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Haloperidol and Clozapine Reverse MK-801-Induced Deficits in Hypoactivity, but Not the Impairment of Spatial Memory in Sprague-Dawley Rats

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Abstract: Blockade of the NMDA receptor by the use of MK-801 during the early postnatal period has been proposed to be an experimental model which induces behavioural changes that mimic positive, negative and cognitive symptoms of schizophrenia. We provide an overview of the effects of early life MK-801 administration on body weight, locomotor activity and spatial memory and assessed the long term behavioural profile arising from this early life manipulation. We found that intraperitoneal administration of MK-801 (0.35 mg kg⁻¹) twice a day for 2 weeks in rat pups on postnatal days 7, showed a significant weight loss, hypoactivity and the damage of spatial memory. The long term behavioural profile showed that hypoactivity continuously reduced until 11 weeks after MK-801 administration in animal model. But for spatial memory, a short term damage was observed in model rats. After the treatment with clozapine or haloperidol, a recovery in locomotor activity was observed in the rats of model group. However, there was no effect on the spatial memory in model rat after drug treatment. The results of the present study demonstrated that clozapine and haloperidol might reverse a long lasting hypoactivity induced by repeated treatment with MK-801 in neonatal rats but no effect on a short term damage of spatial memory.

Key words: MK-801, locomotor activity, spatial memory, schizophrenia, rat

INTRODUCTION

Glutamate, an excitatory neurotransmitter that is abundantly distributed in the central nervous system and is involved in memory processes through the N-Methyl-D-Aspartate (NMDA) receptor (Riedel *et al.*, 2003), a specific type of ionotropic glutamate receptor (Pryce *et al.*, 2002). MK-801 is a selective, non competitive NMDA antagonist with a high affinity for the NMDA receptor (Wong *et al.*, 1986). The synaptic organization takes place chiefly during the first 3 weeks of postnatal life in rodents (Haberny *et al.*, 2002) which in humans extends from the sixth month of gestation to several years after birth. During this period, particularly during postnatal days (PND) 7-14, the brain is highly sensitive to the toxic effects of NMDA receptor modulation (Kocahan *et al.*, 2013). Blockade of NMDA receptor during early neonatal life can cause long term alterations in the anatomical, neurochemical, neurophysiological and behavioral properties of rodents (Viberg *et al.*, 2008). The use of NMDA receptor antagonists has since been extended to young rodents during their early postnatal developmental period,

characterising a model which represents not only NMDA hypofunction but which is also consistent with the neuro developmental component (Baier *et al.*, 2009). Rats exposed to non competitive NMDA receptor antagonists such as MK-801 during the neonatal stage have been shown to elicit behavioral abnormalities related to clinical symptoms of schizophrenia, such as sensorimotor gating deficits, hyperactivity and social withdrawal in addition to spatial memory dysfunctions (Hargreaves and Cain, 1992; Rung *et al.*, 2005; Manahan-Vaughan *et al.*, 2008; Gururajan *et al.*, 2010).

Glutamatergic models have highlighted the role of the anterior cingulate and other parts of the limbic system in the pathophysiology of schizophrenia (Theberge *et al.*, 2002). Despite a large body of research on behavioural profile, such as, locomotor activity and spatial memory, the results were inconsistent in the effects of neonatal repeated treatments of MK-801 in different dose. Numerous studies carried out have failed to detect any long term consequences on locomotor activity following early life MK-801 treatment (Stefani and Moghaddam, 2005; Kawabe *et al.*, 2007; Uehara *et al.*, 2009) and several references in the available literature have provided

evidence of either increases or decreases in activity (Schiffelholz *et al.*, 2004; Baier *et al.*, 2009). Early life MK-801 appears to result in impaired water maze performance that is predominantly manifested only after maturity. Su *et al.* (2011) observed a minor impairment in adolescent rats but a markedly impaired performance in adulthood. However (McLamb *et al.*, 1990) did not detect any changes in water maze performance in adolescent male rats.

