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Original Article

Effect of repeated neonatal sevoflurane exposure on the learning, memory and synaptic plasticity at juvenile and adult age

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Abstract: Currently sevoflurane is the volatile anesthetic most wildly used in pediatric surgery. Whether neonatal exposure to sevoflurane brings about a long-lasting adverse impact even at juvenile and adult age, attracts extensive concerns. However, to date the consensus has not been reached and how exposure to sevoflurane in early life affects long-term ability of learning and memory is not fully elucidated. To obtain further insight into this issue, 32 neonatal SD rats were assigned into control group (group C, n=16) and sevoflurane group (group SEV, n=16). At postnatal day 7 (P7), 14 (P14) and 21 (P21) rats pups in group SEV received repeated exposure to 2.6% sevoflurane for 2 h. At juvenile and adult age, Morris water maze (MWM) was used to determine the spatial memory performance. Subsequently long-term and short-term synaptic plasticity in hippocampal CA1 region were investigated by in vivo electrophysiological method. Our behavioral data revealed that repeated exposure to 2.6% sevoflurane in early life did not result in marked behavioral abnormalities. However, in electrophysiological experiment, long-term potentiation (LTP) in hippocampal neurons of animals neonatally exposed to sevoflurane was significantly inhibited as compared to animals in group C at both juvenile and adult age. Pair-pulse facilitation (PPF) ratio in group SEV at juvenile and adult age was augmented to varying extent. These effects were most noticeable at juvenile stage with tendency of alleviation during adulthood. The present study provides an alternative explanation for the mechanism underlying developmental neurotoxicity of sevoflurane, which may ameliorate future preventive and therapeutic strategies.

Keywords: Synaptic plasticity, neonatal period, sevoflurane, hippocampus, learning and memory

Introduction

Approximately 1.5 million infants suffer from general anesthesia for surgery every year throughout the world [1]. Therefore, the safety of pediatric anesthesia elicits public concerns. Infancy is the period when brain neuronal network develops fastest. During this period, the developing brain is susceptible to various anesthetic agents commonly used in clinical practice, such as dexmedetomidine [2], propofol [3] and volatile anesthetics [4]. Sevoflurane is a volatile anesthetic widely used in pediatric anesthesia. It has been demonstrated that early exposure to sevoflurane may induce the long-term behavioral changes and cognitive abnormalities later on in life in rodents [5] and nonhuman primates [6]. However, the underlying mechanism is still incompletely understood. Previous studies focused on the role of sevoflurane-induced neuronal apoptosis and structural changes of synapse at the cellular level [7-9], whereas increasing researches indicated that the structural damages in the functional brain regions are not the unique mechanism of neurocognitive deficits at juvenile and adult age [10, 11]. Therefore, there are probably extra, or even alternative mechanisms for these sevoflurane-induced deficits in learning and memory ability.

Hippocampal synaptic plasticity, in particular the long-term potentiation (LTP), is widely viewed as a potential functional mechanism of

learning and memory [12]. The impairment of hippocampal synaptic plasticity commonly correlates with cognitive dysfunction [13, 14]. However, the long-term effect of neonatal sevoflurane exposure on synaptic functional plasticity have not been well documented to date. Therefore, in the present study, from the functional perspective, the impacts of neonatal repeated exposure to sevoflurane on the long-term and short-term synaptic plasticity, as well as spatial learning and memory ability at juvenile and adult age were systematically observed. Also, the possible mechanism was probed in depth.

Materials and methods

Animals

The use of animals was approved by the Institutional Animal Care and Use Committee of Zunyi Medical University. Male Sprague-Dawley (SD) rats were purchased from Animal Center of the Third Military Medical University (Chongqing, China). All the rats were housed in a room with 12-h light-dark cycle at constant temperature (22°C ± 2°C, 30% humidity) and fed standard rodent chow and water ad libitum.

