mice (Fig. 1a). There was no difference in PPI (%) at PPI3 among the Con, MK, MK + F5, and MK + F10 groups, and MK-801 and fluoxetine had no effect on PPI (%) at PPI3 in the PPI test (Fig. 1a).

Fig. 1



PPI (a), auditory startle respone to the startle stimulation (b), and auditory response of the no-stimulus (c) in a PPI test in the mice of control (Con), MK-801 (MK), MK-801 + fluoxetine 5 mg/kg/day (MK + F5), and MK-801 + fluoxetine 10 mg/kg/day (MK + F10) groups. Fluoxetine attenuated the decrease of the PPI (%) in the MK-801 mice at PPI6 and PPI12, and fluoxetine and MK-801 had no effects on the PPI (%) at PPI3, auditory startle respone to the startle stimulation and auditory response of the no-stimulus. $n = 10$ in each group. On postnatal day 7, the mouse pups were treated with a total 7 subcutaneous daily injections of MK-801 (0 or 1 mg/kg/day), followed by intraperitoneal injection of fluoxetine (0, 5 or 10 mg/kg/day) starting on postnatal day 14 in the MK-801-injected mice for 4 weeks. On postnatal day 43, the sensorimotor gating in mice was evaluated in a PPI test. Results are expressed as means ± SEM. *$P < 0.05$ vs. Con, #$P < 0.05$ vs. MK. PPI, prepulse inhibition.

The auditory startle response to the startle stimulus alone was measured in the PPI section in mice. As shown in Fig. 1b, there was no significant difference in the auditory startle response to the startle stimulus in the PPI section among the Con, MK, MK + F5, and MK + F10 groups.

In order to evaluate the basal motor activity in the cylinder during the PPI test, mouse movements were evaluated by the no-stimulus trials without any stimulation.

As shown in Fig. 1c, there was no significant difference in the amplitude of response for no-stimulus in the PPI section among the Con, MK, MK+F5, and MK+F10 groups.

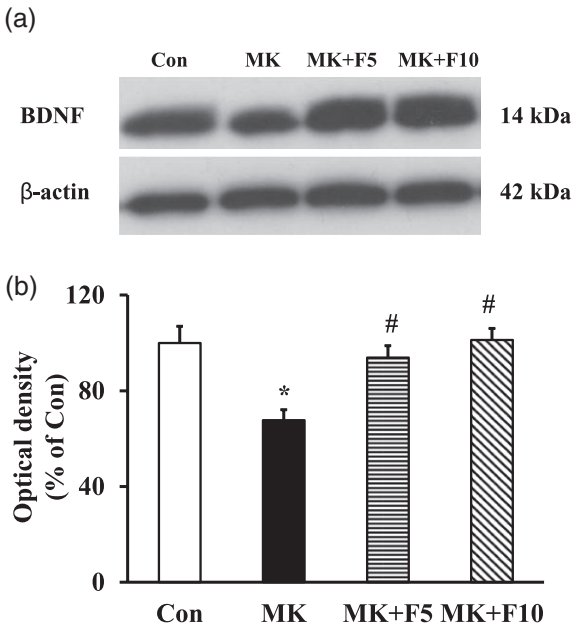
Fluoxetine attenuated the decrease of brain-derived neurotrophic factor level in the frontal cortex of MK-801-treated mice

To investigate the neuroprotective mechanism of fluoxetine involving in its beneficial effects on sensorimotor gating deficit in the MK-801 mice, the expression of BDNF protein level in the frontal cortex of mice was measured by western blot. Representative western blot bands of BDNF in the mice of Con, MK, MK+F5, and MK+F10 are shown in Fig. 2a. The optical densities of western blot bands were quantified. As shown in Fig. 2b, one-way ANOVA showed that MK-801 and fluoxetine produced a significant change in the expression of BDNF in the frontal cortex of mice [F (3,20) = 8.44, P < 0.001] in mice. A post-hoc analysis revealed that the expression of BDNF in the frontal cortex of MK-801 mice was less than that of control mice and that fluoxetine significantly attenuated the decrease of the expression of BDNF in the frontal cortex of MK-801 mice (Fig. 2b).