The dose and administration time of MK-801 may be main reason for inconsistent results in behavioural profile of rats. Metabolic changes caused by MK-801 after a single high dose (0.5 mg kg⁻¹) (Brenner *et al.*, 2005) or continuous low dose (0.1 mg kg⁻¹) (Eyjolfsson *et al.*, 2006) did not resemble the alterations occurring in the patients with schizophrenia. However, repeated high dose MK-801 (0.5 mg kg⁻¹ for six consecutive days) significantly increased the levels of glutamate, taurine and glutathione in frontal, retrosplenial and cingulate cortices (CRFC) which were similar to the alterations occurring in drug-naive patients with first episode schizophrenia (Kondziella *et al.*, 2006). The purpose of the present study was to investigate the effect of repeated treatment of MK-801 (0.35 mg kg⁻¹ twice daily) on long term behavioural profile in rats during the critical brain development period (PND7-20). Moreover it has been shown that the cognition impairing effects of MK-801 can be ameliorated or antagonized by clinically effective cognition enhancers (e.g., cholinesterase inhibitors) (Boess *et al.*, 2004; Csernansky *et al.*, 2005). Therefore, in order to observe whether the MK-801-induced changes could be blocked by atypical (clozapine) and classical (haloperidol) antipsychotic drugs, in our study, antischizophrenic drugs were used to detect the effects on locomotor activity and spatial memory of animal model induced by MK-801 in the early life.

MATERIAL AND METHODS

Ethics statement: The experiments were performed at the department of anatomy of Anhui medical University. The protocol was approved by the local ethics committees Anhui Medical University. All efforts were made to minimize the number of animals used and to ameliorate any distress.

Housing: All rats were housed in ambient temperature (approx. 20-23°C) and humidity (approx. 60%) controlled vivarium. Food and water were available ad libitum, except during testing, when no food was provided. In all experiments, animals were allowed to habituate to the

housing conditions for at least 1 week before behavioral testing. All testing was performed during the light phase of the day/night cycle.

Subjects: Sprague-dawley pups that were fostered by their real mothers (n = 8) and there were 5-6 offspring per litter. The pups were randomly divided into four groups, MK-801 (M group), MK-801+Clozapine (CL group), MK-801+Haloperidol (H group) and normal control group (N group) and each group included eleven sprague-dawley pups. All pups from a given litter received the same treatment and were randomly assigned to the groups, so that mean body weight in each group was almost equal on PND7. The pups of M group, CL group and H group received i.p., injections of the NMDA receptor antagonist dizocilpine (MK-801, 0.35 mg kg⁻¹ δ) and N group received i.p., injections of vehicle (0.9% NaCl) twice a day within 8:00-10:00 am and 14:00-16:00 pm of the light phase from postnatal days (PND)6-21 of age. The animals of CL group and H group were treated with the administration of clozapine (1 mg kg⁻¹ δ) or Haloperidol (0.1 mg kg⁻¹ human dongting pharm. Co. Ltd.) on PND43 and PND56 for one week. The animals were weaned at day 21. Behavioral characteristics of each group were investigated on PND 28, 49, 63 and 84. Schematic diagram of the experimental procedure Fig. 1. One week before the experiments the rats adapted to its environment.

Measurement of body weight: The body weight of the pups was measured before the treatment of MK-801, in the treatment and after the treatment. N and M group rats were weighed during the MK-801 treatment every day and recorded from PND7-PND20. After then, the body weight was still tested every 2 days until 9 weeks and recorded from PND22-PND84. All experiments were worked in 9:00-10:00 am.

Locomotor activity: Locomotor activity was measured in rats using a 100×100×50 cm wooden case with 25 equal squares in 9:00-12:00 am. The case was located in a dim and quiet room. All rats were enmeshed in the middle square and recorded the number of squares which rat crossed in 3 min. During each rat experiment, the case was cleaned by 75% ethanol. Locomotor activity was tested every two days and recorded the last four results on PND 28, 49, 63 and 84 for one week (Fig. 1).