Sevoflurane exposure and experimental groups

Neonatal SD rats at postnatal day 7 (P7) were assigned into control group (group C, n=16) and the group receiving repeated exposure to sevoflurane (group SEV, n=16). Rats in group SEV were placed in a plastic container in which temperature was sustained at 30 ± 1°C with a heating pad. These pups inhaled 2.6% sevoflurane and carrier gas (1 L/min Air+1 L/min O_2) for 2 h on the 7th, 14th and 21th day repeatedly. Gases (sevoflurane, O_2 and CO_2) in the container were monitored using an anesthetic gas monitor (Grager Vamos, Germany). After anesthesia, rat pups were exposed to air until freely moving. During treatment, we investigated the respiratory frequency and skin color to prevent apnea and hypoxia. Body temperature was monitored throughout the treatment as well. Rats in group C inhaled air in the identical container at same time points. After treatment, rat pups were returned to their maternal cages for lactation and then weaned and bred following standard institution procedures.

Morris water maze

The capacity of memory and learning was assessed using the Morris water maze (MWM) test. The circular tank was 120 cm in diameter and 60 cm in height, filled with warm water at 23 ± 1°C to the depth of 30 cm. The maze was divided into four equal quadrants (SE, SW, NE and NW). The escape platform with a diameter of 15cm was situated the middle of the SE quadrant and 1 cm beneath the surface of opaque water. A tracking system was used to record the movement of animals in the pool. On P31 and P91, juvenile and adult rats from group SEV and group C underwent four trial per day with minimal 60 min inter-trial interval for five consecutive days respectively. In each trial, rat was placed into water with its face towards the wall at a random starting point. Trial was ended when all four paws of rat put on the platform or 60 s had elapsed. If the rats cannot find the platform after 60 s, they were guided to the platform and stayed there for 30 s. Escape latency to reach the platform was recorded and analyzed. For each animal, the scores of 4 trials in a day were averaged to acquire the total score. On P36 and P96, the platform was removed from pool for spatial probe test. Rats were placed into pool and allowed to swim for 60 s. The number of entries and the proportion of time spent in the original target quadrant were recorded and measured.

Surgery

On postnatal days 37 (P37) and 97 (P97) 8 rats were randomly extracted from two groups respectively for electrophysiological recording. Rats were anesthetized with pentobarbital sodium (45 mg/kg i.p.) and fixed in a stereotaxic frame (RWD Life Science Co., Ltd., Shenzhen, China). Lidocaine (20 mg/ml) was injected s.c. prior to the surgical incision. For the rats at P97, two holes were drilled at the corresponding sites on the skull for inserting electrodes. A paired parallel stimulating/recording electrode [15] was inserted into the CA1 region of hippocampus. The tip of recording electrode was positioned at the stratum radiatum of CA1 region (3.7 mm posterior to bregma, 2.9 mm lateral to midline, 1.8-2.3 mm from the brain surface). The tip of concentric stimulating electrode was positioned at the Schaffer collateral/commissural pathway (4.2 mm posterior to

