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RESEARCH ARTICLE

Neonatal exposure of ketamine inhibited the induction of hippocampal long-term potentiation without impairing the spatial memory of adult rats

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Abstract

Ketamine is one of general anesthetics and has been commonly used in obstetric and pediatric anesthesia. However, effects of exposure to ketamine on neonatal brain are largely unknown. In this study, we aim to investigate the effect of neonatal exposure of ketamine on spatial memory and long-term potentiation (LTP) in the hippocampus of adult rats. One-week-old neonatal rats were separated into ketamine group and control group. Neonatal rats in ketamine group were received intraperitoneal injection of 25 mg/kg (low-dose group, N = 8) or 50 mg/kg ketamine (high-dose group, N = 8). Neonatal Rats in control group received saline injection (N = 8). After 10 weeks, the spatial memory of adult rats was examined by using Morris Water Maze, and LTP in the hippocampus of adult rats was assessed by electrophysiological experiment. We found that exposure of ketamine to neonatal rats, either low-dose or high-dose, had not induced alteration on their adulthood's escape latency, swimming speed and the percentage of time spent in original quadrant compared with the control. The electrophysiological examination showed that the induction of LTP in hippocampus was significantly reduced in adult rats of ketamine group (either low-dose or high-dose). Our study showed that neonatal exposure of ketamine inhibited the induction of hippocampal LTP without impairing the spatial memory of adult rats.

Keywords Ketamine · Neonatal exposure · Long-term potentiation · Adulthood

Introduction

Ketamine is one of general anesthetics and has been commonly used in obstetric and pediatric anesthesia (Wang et al. 2014; Zou et al. 2009). As a non-competitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist, Ketamine is also being investigated as a new medicine for major depressive disorder (Akeju et al. 2014; Ribeiro et al. 2014b; Williams and Schatzberg 2016). Clinical research indicates that ketamine can attenuate postoperative cognitive dysfunction (POCD) in patients undergoing cardiac surgery (Hudetz et al. 2009). However, several studies in animals have shown that ketamine anesthesia can induce widespread neurotoxicity and neurodegeneration when

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administered in high doses and/or for prolonged periods (Green and Cote 2009). Meanwhile, Ketamine administrated to pregnant rats caused prolonged behavioral disorders in offspring (Zhao et al. 2014). A previous study in humans has been reported that Ketamine abuse during pregnancy results in the birth of an infant with remarkable hypotonia, intrauterine growth retardation, and poor reflex responses (Su et al. 2010). Administration of Ketamine can deteriorate the memory in human (Wang and Orser 2011). Moreover, an animal study has revealed the metaplastic effects of subanesthetic ketamine on CA1 hippocampal function (Izumi and Zorumski 2014). Therefore, it has raised serious concerns about the safety of ketamine anesthesia on immature brain.

Several studies have indicated that Ketamine exposure can induce increased neuroapoptosis in the developing brain of newborn animals (Liang et al. 2010; Slikker et al. 2007; Soriano et al. 2010). Also, early exposure to Ketamine can cause long-lasting cognitive dysfunction in the rhesus monkeys (Paule et al. 2011). It seems that the developing brain, especially during the period of synaptogenesis, is vulnerable and sensitive to general anesthetics (Jevtovic-Todorovic et al. 2003). Synaptic plasticity, as the cellular model of learning and memory, has multiple forms, including long-term potentiation (LTP) (Volianskis et al. 2013). LTP is critically dependent on the activation of *N*-methyl-D-aspartate receptor (NMDAR) (Berberich et al. 2007; Liu et al. 2004). And it has been reported that proper development of synapses in the hippocampus needs activation of NMDAR (Bellinger et al. 2002). The hippocampus plays an important role in spatial memory (Carr et al. 2011). There have been growing concerns regarding the effect of Ketamine on hippocampal synaptic transmission. Neonatal exposure to Ketamine induced a significant LTP impairment in rats (Wang et al. 2014). So far, it still remains uncertain whether the effect of neonatal ketamine anesthesia on hippocampal synaptic plasticity and spatial memory will prolong in adulthood.