Lashley water maze: The Lashley III water maze (80 cm long×50 cm wide×20 cm high) was constructed of black opaque plastic with a terminal platform and four

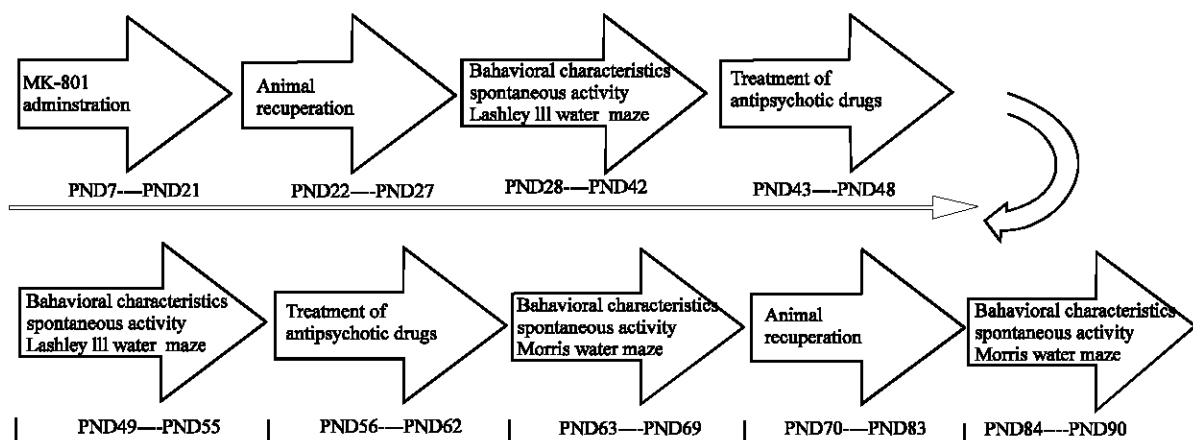


Fig. 1: Schematic diagram of the experimental procedure

blind alleys. In this study, we filled the maze with water at a temperature of $25 \pm 1^\circ\text{C}$ to a depth of 12 cm to provide an extra incentive for the mice to escape. The rats were placed in the maze at start point and had to swim through to the goal box at terminal platform in 180 sec. If the animals failed to find the terminal platform within 180 sec, they were gently guided through the maze to the end and allowed to climb onto the platform for 20 sec during the training time. The training started on PND28 and lasted continuous 5 days. On PND35 and PND49, the trail was tested and recorded the time rats found the terminal platform (Fig. 1). If rats failed to find the platform in 180 sec and the time was regarded as 180 sec. Lashley III water maze was used for spatial search ability testing when the body weight of rats were less than 150 g.

Morris water maze: The Morris Water Maze (MWM) consisted of a black circular pool (160 cm in diameter, 50 cm in height) filled with water at a temperature of $22 \pm 2^\circ\text{C}$ to a depth of 30 cm. The water was rendered opaque by adding a small amount of ink. The maze was located in a room providing an abundance of extra maze cues. Swimming trajectories were monitored by an overhead camera connected to a digital tracking system and data acquisition program. The maze contained a transparent plastic platform (10 cm in diameter, 28 cm in height) located in the centre of the first quadrant that was labeled based on compass directions. All experiments were worked in 13:00-18:00. In the visible platform sessions, the rats were released in the water facing the section of the wall at 1 of 4 equally quadrant of the pool and recorded the time when rats found and climbed onto the platform in 60 sec. If a rat failed to locate the platform within 60 sec it was placed on the platform for 10 sec. Each rat was submitted to 4 trials in at least 15 min intervals per day and the average data of the 4 trials was

regarded as the escape latency of MWM. Subjects were tested in a continuous 5 day. On day 6-7, the platform was removed, the spatial search ability of animals were tested. All rats were released in the water facing the wall at the second quadrant and recorded the times which rats crossed platform in 60 sec. On PND63 and PND84, MWM was tested and recorded the time of the escape latency and spatial search shown in Fig. 1. MWM was used for spatial search ability testing in 150-300 g weight rats.