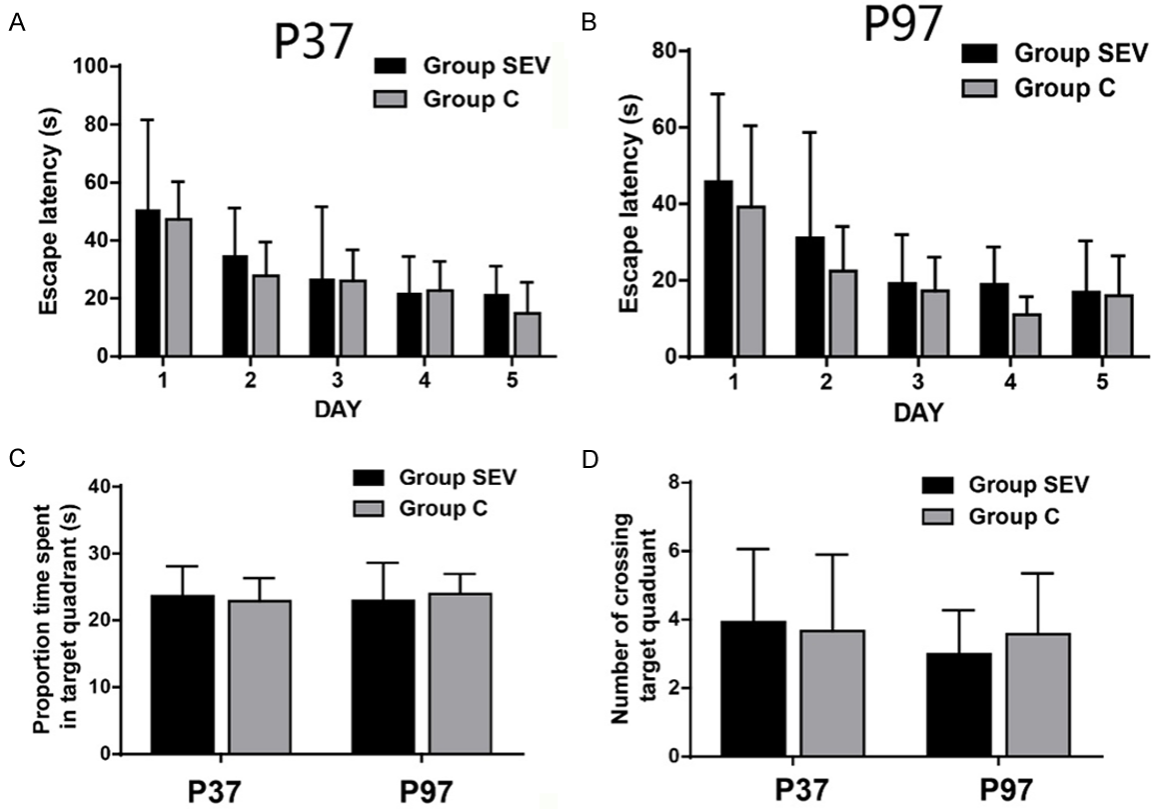

Figure 1. Effect of neonatal sevoflurane exposure on the ability of spatial learning and memory in the Morris water maze test. The escape latency (A and B), the percentage of swimming time spent within the target quadrant (C) and the number of entries into the target quadrant (D) did not differ between group SEV and group C at both P37 and P97 ($P > 0.05$).

bregma, 3.8 mm lateral to midline, 2.6-3.1 mm from the brain surface). Reference electrode was placed in the epidural space. For the immature rats at P37, the position of target regions was determined via the ratio of the distance from bregma to lambda at P97 to that at P37. The correct position of electrodes was firstly corroborated by electrophysiological criteria during experiment [15]. The body temperature was monitor and sustained at 37°C ± 1°C with a heating pad during the experiment. Subjects breathed spontaneously through a mask connecting ventilator that provided 21% oxygen and the end-tidal carbon dioxide was maintained between 35 to 45 mmHg.

Electrophysiological recording

During the process that electrodes were lowered down to the target regions, test stimuli (frequency 0.1 Hz, pulse duration 0.2 ms, intensity 3-6 mA) were delivered to seek for the maximum response. Baseline field excitatory postsynaptic potentials (fEPSPs) and population spike amplitude (PSA) were elicited by stimuli with an interval of 30 s and an intensity that can induce approximately 50% of maximum response. Electrophysiological signals were amplified by a Model 3000 High-Gain AC/DC Differential Amplifier (1 Hz-1 kHz, A-M systems, Inc., Sequim, WA, USA) and recorded by Spike 2 system and software (Cambridge Electronic Design, Cambridge, UK). The average fEPSPs and PSA were calculated and recorded every 5 min. After 30-min steady basal stimulation, paired stimulation with constant intensity (half of maximum stimulation intensity) and increasing interstimulus intervals of 25, 50, 75, 100, 150, 200, 500 ms were implemented to induce paired-pulse facilitation (PPF). 3 paired-pulse stimulus with identical interval were given every 30 seconds. The pair-pulse ration (PPR) was calculated by the value of amplitude of second response/first response. Then 3 trains of high frequency stimulation (HFS: 200 Hz/20 pulses) with train interval of 30 s were delivered to elicit LTP. A significant induction of LTP was characterized by a 30% increase in PSA or

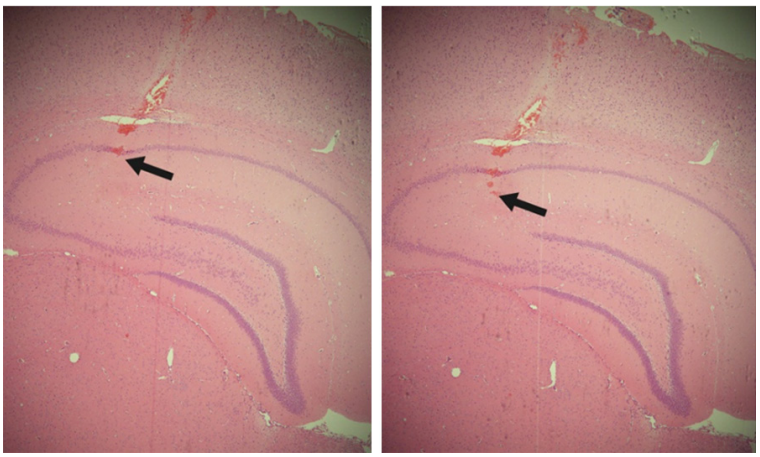

Figure 2. Hematoxylin-eosin stained microphotographs showing the electrode location. The black arrows mark the position of recording electrode tip in CA1 region (left) and stimulating electrode tip in the Schaffer collateral/commissural pathway (right).

