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Short Communication

The effects of sevoflurane on short memory impairment in mice

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This study was aimed at investigating the effects of sevoflurane on short memory impairment and the relative synaptic mechanism. To achieve this, at 12, 24 and 72 h after the mice were exposed to 1.5% sevoflurane for 1 h, the spontaneous alternation and locomotor activity was assessed by Y maze and the short term potentiation (STP) were measured with extracellular recording technique in hippocampal slices. Results indicated that at 12 h after administration with sevoflurane *in vivo*, the spontaneous alternation and locomotor activity decreased significantly compared with that of control group, and the population spike amplitude after induction of STP decreased significantly in hippocampal slices. However, there was no difference at 24 and 72 h. After administration with sevoflurane *in vitro*, the basic or titanic population spike amplitude decreased significantly in hippocampal slices, but the amplitude could be recovered after wash-out. Therefore, sevoflurane impaired the short memory by suppressing synaptic transmission in the near future but not the long future.

Key words: Sevoflurane, memory, anesthesia, Y-maze.

INTRODUCTION

The post-surgery cognitive decline has been a hotspot in the past decades. Patients demonstrated partial loss of cognitive function after the surgery, which could last for weeks (Rohan et al., 2005). The underlying mechanism is not fully elucidated yet. One theory was that the inflammation affected the cognitive function, while the other one was that general anesthesia can cause transient functional changes of neural circuits and therefore the cognitive function. Meanwhile, the negative effects of general anesthesia on cognitive function have been reported in both neonates and adults.

Sevoflurane is one of the most widely used anesthesia agents clinically, with pharmacological effects through γ-aminobutyric (GAB) acid receptor and N-methyl-d-aspartate (NMDA) receptors (Eom et al., 2011; Petrenko et al., 2008). Sevoflurane was found to be associated with many side effects on other body regions (Ping et al., 2011; Xie et al., 2012). However, whether sevoflurane administration can cause specific loss of cognitive functions is yet unknown. Additionally, how long this will last is not studied as well. Hence, the present study was aimed at investigating the effects of sevoflurane administration on the short term memory of mice. We employed Y-maze, which is a hippocampus dependent-task (Wan et al., 2007), to test the short memory changes of the mice. We further examined the electrophysiological changes in acute slices from hippocampus. The results obtained would provide rationales for clinical practices with sevoflurane administration and post-operative cares.

MATERIALS AND METHODS

Animals and the brain slices

Fifty-six Kunming mice (male and female, 2 months old) from the animal experimental center of Xuzhou Medical College, were

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Table 1. Effect of isoflurane on spontaneous alternation and locomotor activity in the Y-maze (mean ± SEM, n=8).

Group		Alternation behavior (%)	Number of arm entries
Control		64.3 ± 2.5	21.3 ± 2.3
oxygen	12 h	65.5 ± 2.9	22.3 ± 1.9
	24 h	65.7 ± 3.1	22.6 ± 2.5
	72 h	65.2 ± 2.4	22.1 ± 2.6
Sevoflurane	12 h	54.7 ± 1.7**	16.4 ± 1.3**
	24 h	64.5 ± 2.6	22.9 ± 1.8
	72 h	64.9 ± 3.1	23.2 ± 2.6

*p<0.05, **p<0.01 vs. control group.

Table 2. The change of population spike amplitude (PSA) in hippocampal slices after isoflurane administration *in vivo* (mean ± SEM, n = 8).

Group		PSA after tetanic stimulation (%)
Control		142.3 ± 16.3
oxygen	12 h	141.6 ± 15.1
	24 h	145.1 ± 17.2
	72 h	143.6 ± 16.4
Sevoflurane	12 h	122.3 ± 13.9*
	24 h	139.6 ± 18.5
	72 h	142.1 ± 17.6

*p<0.05, **p<0.01 vs. control group.

randomly assigned into 7 groups with 8 each (sevoflurane or oxygen for 12, 24 and 72 h each, as well as one control group without any treatment). For sevoflurane-inhalation group, 1.5% sevoflurane in 100% oxygen were given for 1 h (Kimura et al., 1994); while for oxygen-inhalation group the mice just receive 100% oxygen.