In this study, we will expose a low-dose or high-dose Ketamine on neonatal rats whose adulthood's spatial memory and induction of hippocampal LTP will be examined by Morris Water Maze (MWM) test and electrophysiological examination respectively.

Methods

Animals

All experiment procedures were ethically approved by the Institutional Animal Care and Use Committee at Tianjin Medical University. Sprague–Dawley (SD) rats (male and female in half) were obtained from the Experimental Animal Centre of Institute of Radiation Medicine Chinese Academy of Medical Sciences, Tianjin, China. SD rats were housed in cages with 12 h light–dark cycle, and allowed to food and water freely at room temperature (about 22 °C). 1-week-old SD rats were randomly assigned to Control group (Saline, N = 8), Low-dose group (25 mg/kg ketamine, N = 8), and High-dose group (50 mg/kg ketamine, N = 8) to receive administration of drugs. In addition, additional set of adult rats (10-week old) were used in electrophysiological experiment, Adult-treatment group (50 mg/kg ketamine, N = 8).

Ketamine anesthesia

According to the previous studies, the treatment of Ketamine was operated at age of 1-week-old, which during the period of rapid synaptogenesis and vulnerability to the neurotoxic effect of Ketamine, (Ikonomidou et al. 1999). For Ketamine-treated groups, rats were respectively administered intraperitoneal injection with Ketamine at the dose of 25 mg/kg (Low-dose), 50 mg/kg (High-dose). Rats in the control group administered intraperitoneal injection with saline at the volume of 0.2 ml. All rats were placed into human-made chamber to receive oxygen with a gas flow of 0.5 l/min until they recovered from anesthesia. The SpO_2 and HR of rats were monitored. Meanwhile, there was calcium lime on the bottom of chamber to absorb carbon dioxide and the body temperature was maintained at 35–37 °C during Ketamine anesthesia. After Ketamine anesthesia, all of rats were placed back into their maternal cages. The blood gas analysis performed on rats of all groups before Ketamine anesthesia and after Ketamine anesthesia was not significantly different.

Morris Water Maze test

Ten weeks after Ketamine anesthesia, the spatial memory of the rats was studied using the Morris Water Maze (MWM) test Wang and Slikker 2008). The MWM test was applied in a quiet room with dimmed lights. The water maze pool was a round and black painted water tank (150 cm in diameter and 50 cm in height), which was divided into four equal imaginary quadrants with a platform placed in the center of third quadrants. The pool was filled with water to 1 cm above the top of platform and the water was opacified with milk powder. The water temperature was maintained at 25 ± 1 °C. The MWM test was performed for 6 consecutive days. Place navigation training was carried out at the first 5 days (four trails per day). Each rat was placed into water from different start positions (east, west, south and north) and allowed freely 60 s to

look for the hidden platform and stay on it for 10 s. If the platform was not reached within 60 s, the rat was gently guided to the platform and allowed to stay on it for 10 s. The time from immersing into water to locating the platform, which was called escape latency, swimming distance and swimming speed were recorded. Spatial probe test was performed on the sixth day. The platform was removed. Rat was placed into water from opposite quadrant and allowed to swim for 60 s. Swimming time spent in the target quadrant (where the platform was located during hidden platform training) was recorded.