fEPSP slope, which could be sustained for more than 30 min. Thereafter 60-min basal stimulation were delivered. The amplitude of PSA, slope of fEPSP and the response to paired stimulation with different interstimulus interval were recorded 30 min before and 90 min after HFS on both P37 and P97. The mean value of fEPSP slope and PSA in the duration 30 min before HFS was regarded as 100%. Other recorded responses were normalized to the mean value. To verify whether electrodes were placed appropriately, histological examination were subsequently implemented after all the procedures.

Statistical analysis

Data analysis of electric signal was implemented with Spike 2 software. All statistical analyses were performed with Origin 8 and SPSS 19.0. All values were presented as mean ± SEM. The one-sample Kolmogorov-Smirnov test and Shapiro-Wilk test were performed, which displayed that all data were normally distributed. Student's t test was used to estimate differences between data from two groups. $P < 0.05$ was were considered statistically significant.

Results

Repeated neonatal exposure to clinically relevant concentration of sevoflurane did not induce learning and memory deficits at juvenile and adult age

Data from Morris water maze exhibited that neonatal sevoflurane exposure did not significantly affect the escape latency during place navigation test at both juvenile and adult age ($P > 0.05$) (**Figure 1A** and **1B**). Likewise, in spatial probe test, there was no remarkable difference between SEV group and control group in the number of entries into the target quadrant and the percentage of swimming time spent within the target quadrant ($P > 0.05$) (**Figure 1C** and **1D**).

Repeated neonatal exposure to sevoflurane induced suppression of LTP at juvenile and adult age

The tips of stimulating and recording electrode were identified by hematoxylin-eosin staining, with an example shown in **Figure 2**. All animals with inappropriate electrode position were excluded. In our experiments, LTP was availably elicited by HFS. As shown in **Figure 3**, the increments of PSA and fEPSP slope after HFS were both more than 30% and maintained for more than 30 min. In P37, The PSA of two groups rose up dramatically after HFS. However, the increments in group SEV were significantly lower than group C at all the time points after HFS ($P < 0.05$) (**Figure 4C**). Similarly, in P97, the increments of group SEV at most of the time points after HFS were remarkably lower than group C ($P < 0.05$) (**Figure 4D**).

In terms of fEPSP slope, at P37, the increments of fEPSP slope in group SEV were inhibited mainly at 5 min, 10 min, 15 min, 25 min and 55 min after HFS ($P < 0.05$), as compared to group C. However, there was no significant difference the increments between group SEV and group C at P97 ($P > 0.05$) (**Figure 4E**, **4F**).

Repeated neonatal exposure to sevoflurane augmented PPF in CA1 region of juvenile and adult rats

For investigating the effect of repeated neonatal exposure to sevoflurane on the short-term synaptic plasticity, paired-pulse stimulation with increasing interstimulus was given to elicit PPF. At P37, PPF ratio induced by paired stimulation with interval of 100 ms, 150 ms, 200 ms and 250 ms in group SEV was significantly augmented ($P < 0.05$) (**Figure 5B**). At P97, PPF ratio