Statistics: Body weight differences were analyzed by a repeated two-way analysis of variance (ANOVA) followed by a *post hoc* Newman-Keuls test. In the open field test, the numbers of traversed sections were tested by a repeated two way ANOVA and a Newman-Keuls test and the α level set at 0.05. All data of water maze were analyzed with repeated measures ANOVA, followed by Tukey-kramer HSD *post hoc* test to compare means of interest, α level set at 0.05.

RESULTS

Body weights after the treatment of MK-801: Body weights of all rats had no significant difference before experiment ($p > 0.05$). After treating with MK-801, the body weights of M group were increased slowly and had significant difference from PND10 compared to N group ($p < 0.01$) (Fig. 2a). After the end of treatment, body weights of M group were significantly reduced compared to N group ($p < 0.01$) (Fig. 2a). The weights of M group recovered gradually in the eighth week after the end of MK-801 administration (Fig. 2b).

Locomotor activity after the treatment of MK-801: Locomotor activity was tested on PND28, 49, 63 and 84. The experiment were performed every two days and a total

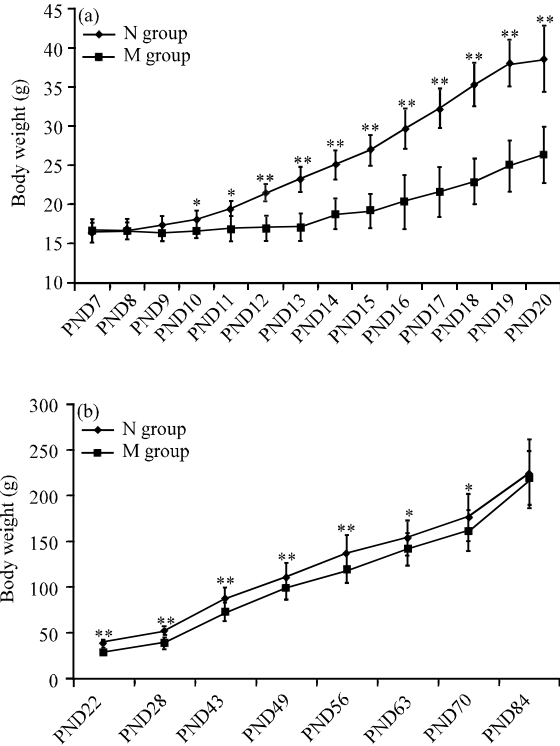


Fig. 2(a-b): Body weight during and after the administration of MK-801, compared to N group: *p<0.05, **p<0.01

of 5 times in one week. The first time was to make animals adapted to the environment and the data didn't collect. The data of later four experiments were recorded and the mean value represented the scores of locomotor activity. As shown in Fig. 3, the locomotor activity of rats in N group was basically stable and the number of crossed square was from 60-80 in different times after the administration of MK-801. However, in rats of M group, a transient increase in locomotor activity was detected on PND28 (Fig. 3). Then, the decreasing trend presented in locomotor activity of M group. On PND49, 63 and 84, the locomotor activity of M group was significantly lower than the control group (p<0.01) (Fig. 3).

Spatial memory ability after the treatment of MK-801:

The spatial memory of rats were detected by Lashley III water maze and Morris water maze respectively on PND28, 49 and PND63, 84. As shown in Fig. 4a, compared to N group, the escape latency of Lashley III water maze in M group rats were significantly long on PND28 after the treatment of MK-801 (p<0.01). The data suggested that the learning ability of M group rats was reduced significantly. On PND49, the time of M group rats on Lashley III water maze was also significantly long

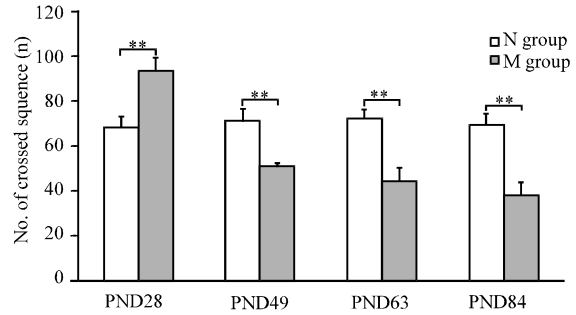


Fig. 3: Locomotor activity after the administration of MK-801, compared to N group: *p<0.05, **p<0.01

(p<0.01) (Fig. 4a). The results suggested that long memory ability was damaged in M group rats.