Electrophysiological experiment

After the MWM test, the electrophysiological experiment was studied in adult rats (2.5 months of age) of all groups according to a previously-published procedure (Gruart et al. 2006). Rats were anesthetized with 20% urethane with a dose of 1.5 ml/kg by intraperitoneal injection. For electrophysiological recording, they were placed in a stereotaxie apparatus (SN-2 Narishige, Japan) using an electric blanket to maintain their body temperature at 35–37 °C. After subcutaneous injection with lidocaine, the scalp of rats was cut off to expose clearly their skull. Keep the bregma and lambda in the same horizontal plane. The stimulating electrode was inserted into perforant path (PP) of entorhinal area (4.4 mm lateral and 7.5 mm posterior to Bregma; depth from brain surface, 3.4–4.0 mm). while the recording electrode, which was pulled from borosilicate glass capillaries by P-95 vertical puller (Heka, Germany) and filled with 2 mol/L sodium chloride, was implanted in the hippocampal dentate gyrus (DG) region (2.5 mm lateral and 3.7 mm posterior to Bregma; depth from brain surface, 3.4–3.6 mm). The test stimuli (frequency 0.5 Hz, duration 150 us) was produced by Master-8 stimulator (A.M.P.I, Israel) and delivered by stimulation electrode to evoke population-spike (PS). And the intensity of test stimuli was adjusted to elicit 50% of the maximal PS amplitude. The amplitude of PS was allowed to stabilize for 20 min. After the baseline was recorded under the test stimulation for 30 min, LTP was induced by high-frequency stimulation (HFS, 10 bursts of 20 pulses at 200 Hz, each burst separated by 2 s) with the intensity was adjusted to elicit 75% of the maximal PS amplitude. Then, the PS was persistently recorded for 60 min under test stimuli and the intensity of baseline recording. Signals were amplified, low-pass filtered at 2 kHz and digitized at 10 kHz with Axonpatch 2B patch-clamp amplifier (Molecular Devices, Foster City, CA, USA) and Digidata1320 interface (Molecular Devices, Foster City, CA, USA). The PS was collected and analyzed by pCLAMP 10.0 (Molecular Devices, Foster City, CA, USA).

Statistical analysis

Statistical comparisons among groups were performed by one-way analysis of variance (ANOVA) followed by Fisher's least significant difference for post hoc comparisons. All data were presented as mean ± SEM. A value of $p < 0.05$ was regarded as statistical significance.

In Morris water maze experiment, escape latency, swimming distance and swimming speed were averaged within each day for each animal. To determine the difference between each day, data were analyzed using repeated measures ANOVA's with day as within-subjects factor and different treatment as between-subjects factor.

Results

Neonatal exposure of ketamine did not alter adulthood's spatial cognition

In the place navigation test of the MWM test, the escape latency of each group gradually decreased with the increase of training days ($F = 68.91$, $p < 0.001$) (Fig. 1). However, there was no significant difference of escape latency among the three groups on the first, the second, the third, the fourth, and the fifth day ($p > 0.05$) (Fig. 1).

We had observed a gradually decreased swimming distance from day 1 to day 5 in all groups ($F = 42.67$, $p < 0.001$). However, there was no significant difference of swimming distance among the three groups on the first, the second, the third, the fourth, and the fifth day ($p > 0.05$) (Fig. 2a). The average swimming speed in all groups was relatively consistence from day 1 to day 5 (Fig. 2b). There was no significant difference of swimming speed among the three groups ($p > 0.05$).

The percentage of time spent in the quadrant with the platform beforehand recorded in the spatial probe test was 25.31 ± 1.94%, 23.31 ± 1.89%, and 21.93 ± 1.63%

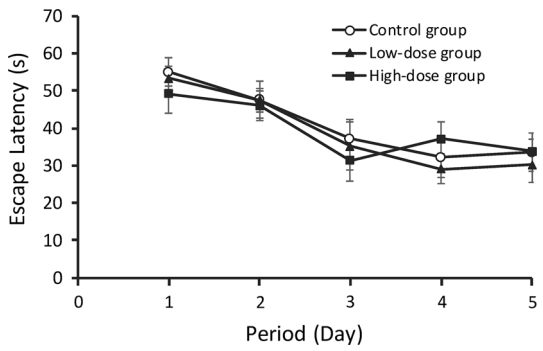

Fig. 1 Escape latency of the neonatal-ketamine-exposed adult rats in MWM test. Neonatal ketamine exposure did not affect the escape latency of adulthood