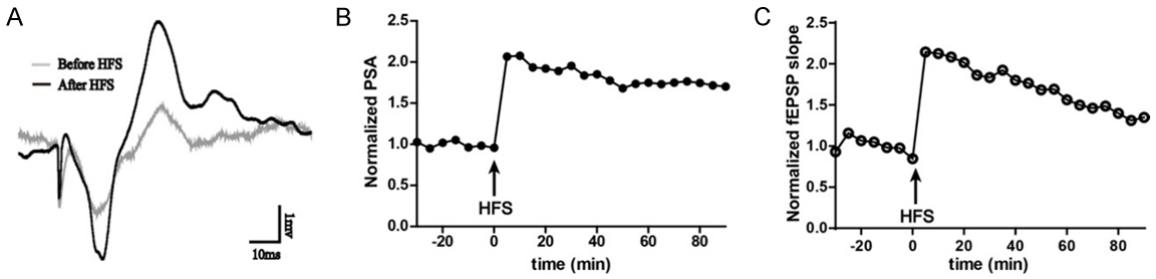

Figure 3. LTP of PSA and fEPSP slope was successfully elicited by HFS in a single experiment. (A) Waveforms induced by single stimulation before and after HFS. Time course responses of PSA (B) and fEPSP slope (C) 30 min before and 90 min after HFS (indicated by up arrow) in the same subject. Note that the increments of PSA and fEPSP slope were more than 30% and maintained for more than 30 min.