When the body weights of rats were more than 150 g, Morris water maze were used for the testing of animal spatial search ability. As shown in Fig. 4b, compared to N group, the escape latency of Morris water maze in M group rats were significantly long on PND63 after the treatment of MK-801 (p<0.01). Similarly, the dwell time in the former target quadrant and the number of platform position crossings in Morris water maze in M group were also significantly long on PND63 after the treatment of MK-801 (p<0.05) (Fig. 4c and d). However, on PND84 after the treatment of MK-801, the results had no significant difference between N group and M group (p>0.05) (Fig. 4b). The data suggested that long memory ability gradually recovered in M group rats. Unlike the escape latency of Morris water maze, the inconsistent results were found in the dwell time in the former target quadrant and the number of platform position crossings on PND84 (p<0.05) (Fig. 4c-d).

Effects of clozapine and haloperidol on locomotor activity:

Comparison of M group, the locomotor activity of CL group increased significantly on PND 49 after a week of treatment of clozapine (p<0.01), while H group was no significant difference (p>0.05) (Fig. 5). Furthermore, as shown in Fig. 5, the locomotor activity of CL group and H group were markedly higher than M group on PND63 and 84 (p<0.01) but had no difference compared to N group (p>0.05). The locomotor activity between CL group and H group had no significantly difference on PND63 and 84 after the treatment of antipsychotic drugs (p>0.05). In contrast, M group still maintained an inferior level. these results demonstrated that atypical (clozapine) and classical (haloperidol) antipsychotic drugs could reverse MK-801-induced deficits in hypoactivity.