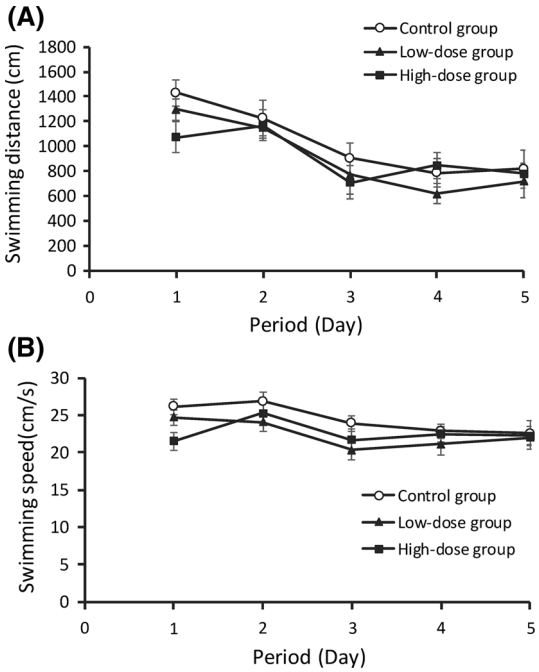

Fig. 2 **a** Swimming distance and **b** swimming speed of the neonatal ketamine-exposed adult rats in MWM test

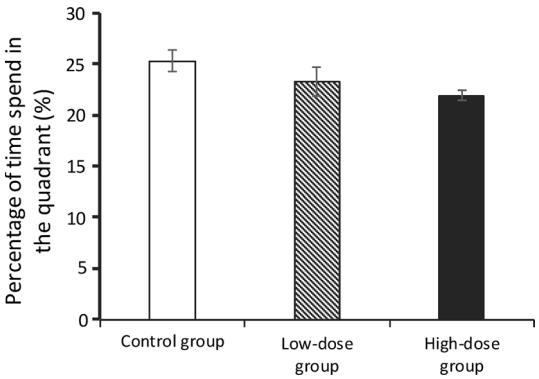

Fig. 3 Percentage of time spent in the quadrant with the platform beforehand of the neonatal ketamine-exposed adult rats in MWM test

respectively in control, low-dose group and high-dose groups (Fig. 3). There was no significant difference of the percentage of time spent in the quadrant among the three groups ($p > 0.05$).

The above evidence indicated that both low-dose and high-dose ketamine treatment on neonatal rats did not impair their adulthood's spatial memory.

Ketamine impaired the induction of LTP in adult rats

To validate whether ketamine could impair synaptic plasticity in adult rats, we employed additional set of adult rats (11-week old) to be administrated with high dose

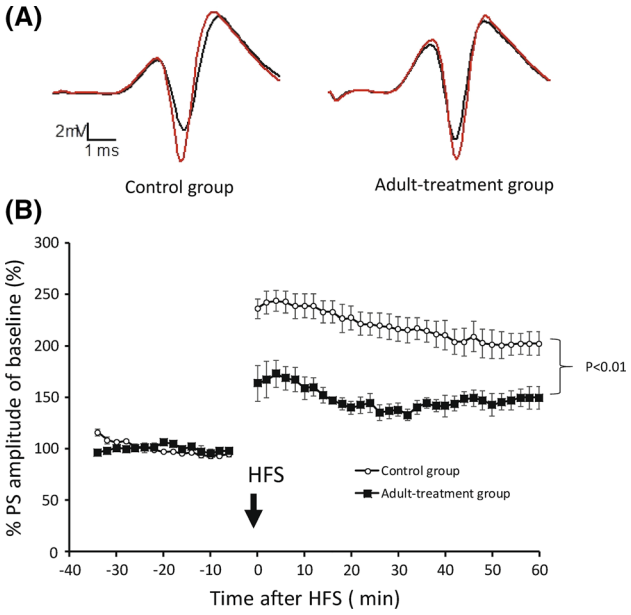

Fig. 4 **a** Insets showed the traces of fEPSPs before and after HFS. **b** The effect of ketamine in LTP induction of adult rats. The arrow indicates the time for applying HFS

ketamine(ip 50 mg/kg), named as adult-treatment group, for electrophysiological experiment. The HFS could increase the PS amplitude of all the adult rats (Fig. 4). Compared with control rats treated with saline, the adult-treatment group showed significantly lower induction of PS amplitude at all time points after HFS (Fig. 4). The average PS amplitudes at 60 min after HFS in control group and adult-treatment group were 202.32 ± 15.47% and 149.60 ± 14.92% respectively (Fig. 4). The result showed that ketamine could repress more than one-third of LTP induction in adult rats.