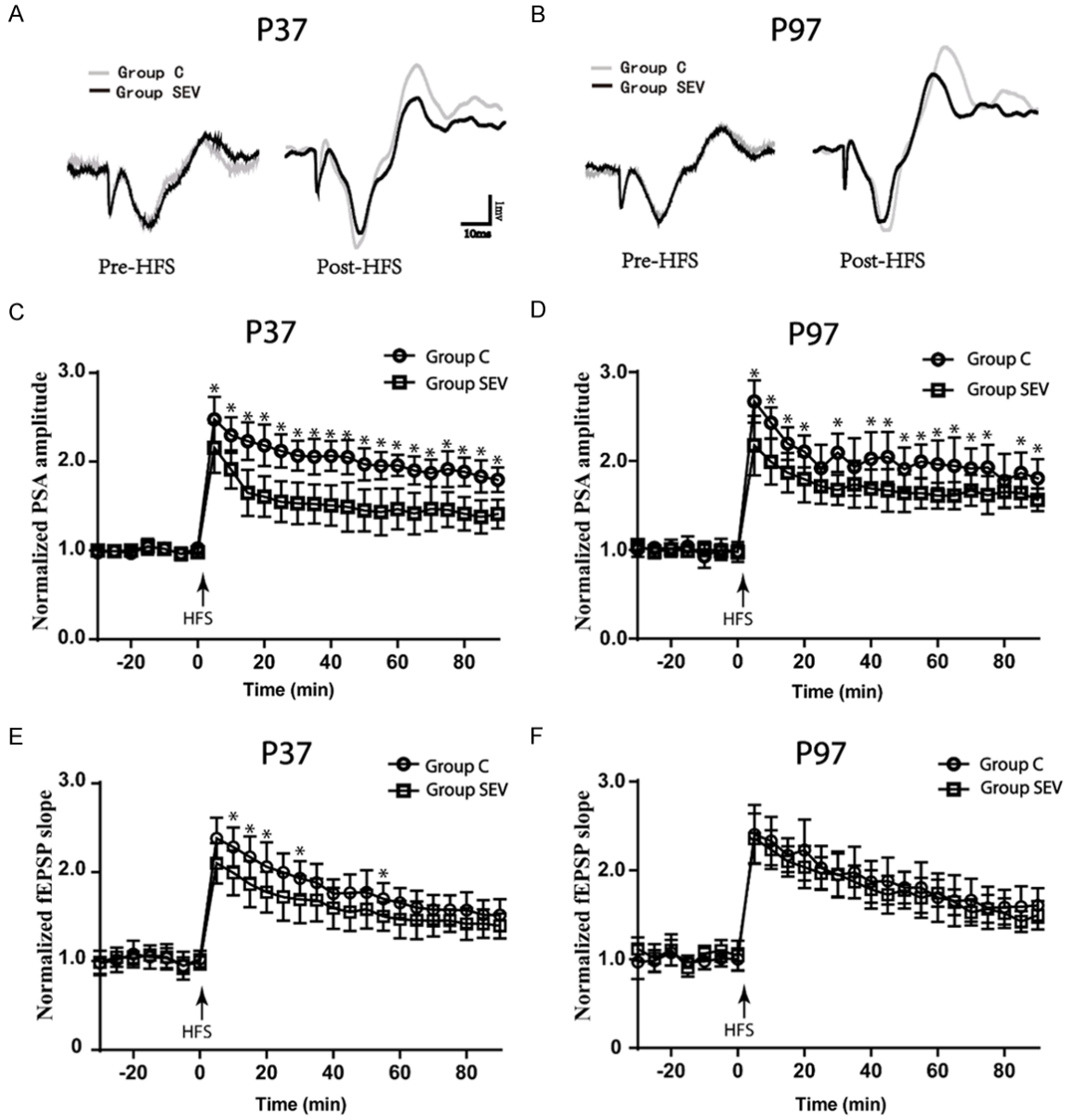

Figure 4. The effect of neonatal repeated exposure to 2.6% sevoflurane on the LTP in PSA and fEPSP slope (n=8). The sample traces of representative PSA of both group before and after HFS in P37 and P97 are demonstrated in

(A and B). The increment in PSA after HFS of group SEV was remarkably inhibited at both P37 (C) and P97 (D) ($P < 0.05$). (E) At P37, the increment of fEPSP slope in group SEV decreased merely at 5 min, 10 min, 15 min, 25 min and 55 min after HFS ($P < 0.05$). (F) There was no significant difference between group C and SEV in fEPSP slope at P97. Each point is shown as mean ± SEM, * represents $P < 0.05$.