For acute brain slice preparation, the animals were euthanized and the brain was harvested immediately, placed in 4° artificial cerebrospinal fluid (aCSF) saturated with oxygen-carbon (95% O_2, 5% CO_2). Then coronal 400 µM hippocampal brain slices were cut with a Leica V1000 vibratome. The slices were incubated in 32° aCSF for 2 - 3 h for recovery before recording. The components for the aCSF were (in mmol·L^{-1}): NaCl 124, KCl 3.3, NaH_2PO_4 1.24, $MgSO_4$ 2.4, $NaHCO_3$ 25.7, $CaCl_2$ 2.4, glucose 10.0 (pH 7.35 - 7.45). For *in vitro* application of the sevoflurane, 1.5% sevoflurane in oxygen-carbon was used to saturate the aCSF before perfusion onto the brain slices.

Y-Maze test

The Y-maze test was performed as described by Hidaka et al. (2011). Briefly, three 30 cm long arms with 120° inter val each were used; the height and width of the arms were 15 and 15 cm. The mice were allowed for free exploration of the Y-maze for 8 min. The numbers of spontaneous alternation (continuous three entries into three different arms) were recorded. The locomotor activity was evaluated as the total entries to all arms.

The population spike recording and STP induction

Bipolar stimulation electrode was placed on the Schaffer afferents from the CA3 neurons, and the micropipette (internal solution 2 mM NaCl, 2 - 10 MΩ) was placed in CA1 neuron area to record the population spikes. A tetanic stimulation at 100 Hz for 200 stimuli was given after 10 min baseline to examine the occurrence of STP.

Statistical analysis

The data was presented in mean ± standard error of mean (SEM), and t test was used to compare between groups. P<0.05 was determined as statistically significant.

RESULTS

The behavioral changes after sevoflurane inhalation

Twelve hours after sevoflurane inhalation, the percentage of spontaneous alteration and locomotor activity of the mice decreased compared to the control group (P<0.01); while there is no change in these indices for the oxygen inhalation group. For 24 and 72 h after sevoflurane or oxygen inhalation, there were no changes (Table 1).

The STP induction on the hippocampal slices

Thirty minutes after the tetanic stimulation, the PS amplitude was 142.3 ± 16.3%, suggesting the induction of STP (Table 2). For the slices prepared mice with 12 h after sevoflurane inhalation, the PS amplitude of STP decreased, which was 122.3 ± 13.9% (P<0.01). There were no differences in STP induction for bran slices prepared from mice with 24 or 72 h after sevoflurane inhalation (Table 2). With *in vitro* application of sevoflurane, the PS amplitude decreased to 83.5 ± 8.9% (P<0.05), and was recovered during the washout phase

Table 3. The change of population spike amplitude (PSA) in hippocampal slices after isoflurane administration *in vitro* (mean ± SEM, n=8).

Group	PSA (%) during isoflurane administration		Wash out
	Before tetanic stimulation	After tetanic stimulation	
Control	100.3 ± 0.5	142.3 ± 16.3	143.7 ± 15.8
Sevoflurane	83.5 ± 8.9**	116.5 ± 14.9**	137.5 ± 12.4

*p<0.05, **p<0.01 vs. control group.

(Table 3). Additionally, during sevoflurane wash-in, the STP induction was decreased (116.5 ± 14.9%) (P<0.01) compared to the control group; this was also recover in the washout phase (Table 3).

DISCUSSION

Post-operative cognition disorder (POCD) is common in patients, especially for aged patients (Rohan et al., 2005). POCD has been found to be associated with the anesthesia performed, age, lack of oxygen during the surgery and the low perfusion into the brain tissues (Hudson and Hemmings, 2011). Sevoflurane administration was found to cause POCD syndromes in clinical practices (Li et al., 2011). However, animal studies have showed controversial results (Alkire et al., 2005; Li et al., 2011; Shih et al., 2012). In the present study, we found that the decreased spontaneous alteration and locomotor behavior in mice was only at 12 h following sevoflurane inhalation, suggesting that short-term memory rather than long-term memory was affected. Moreover, the electrophysiological evidences demonstrated that STP induction was only impaired at 12-h time point. The acute application of sevoflurane could also interrupt synaptic transmission, such as the PS amplitude and the STP induction. These effects could be washed out, indicating for a transient inhibition.

Taken together, the present study showed that sevoflurane would not cause long-term (at least for 72 h) deficits in short-term memory production in a Y-maze test. Hence, there could be other changes going on but left uninvestigated. Additionally, some factors other than the anesthesia might contribute to the POCD as well. Further studies are, therefore, required to investigate the effects of sevoflurane on different types of synaptic transmission and brain functions.

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