Fluoxetine had no effect on prepulse inhibition behavior or cerebral brain-derived neurotrophic factor level in the control mice

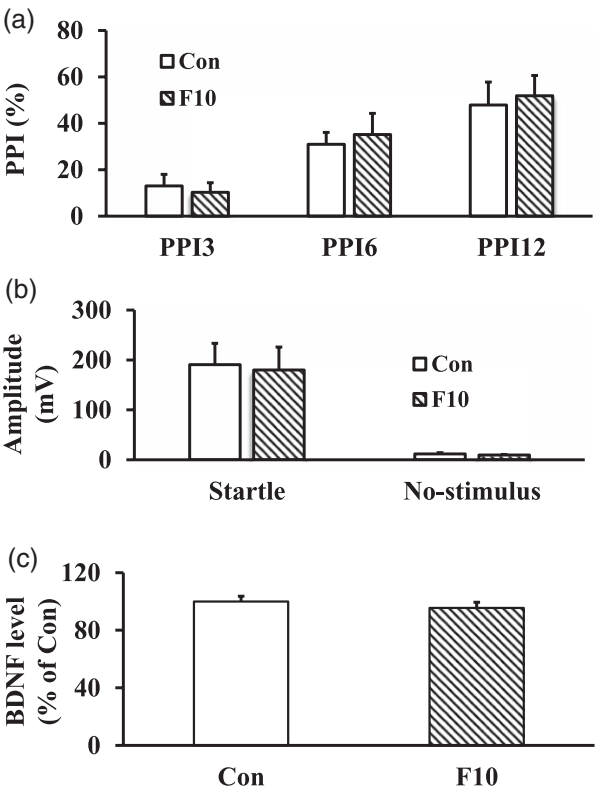
As shown in Fig. 3a, there was no significant difference in PPI (%) between the Con and F10 groups at PPI3 (P > 0.05; Con vs. F10: 12.97 ± 4.98 vs. 10.24 ± 4.11), PPI6 (P > 0.05; Con vs. F10: 30.96 ± 5.12 vs. 35.14 ± 9.14) and PPI12 (P > 0.05; Con vs. F10: 47.83 ± 9.89 vs. 51.854 ± 8.7). In addition, as shown in Fig. 3b, there was no significant difference in the amplitude (mV) of response for startle pulse alone (P > 0.05; Con vs. F10: 190.81 ± 42.55 vs.

Fig. 2



(a) Representative western blot bands of BDNF protein expression in the frontal cortex of mice in control (Con), MK-801 (MK), MK-801 + fluoxetine 5 mg/kg/day (MK+F5), and MK-801 + fluoxetine 10 mg/kg/day (MK+F10) groups. (b) Histogram showing the quantification of the immmunochemically reactive bands in the western blot of BDNF in the frontal cortex of mice in the Con, MK, MK+F5 and MK+F10 groups. Fluoxetine attenuated the decrease of BDNF level in the frontal cortex of MK-801 mice. n=6 in each group. On postnatal day 7, the mouse pups were treated with a total 7 subcutaneous daily injections of MK-801 (0 or 1 mg/kg/day), followed by intraperitoneal injection of fluoxetine (0, 5 or 10 mg/kg/day) starting on postnatal day 14 in the MK-801-injected mice for 4 weeks. One day after PPI behavioral testing, the mice were sacrificed for BDNF protein analysis by western blot. Results are expressed as means ± SEM. *P<0.05 vs. Con, #P<0.05 vs. MK. BDNF, brain-derived neurotrophic factor; PPI, prepulse inhibition.

Fig. 3



PPI (a), auditory respone to the startle pulse alone and the no-stimulus (b) in a PPI test and BDNF protein level in the frontal cortex (c) of mice in the control (Con) and the fluoxetine 10 mg/kg/day (F10) groups. Fluoxetine had no effect on PPI behavior or cerebral BDNF level in the control mice. n=6 in each group. On postnatal day 7, the mouse pups were treated with a total 7 subcutaneous daily injections of saline, followed by intraperitoneal injection of fluoxetine (0 or 10 mg/kg/day) starting on postnatal day 14 in the saline-injected mice for 4 weeks. On postnatal day 43, the sensorimotor gating in mice was evaluated in a PPI test. One day after PPI behavioral testing, the mice were sacrificed for BDNF protein analysis by ELISA. Results are expressed as means ± SEM. BDNF, brain-derived neurotrophic factor; PPI, prepulse inhibition.