Neonatal exposure of ketamine impaired synaptic plasticity in the hippocampus of adult rats

There was no significant difference of induction of PS amplitude at HFS time among the three groups ($p > 0.05$) (Fig. 5). PS amplitude values of high-dose group were 164.28 ± 8.55, 166.49 ± 7.43, 187.49 ± 4.93, 181.19 ± 3.39, 168.67 ± 4.15, and 167.04 ± 6.24% at 10, 20, 30, 40, 50 and 60 min after HFS. PS amplitude values of low-dose group were 189.18 ± 7.95, 171.49 ± 7.43, 166.49 ± 5.25, 169.23 ± 5.88, 167.16 ± 7.71, and 163.04 ± 9.02% at 10, 20, 30, 40, 50 and 60 min after HFS. PS amplitude values of control group were 240.51 ± 8.53, 237.97 ± 6.49, 233.81 ± 9.13, 225.61 ± 7.39, 218.73 ± 5.82 and 212.32 ± 8.77% at 10, 20, 30, 40, 50 and 60 min after HFS. Both low-dose and high-dose groups showed significant lower PS amplitude at

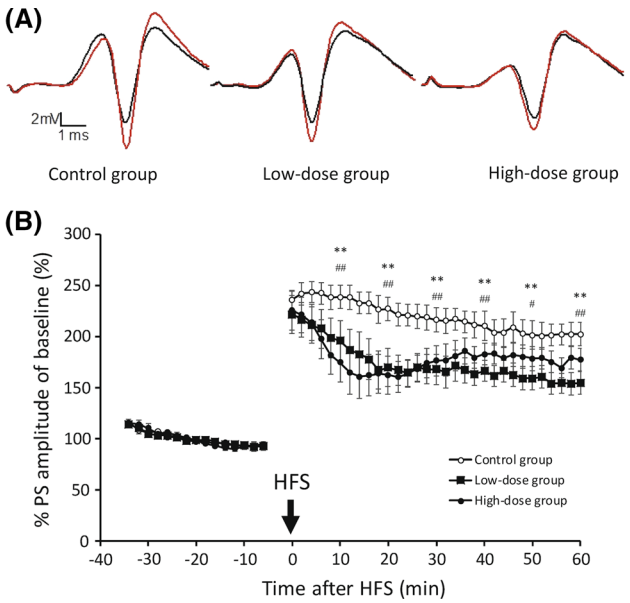

Fig. 5 **a** Insets showed the traces of fEPSPs before and after HFS. **b** The effect of neonatal ketamine exposure on adulthood's LTP induction The arrow indicates the time for applying HFS. Statistical analysis was performed at the time points after HFS including 0, 10, 20, 30, 40, 50 and 60 min. **, $p < 0.01$ (Control vs low-dose); #, $p < 0.05$ (Control vs high-dose); ##, $p < 0.01$ (Control vs high-dose)

10, 20, 30, 40, 50 and 60 min after HFS compared with control group ($p < 0.05$) (Fig. 5). There was no significant difference of PS amplitude between low-dose and high-dose group at all time points after HFS ($p > 0.05$). These results indicated that exposure of ketamine to neonatal rats may impair their adulthood's synaptic plasticity.

Discussion

Morris Water Maze (MWM) test, which has been well established to be sensitive to hippocampal impairments (Jia et al. 2015), was used to evaluate spatial memory performance of rats in our study. We found that exposure of ketamine to neonatal rats did not alter their adulthood's spatial learning and memory evidenced by similar escape latency, swimming ability and the time spent in original quadrant. However, recent study found out that exposure to ketamine (75 mg/kg) for 3 days resulted in long-term memory dysfunction in MWM test in young SD rats (1 month old) (Huang et al. 2014a). And spatial memory ability was declined in mice with intraperitoneal injection of ketamine (30 mg/kg, twice per day) for 4 weeks (Huang et al. 2014b). The different effects on spatial learning and memory in MWM test maybe due to the repeated use and different dose of ketamine.