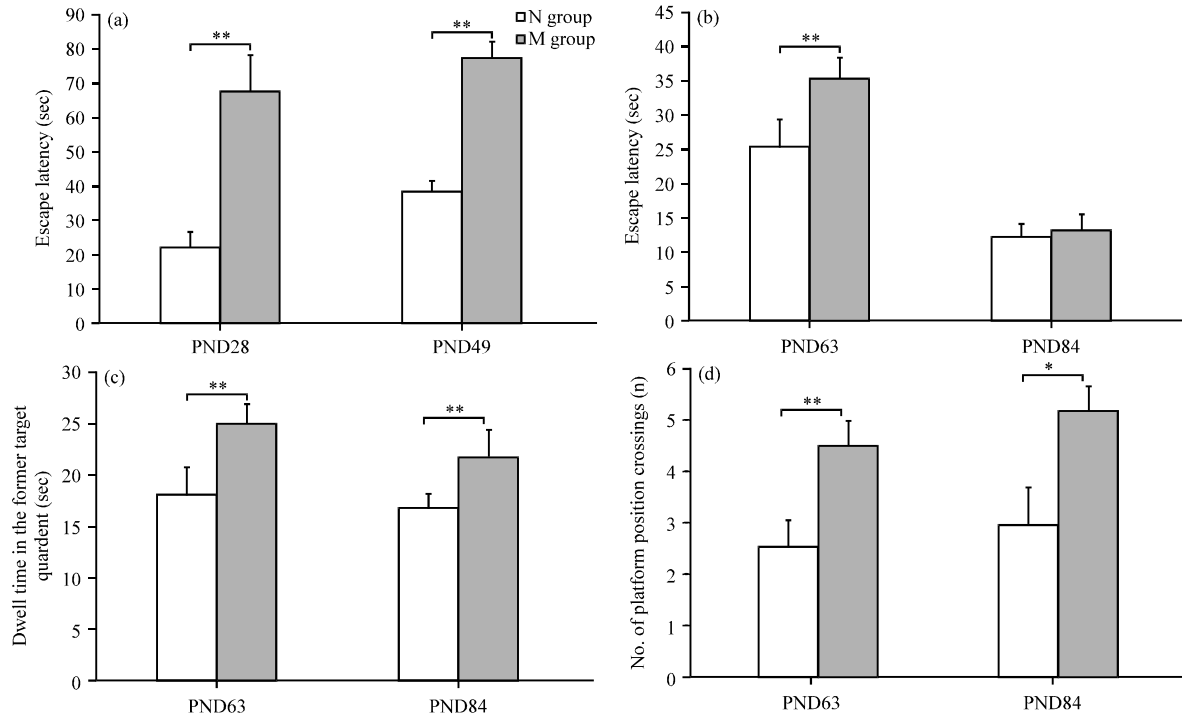


Fig. 4(a-d): Spatial memory after the administration of MK-801. The escape latency of (a) Lashley III water maze, (b) Morris water maze, (c) Dwell time in the former target quadrant of Morris water maze and (d) No. of platform position crossings in Morris water maze, compared to N group: * $p < 0.05$, ** $p < 0.01$

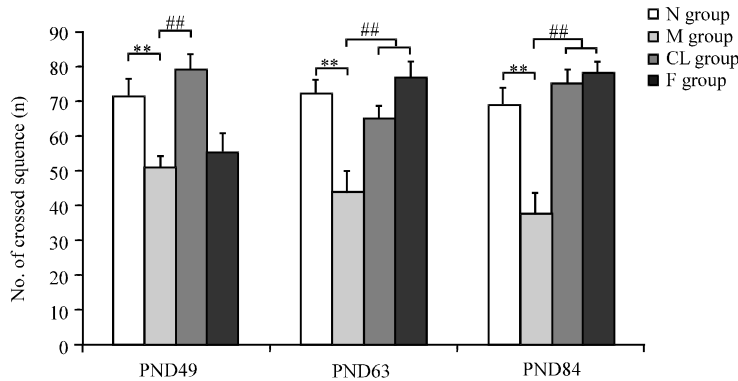


Fig. 5: Locomotor activity after the treatment of antipsychotic drugs, compared to N group: ** $p < 0.01$, compared to M group: ## $p < 0.01$

Effects of clozapine and haloperidol on spatial memory ability: Compared to M group, the results of Lashley III water maze had no significant difference on PND49 after one week of clozapine and haloperidol therapy (Fig. 6a). The escape latency of Morris water maze was significantly prolonged in M group compared to N group on PND63 ($p < 0.01$) (Fig. 4b and 6b). Through twice treatments of clozapine and haloperidol, respectively on PND43 and PND56, compared with M group, there had no significant

difference in the escape latency, the dwell time in the former target quadrant and the number of platform position crossings of Morris water maze in H group and CL group rats ($p > 0.05$) (Fig. 4b-d). These revealed that antipsychotic drugs clozapine and haloperidol couldn't significantly ameliorate the spatial memory ability of schizophrenic rats. Moreover, on PND84, the time completed the task of Morris water maze had no significant difference between N, M, H and CL group

