Original Article

Effect of multiple neonatal sevoflurane exposures on hippocampal apolipoprotein E levels and learning and memory abilities

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Background: Sevoflurane anesthesia is widely used in pediatric patients. In this study, we investigated whether early multiple exposures to sevoflurane induced cognitive dysfunction by altering the hippocampal expression of ApoE later in development. Methods: Sprague–Dawley rats were exposed to 2.6% sevoflurane at postnatal day 7 (P7), P14, and P21 for 2 h. The ability of learning and memory was assessed using the Morris water maze at P37 and P97. The hippocampal volume was measured by magnetic resonance imaging (MRI) at P37 and P97. The hippocampal expression of ApoE was assessed by immunohistochemical analyses and real-time polymerase chain reaction (PCR).

Results: Behavioral testing revealed that the ability of learning and memory in the sevoflurane-exposed rats was decreased compared with the control animals; however, there was no significant difference (P > 0.05). The MRI results showed a significant decrease in the left hippocampal volume, left maximum hippocampal length, and right maximum hippocampal length in the sevoflurane young group compared with the control young group (P < 0.05). The brain volume, left maximum hippocampal length, right hippocampal volume, and maximum brain length were significantly lower in the sevoflurane adult group than in the control adult group (P < 0.05). In young animals, the ApoE expression in the hippocampal CA1 and CA3 regions and the ApoE mRNA level were significantly higher compared with the control group (P < 0.05), but not in the dentate gyrus region (P > 0.05). Among the adult animals,
1. Introduction

The neonatal period is critical for the development of the brain. During this period, neuronal proliferation and differentiation are at the peak of their activity, and the nervous system is susceptible to damage by exogenous drugs. Sevoflurane, a volatile gas, is the most common anesthetic drug for children, because of the low toxicity and fast onset and recovery. Several studies suggested that exposure of the young population to sevoflurane may negatively influence the learning and memory ability. Interestingly, several studies have found that apolipoprotein E (ApoE) may cause the aggregation of β-amyloid (Aβ) and subsequently accelerate the development of Alzheimer’s disease (AD). Further studies demonstrated that sevoflurane also induces the aggregation of Aβ. Thus, we speculated that ApoE is a mediator between sevoflurane and Aβ aggregation. In the present study, we investigated whether or not there is relationship between sevoflurane and ApoE.

2. Materials and methods

2.1. Animal treatment and anesthesia

Pregnant Sprague-Dawley rats (provided by the Experimental Animal Center of Third Military Medical University; scxk [Chongqing] 2012-0005) were maintained under standard laboratory conditions (temperature, 21 ± 2 °C; relative humidity 50%; and 12-h light/dark cycle). Neonatal rats were randomly divided into the following four groups (n = 12 per group): control young group, sevoflurane young group, control adult group, and sevoflurane adult group. The experimental protocol was approved by the Ethics Committees of the Zunyi Medical College.

All neonatal rats in the sevoflurane groups were subjected to a 2-h exposure to 2.6% sevoflurane and 2 L/min O2 at postnatal day 7 (P7), P14, and P21. In contrast, the control groups only received 2 L/min O2. The concentration of O2 and sevoflurane were constantly monitored using a gas analyzer (Vamos Variable Anesthetic Gas Monitor, Draeger, Lubeck, Germany). The temperature in the anesthesia chamber was maintained at 28 °C, and the relative humidity 50%; and 12-h light/dark cycle). Neonatal animals (n = 12 per group) were acclimated for 1 day. Each rat was placed at a random position in the pool (120 cm in diameter and 60 cm high) and was allowed to swim for 120 s.

2.2. Morris water maze

The behavioral testing was performed at P31 in the young groups and at P91 in the adult groups. The memory and learning abilities were evaluated using the Morris water maze (Chengdu Taimeng Technology Ltd., Chengdu, China).

2.2.1. Acclimatization training

Young (P31) and adult groups (P91) were subjected to acclimatization training for 1 day. Each rat was placed at a random position in the pool (120 cm in diameter and 60 cm high) and was allowed to swim for 120 s.

2.2.2. Place navigation test

Young groups, at P32, and adult groups, at P92, were placed in the pool with the water level at 1.0 cm above the top of a 15-cm-diameter platform. All rats underwent four trials every day in four quadrants, and were given 120 s to locate the hidden platform. If an animal failed to locate the platform within this time, it was guided to the platform and allowed to remain there for 30 s. The rats were removed from the water after remaining on the platform for 15 s. The rats were tested for 5 days consecutively. The escape latency and the total swimming distance were recorded using a WMT-100 maze video tracking system (Chengdu Taimeng Software, Chengdu, China).

2.2.3. Spatial probe test

The platform was removed, and rats at P37 and P97 were placed in the quadrant opposite the trained platform and allowed to swim for 120 s. The time spent in the trained platform quadrant, the distance traveled in the trained platform quadrant, and the times of crossing the trained platform were recorded.

2.3. Magnetic resonance imaging (MRI)

After the spatial probe test, young and old rats were subjected to MRI scanning (HDXT3.0T; General Electric Company, USA) under anesthesia with 1% sodium pentobarbital at P37 and P97, respectively. The hippocampal volumes and other correlative indexes were subsequently measured using a visual assessment method. The MRI scanning parameters were as follows: repetition time (TR)/echo time (TE), 12.9/5.1 ms; inversion time interval (TI), 450 ms; flip angle, 12°; matrix, 224 × 192; voxel, 0.3 mm × 0.3 mm × 0.3 mm; field-of-view (FOV), 5 mm × 5 mm; and band width, 19.2 kHz.

There was no significant difference between the groups in any parameter tested (P > 0.05).

Conclusion: Multiple exposures to sevoflurane during the neonatal period decreased the volume of the hippocampus and increased the hippocampal expression of ApoE. The differential expression level of ApoE in different hippocampal subdivisions suggested that the expression of ApoE was regionally specific and reversible.

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