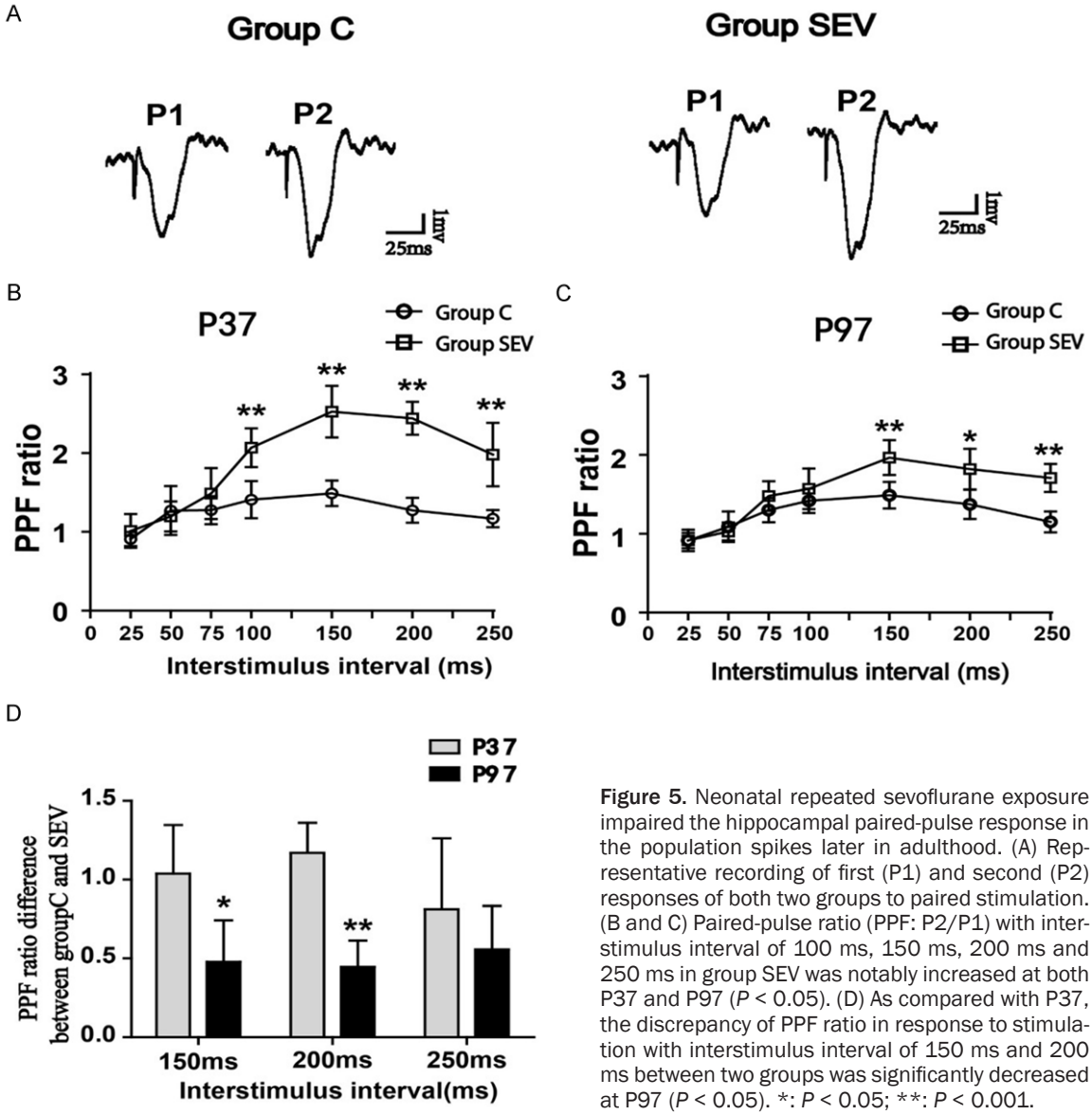

Figure 5. Neonatal repeated sevoflurane exposure impaired the hippocampal paired-pulse response in the population spikes later in adulthood. (A) Representative recording of first (P1) and second (P2) responses of both two groups to paired stimulation. (B and C) Paired-pulse ratio (PPF: P2/P1) with interstimulus interval of 100 ms, 150 ms, 200 ms and 250 ms in group SEV was notably increased at both P37 and P97 ($P < 0.05$). (D) As compared with P37, the discrepancy of PPF ratio in response to stimulation with interstimulus interval of 150 ms and 200 ms between two groups was significantly decreased at P97 ($P < 0.05$). *: $P < 0.05$; **: $P < 0.001$.

induced by paired stimulation with interstimulus interval of 150 ms, 200 ms and 250 ms in group SEV was remarkably higher than group C ($P < 0.05$) (**Figure 5C**).

The discrepancy between group SEV and group C reduced at P97

Comparing with P37, the discrepancy of PSA between group SEV and group C at P97 shrunk, but the variation had no statistical significance ($P > 0.05$). As compared with P37, the discrepancy of PPF ratio in response to stimulation with interstimulus interval of 150 ms and 200 ms between two groups at 97 was strikingly decreased ($P < 0.05$) (**Figure 5D**).

Discussion

In the past few years, with the growing number and category of pediatric surgery, early and repeated exposure to sevoflurane has increas-

ed dramatically. It has been demonstrated by previous laboratory and clinical studies that sevoflurane exposure in early life can induce structural and functional changes in the developing brain, thereby further give rise to long-term learning deficits and abnormalities in social behaviors later in life. However, there remain a few studies indicating that neonatal repeated exposure to sevoflurane does not impair the spatial cognition [16] and attentional processing [17] at juvenile and adult age. Likewise, our results of behavioral tests revealed that the ability of spatial learning and memory is not influenced by repeated neonatal exposure to clinically relevant concentration of sevoflurane. These results may probably mainly arise from several aspects as follow. Firstly, the concentration in most of literatures that showed remarkable deficits in learning and memory after neonatal exposure was 3% or more [18-20], whereas several studies using concentration less than 3% turned out negative results [16, 17]. Our sevoflurane concentration for neonatal exposure was maintained at 2.6%. This concentration that equals to 1.3 MAC can prevent movement of 99% animals in our experiment, which is also clinically relevant and commonly used in pediatric surgery [21]. Therefore, relatively low concentration we used may underlie the current results. On the other hand, Shen et al [22] indicated that the younger the animal's age when exposed and the shorter the interval between exposures, the greater the severity. Repeated exposure to sevoflurane for 2 h daily at postnatal days 6, 7, and 8 [19], or 4, 5 and 6 [23] consecutively can induce significant memory impairment. Nevertheless, in our experiment the time points when pups were exposed to sevoflurane were P7, P14 and P21, with 7-days interval, which were relatively older and discrete. This may be a possible reason for the negative result in behavioral tests.