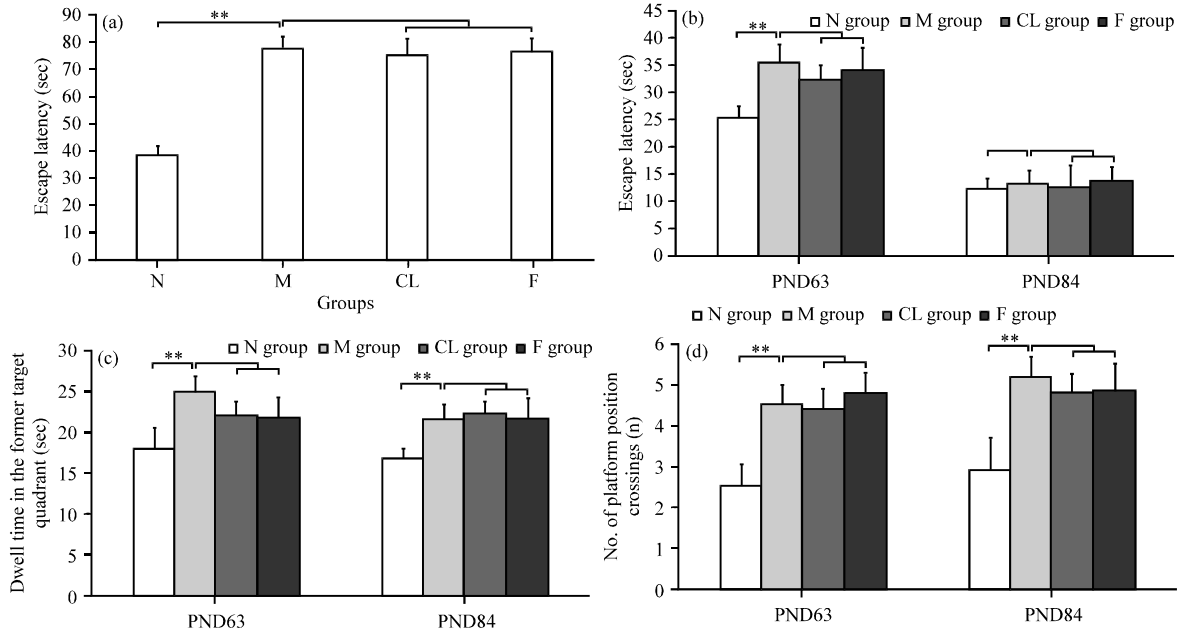


Fig. 6(a-d): Spatial memory after the treatment of antipsychotic drugs. The escape latency of (a) Lashley III water maze on PND49, (b) Morris water maze, (c) Dwell time in the former target quadrant of Morris water maze and (d) No. of platform position crossings of Morris water maze, compared to N group: ** $p < 0.01$, compared to M group: ## $p < 0.01$

($p > 0.05$) (Fig. 4b). Comparison within M group, the escape latency of Morris water maze reduced significantly in a time dependent manner ($p < 0.01$) (Fig. 4b). Our current findings indicated that MK-801 induced schizophrenia rats still owned spatial memory ability and MK-801-induced deficits in spatial memory in neonatal rats could spontaneously recover in adulthood. Although, the escape latency of Morris water maze had no significantly difference between N and M group on PND84, the dwell time in the former target quadrant and the number of platform position crossings in M group were significantly longer or more than that in N group ($p < 0.01$) (Fig. 4c-d). The results suggested that the damage induced by MK-801 in neonatal rats only partially restored during adulthood.

DISCUSSION

Schizophrenia is a chronic and severe CNS disease which characterized by disturbances of three distinct symptoms: Positive, negative and cognitive symptoms (Pearlson, 2000; Kato *et al.*, 2011). In recent years, the “glutamatergic hypothesis” of schizophrenia has received significant attention and non competitive NMDA receptor antagonists MK-801 induced schizophrenia is able to imitate schizophrenia like symptoms in human and animals

(Reynolds *et al.*, 2005; Vigano *et al.*, 2009). In the present study, we confirmed that MK-801 chronic administration produced lower weight, less locomotor activity and worse spatial memory ability.

Atypical antipsychotic drugs such as clozapine has superior effects on both positive and negative schizophrenia and cognitive impairment without producing extra pyramidal side effects, compared to haloperidol, a typical antipsychotic drug (Arif *et al.*, 2006). To delineate the possible mechanisms of MK-801 induced schizophrenia, we further investigated the effect of antipsychotic drugs and revealed whether alterations in behavior were completely reversed by an atypical or typical antipsychotic drug.

Amounts of evidences showed that MK-801 induced schizophrenia rats had a light weight compared to the normal rats and recovered to the regular levels in the puberty and adults after the terminal of MK-801 treatment (Gorter and Brady, 1994; Su *et al.*, 2011). In the contrast, some researchers found that the weight decrease was maintained until adult stage and lower than normal group in the 60 days after birth (Schiffelholz *et al.*, 2004; Kawabe and Miyamoto, 2008). These findings were ascribed to age depended switches after neonatal MK-801 treatment. In our study, the body weights were inhibited under neonatal MK-801 treatment and had a significant

difference 4 days after treatment in comparison of normal rats. The lower weights could last 8 weeks long in minimum and then gradually recovered after the end of the treatment of MK-801.