Evidence has suggested that hippocampal LTP in vivo is immediately abolished after exposure to ketamine (Huang et al. 2014b). The induction and maintenance of LTP were altered in hippocampal slices from adult C57BL/6 mice after ketamine anesthesia, but that change was not persistent (Ribeiro et al. 2014a). We administrated a lateral ventricle injection with 50 ug ketamine to adult rats (Adult-treatment group) and assessed the LTP induction and LTP maintenance in the hippocampus in vivo. We found that ketamine indeed could significantly suppress the induction of hippocampal LTP in adult rats. Meanwhile, a research has reported that neonatal exposure to ketamine reduces the induction of LTP in the anterior cingulate cortex of young rats (3–4 weeks) using in vitro whole-cell patch-clamp recordings (Wang et al. 2014). We found that neonatal exposure of ketamine, either with low-dose or with high-dose, also extend the impairment on induction of LTP to their adulthood.

Neurotransmitter-gated ion channels are regarded as the most likely molecular targets for general anesthetics. NMDAR, HCN1, $GABA_A$, and 5-HT3 are the main molecular targets of ketamine (Rudolph and Antkowiak 2004). It is widely believed NMDAR is the principal molecular target of Ketamine (Brown et al. 2011; Sinner and Graf 2008). NMDARs are critically involved in synaptic plasticity and central to learning and memory (Morgan et al. 2012). It has been reported that neonatal NMDARs antagonist exposure causes a lasting reduction of synaptic strength in the hippocampus (Bellinger et al. 2002). Besides NMDAR, Chen showed that HCN1 channel subunits are also a molecular substrate for hypnotic actions of ketamine, and Grasshoff reported that ketamine could affect $GABA_A$, and 5-HT3 ligand gated ion Channels as well (Chen et al. 2009; Snyder et al. 2007). Ketamine is a purported non-competitive NMDA receptor antagonist (Yamamura et al. 1990). That may provide a possible mechanism that antagonism induced by Ketamine on NMDA receptor contributes to the suppression of long-term synaptic plasticity and spatial memory dysfunction. The alternations of HCN1, $GABA_A$, and 5-HT3 induced by ketamine also provide a plausible neuronal mechanism for enhanced cortical synchronization during anesthesia and might contribute to actions of ketamine.

In our paper, the induction of LTP (PP → DG) in hippocampus was significantly reduced in adult rats of ketamine group while the spatial memory of adult rats of ketamine group was not impaired. It has been recognized that the hippocampus plays a vital role in spatial memory. Besides hippocampus, the integrity of connections between the hippocampus, subiculum, and cortical areas is necessary for synthesis of all components of spatial memory (Squire 1992). Long-term potentiation (LTP) and long-term depression (LTD) are cellular memory storage mechanisms. There are several important pathways which have been shown to sustain LTP. The pathways are

including Entorhinal cortex → dentate gyrus (PP-DG), Mossy fibers → CA3, Commissural fibers → CA3, Schaffer collaterals → CA1, Hippocampus (CA1) → Subiculum, Hippocampus (CA1) → prefrontal cortex, and Subiculum → prefrontal cortex (Lynch 2004). In our paper, we found the induction of LTP (PP → DG pathway) was significantly reduced in adult rats by neonatal ketamine exposure. But we did not test LTP of other pathways, and could not conclude that LTPs of the integrity of connections between the hippocampus, subiculum, and cortical areas are impaired in adult rats by neonatal ketamine exposure. That may be a possible reason that the spatial memory of adult rats of ketamine group was not impaired.

In conclusion, our study demonstrated that neonatal exposure of ketamine inhibited the induction of hippocampal LTP without impairing the spatial memory of adult rats. Although the clinical impact of many preclinical findings has not been established, anaesthesiologists should strive to minimize unnecessary exposure to general anesthetic agents that might potentiate toxicity in neonatal and pediatric patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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