In our electrophysiological experiment, remarkable decreased increments in PSA were observed at juvenile age and adulthood of animals exposed to sevoflurane, as compared with normal rats. Our data were consistent with several in vitro studies which revealed neonatal exposure to sevoflurane inhibits hippocampal LTP in brain slices at juvenile age [24, 25]. Also, study in vivo has shown inhalation of sevoflurane at P7 gives rise to long-lasting suppression of hippocampal LTP at postnatal 63 to 70 [26]. Of note, in our results the discrepancy of PSA between two groups was more notable than slope of fEPSP in both juvenile and adult age. This dissociation between EPSP and population spike (PS) was also observed in other studies. For instance, Tabassum et al [27] revealed that acute stress leads to a long-term depression in baseline values of PSA but partially fEPSP. Despite both PSA and slope of fEPSP can be used to assess LTP, their internal implication differ. EPSP of pyramidal neurons reflects glutamatergic excitatory synaptic transmission [28], whereas PSA is the postsynaptic population discharge of neurons, representing the neuronal responses to a given EPSP [29]. Apart from glutamatergic transmission, other excitatory and inhibitory transmissions such as acetylcholinergic and GABAergic play important roles in the modulation on postsynaptic population responses as well. Therefore, our data implied that neonatal exposure to sevoflurane presumably brings about impacts on a variety of synaptic transmissions and modulations including glutamatergic transmission, of which PSA is the comprehensive results. Intriguingly, there exists an inconsistency between electrophysiological and behavioral results in the present study. This phenomenon has been reported in a study which exhibited that behavior of short- and long-term memory are not affected, whereas synaptic plasticity is altered by exposure to sevoflurane in early life [9]. Combining with the accumulating evidence that showed the extent of neuronal degeneration induced by neonatal anesthetics exposure is inconsistent with that of alteration in spatial learning and memory performance [30], we speculate that although there exists a close link between alteration in synaptic plasticity, morphological and behavioral changes, the relationship is not absolute cause and effect. The potential mechanism remains to be elucidated.

PPF, a primary form of short-term plasticity, represents presynaptic facilitation in response to repetitive stimulation and is involved in learning and memory function [31, 32]. In the current study, neonatal sevoflurane exposure resulted in enhanced PPF ratio to different extent at juvenile and adult age. Similar results were previously reported. Qiu et al [9] indicated that 30-min exposure to 2.5% sevoflurane in

the early postnatal period leaded to larger PPF in the brain slice of adult animals. Likewise, neonatal treatment with pentobarbital causes a greater facilitation of test pulse in adulthood [33]. The potential mechanism underlying this enhanced PPF is probably two-fold. Firstly, it has been demonstrated that volatile anesthetics can increase presynaptic calcium concentration via the mitochondrial pathway [34], thereby mediating neurotoxic effects in the brain [35]. Due to increased presynaptic residual calcium, second pulse could elicit more transmitter release, and thus induce larger postsynaptic population responses. Secondly, sevoflurane is a GABAergic agonist. Exposure to sevoflurane during developing period can influence expression of $GABA_A$ receptor in hippocampal synapse, even downregulating the development of GABA ergic inhibitory synapse [36, 37]. Therefore, the imbalance between excitatory and inhibitory synaptic transmission may contribute to the enhanced PPF in this study as well. On the other hand, the hyperexcitability induced by damage of GABA ergic inhibition interferes with the maturation of glutamatergic synapses, which is indispensable for LTP [38]. Besides, aforementioned calcium derangement in the presynaptic membrane can elicit neuroapoptosis and influence the synaptic function [39]. Thus, neonatal sevoflurane exposure may impact the long-term and short-term synaptic plasticity by similar molecular mechanism.

The dynamic changes of abnormal behavior, neuronal function and structure with growing age in the animals neonatally exposed to sevoflurane were documented previously. Ji et al [40] showed neonatal exposure to sevoflurane resulted in behavioral abnormality and decreased parvalbumin expression at P42 rather than P90. It also has been demonstrated that the histopathological impairment induced by neonatal anesthetics exposure gradually recovered and even vanished at adult age [30, 41]. In line with their results, our electrophysiological data also found a tendency that the discrepancy in PSA, slope of fEPSP and PPF ration between animals exposed to sevoflurane at neonatal period and controls noticeably shrunk at adult age comparing with juvenile age. The reason behind this phenomenon may primarily derive from the neuronal compensation and self-repair during development [42]. These data also indicated that sevoflurane-induced effects on the developing brain might be transient in feature.

Collectively, our study indicated that repeated exposure to 2.6% sevoflurane in early life does not result in significant behavioral abnormalities, whereas induces impairment to both long-term and short-term synaptic plasticity in the neurons of hippocampal CA1 region at juvenile and adult age. This effect is most noticeable at juvenile stage with tendency of alleviation during adulthood. This results may provide a new perspective for understanding the mechanism of sevoflurane-induced toxic effects.

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Disclosure of conflict of interest

None.

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