The open field experiment was evaluated to the center excitability, locomotor activity, search ability and emotion of rats in the nature condition (Beninger *et al.*, 2002). In the previous studies, researchers reported that locomotor activity was double regulated by treating with MK-801, the locomotor activity was increased in low dose treatment but decreased in high dose treatment (Lyll *et al.*, 2009). The reason was that high dose MK-801 was able to induced ataxia and stereotyped behavior and interfere the locomotor activity. The researches on MK-801 induced locomotor activity were not conformity, some reported that there was no change in the neonatal MK-801 treatment (Kawabe *et al.*, 2007; Uehara *et al.*, 2009) and others found that the locomotor activity was reduced in a short time after treating with MK-801 (Latysheva and Rayevsky, 2003). While our results were out line with previous studies and found that although a transient increase in locomotor activity was detected on PND28 one week after the end of MK-801 treatment it was significantly decreased in medium dose and last for 6 weeks at least. This might be connected to the dose of MK-801, time of injection etc. and still need to investigate for a long time. Furthermore, more studies focus on different kinds of antipsychotic drugs. Mouri found that the first and second generation antipsychotic drugs could reverse the locomotor activity increase induced by PCP (Mouri *et al.*, 2007). Bradford showed that all antipsychotic drugs were able to reverse the locomotor activity induced by MK-801 in a dose dependent manner (Bradford *et al.*, 2010). Our results showed that the locomotor activity was significantly enhanced after treating with clozapine and haloperidol compared to model group and had no significant difference between treatment group and control group. These results suggested that both atypical and typical antipsychotic drugs were able to ameliorate the abnormality of locomotor activity in MK-801 induced schizophrenia.

Cognitive impairments including deficits in attention, short and long-term memory, abstract thinking ability and executive function etc., are core symptoms of schizophrenic patients (Glahn *et al.*, 2003; Green *et al.*, 2004; Harvey *et al.*, 2004). McLamb reported that there was no alteration of spatial learning ability in immature female rats (Bremner *et al.*, 2005). However, Su found that, after treating with MK-801, female rats exhibited slightly impaired working memory during adolescence but remarkably disrupted in adult (Su *et al.*, 2011). In our study, Lashley III water maze results showed that the time

rats searched the platform was significantly long compared to normal group. After 5 continuous days tested, the escape latency between model group and normal group was curtailed gradually and had a significant difference to the previous results. These data suggested that although spatial memory deficits were occurred in MK-801 induced schizophrenia, the learning speed was decreased only. In the retest after 2 weeks, the scores of Morris water maze in MK-801 group rats were still higher than normal and released that long-term memory were also damaged in model rats.

Furthermore, the effects of clozapine and haloperidol were also observed in our study. Several studies reported that clozapine was able to improve working memory of schizophrenia rats. In addition, Takeo Ishiyama showed the spatial memory ability deficits were ameliorated by clozapine but not haloperidol (Ishiyama *et al.*, 2007), while Takeshi Enomoto found that both clozapine and haloperidol could reverse the spatial memory impairments (Enomoto *et al.*, 2008). In contrast, other researches demonstrated that both clozapine and haloperidol couldn't remedy the cognitive impairments. In this study, we found that the escape latency had no significant difference between model rats and therapy group after treating with clozapine and haloperidol. It is suggested that clozapine and haloperidol had no therapeutic effects on spatial memory. In the retests 2 weeks after treatment, results of Morris water maze were not significantly different between model group and normal group. These suggested that the spatial memory deficits which induced by MK-801 were able to recover spontaneously.

In conclusion, our present study has shown that chronic neonatal MK-801 treatment results in a minor weight, hypoactivity and spatial memory impairment. Moreover, clozapine and haloperidol could reverse MK-801-induced deficits in hypoactivity but not the impairment of spatial memory in neonatal rats.

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