180.08 ± 45.80) and no-stimulus ($P > 0.05$; Con vs. F10: 11.57 ± 2.50 vs. 9.37 ± 1.33) between the Con and F10 groups.

To investigate the effect of fluoxetine on cerebral BDNF in the Con mice, the BDNF level in the frontal cortex of mice was measured by ELISA. As shown in Fig. 3c, there was no significant difference in the cerebral BDNF level (the Con group as 100%) between the Con and F10 groups [$P > 0.05$; Con vs. F10: (100 ± 3.62)% vs. (95.53 ± 3.90)%].

Discussion

Administration of NMDA antagonists during brain maturation could induce cellular and behavioral alterations that mirror symptoms of schizophrenia [1]. The deficit of sensorimotor gating affecting the processing of extraneous sensory, cognitive, and motor information is a characteristic symptom of schizophrenia, and sensorimotor gating impairment may be correlative to the cognitive deficits and positive symptoms in schizophrenia [9,11,13]. PPI of the startle response provides an operational measure of sensorimotor gating, and disruption of PPI has been well documented in schizophrenia patients [10,11,13]. Consistent with previous studies that presented PPI deficit in the schizophrenia rodent models of NMDA antagonists [14,15], the mice have demonstrated the deficit of sensorimotor gating in a PPI test after neonatal administration of MK-801. In addition, we have demonstrated fluoxetine could attenuate PPI deficit in the MK-801-treated mice. Previous study has shown fluoxetine treatment from postnatal day3 to postnatal day 21 attenuated prenatal hypoxia-induced PPI deficit in mice [16]. In the present study, the auditory startle response to the startle stimulus alone and basal motor activity in the no-stimulus trials was measured in the same PPI section in mice. There were no response differences in startle pulse alone and no-stimulus trials among the control, the fluoxetine-treated control, the MK-801-injected, and the fluoxetine-treated Mk-801 mice. Therefore, the attenuating effect of fluoxetine on the MK-801-induced PPI deficit was not due to the effect of fluoxetine on the changes of the auditory startle response and basal motor activity.

Fluoxetine may attenuate the MK-801 (from postnatal day 7 to 13)-induced PPI deficit by modulating cerebral BDNF level. Repeated administration of MK-801 reduced the cerebral expression of BDNF and induced memory impairment in rats [17]. Fluoxetine, an SSRI antidepressant, may exert its anti-depressive and neuroprotective effects through increasing the level of BDNF in the brain of animals [6]. Fluoxetine has been used to treat depression in schizophrenia and has shown to be effective in augmenting therapeutic effects of second-generation antipsychotics in schizophrenia [4]. BDNF signaling pathway may be involved in the pharmacological mechanism of combined SSRI-antipsychotic treatment in schizophrenia [18]. BDNF, a neuroprotective protein, is the most abundant neurotrophin in the brain, and its expression in hippocampus and prefrontal cortex can be affected by prenatal stress [19]. BDNF regulates neuronal proliferation, survival, and brain development, and represents a potentially relevant gene for schizophrenia [20]. Reduced expression of cerebral BDNF has been implicated in the pathophysiology of schizophrenia and has been considered to be related to the deficit of PPI, a behavioral endophenotype of schizophrenia [7,21]. There was an altered PPI of the acoustic startle response in an early postnatal hypoxia BDNF-deficient mouse model of schizophrenia [22]. Clozapine, an atypical antipsychotics for schizophrenia treatment, attenuated the PPI deficits and modulated the alteration of BDNF mRNA expression in the prefrontal cortex of rats suffered adolescent social isolation [23]. Therefore, modulating cerebral BDNF may be one of the important mechanisms of fluoxetine working similarly as atypical antipsychotics in reserving sensorimotor gating function in schizophrenia. However, further studies are necessary to elucidate the role of BDNF and other neuroprotective factors in the attenuating effect of fluoxetine in the PPI deficits and other schizophrenia-like behaviors in schizophrenia animal models.

Conclusion

The novel findings of the present study are that fluoxetine can attenuate sensorimotor gating deficits in a neurodevelopmental mouse model of schizophrenia induced by neonatal administration of MK-801, and indicates that the attenuating effect of fluoxetine on the MK-801-induced sensorimotor gating deficits may be related to fluoxetine's neuroprotective effect targeting on the modulation of cerebral BDNF.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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