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Original Article

# Sirtuin 3 (SIRT3) improves sevoflurane-induced postoperative cognitive impairment by regulating mitochondrial oxidative stress

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**Abstract**

One of the most prevalent co-operative disorders is postoperative cognitive dysfunction (POCD), however, its pathogenesis remains unclear. Thus, this work aimed to evaluate SIRT3's impact on cognitive decline in aged mice under anesthesia. Adeno-associated virus SIRT3 vector (AAV-SIRT3) or empty vector (AAV-VEH) was injected into the hippocampal region of aged mice after sevoflurane induction in order to upregulate the expression of SIRT3. The expression levels of SIRT3, pro-inflammatory cytokines, and apoptotic factors in hippocampus tissues were identified by PCR, Western blotting, TUNEL staining, and enzyme-linked immunosorbent assay (ELISA), and the cognitive function of mice was assessed. The SIRT3 expression was downregulated in the hippocampal tissue of anesthetized mice. SIRT3 overexpression can improve the learning and memory ability, reduce the escape latency, and increase the residence time in the platform and platform crossing ability of mice. The overexpression of SIRT3 in hippocampus can reduce the oxidative stress response and inflammatory response induced by anesthesia in mice, increase the superoxide dismutase (SOD) expression level, and decrease the expression level of MDA and inflammatory factors in hippocampus. In addition, SIRT3 overexpression can also reduce anesthetic-induced hippocampal cell apoptosis. By reducing the hippocampus mitochondrial oxidative stress response, SIRT3 plays a significant role in the pathophysiology of POCD in mice and is a potential target for POCD treatment and diagnosis.

**Keywords:** Post-surgical cognitive impairment, Sevoflurane, Sirtuin 3 (SIRT3), Mitochondrial oxidative stress, Inflammatory response.

## 1. Introduction

Postoperative cognitive function (POCD) is common in elderly stroke patients and manifests as cognitive decline in various aspects such as memory, language, understanding, thinking or attention [1]. Existing studies have proven that risk factors such as older age, low education level, and preoperative mental health can promote the occurrence of POCD [2]. Evidence from clinical research indicates that POCD may increase mortality, negatively impact quality of life, and require longer hospital stays [3]. The cause of POCD is related to multiple factors, including patient, surgery, anesthesia, or a combination thereof, and its internal mechanism is complex and unclear.

Sevoflurane is a safe and effective anesthetic commonly used in clinical practice. Although the cardioprotective effect of sevoflurane has been widely recognized, the cognitive function caused by anesthesia surgery requires further research [4]. Previous studies have shown that sevoflurane can enhance the rats' capacity for spatial memory [5]. In addition, some studies have reported potential mechanistic pathways by which sevoflurane anesthesia induces cognition, including endoplasmic reticulum stress, mitochondria, inflammation, and neuronal apoptosis [6]. Sevoflurane seems to exacerbate cognitive deficits to a greater or lesser extent, However, more investigation is still needed to determine the precise underlying mechanism of sevoflurane-induced POCD.

Within mitochondria, sirtacetylase protein 3 (SIRT3) plays a role in controlling both the oxidative stress response and mitochondrial activity in cells [7]. The only sirtuin that is directly linked to a longer human lifespan is SIRT3, which is also linked to neurodegenerative disorders [8]. It has been reported that SIRT3 can bind to PTEN-inducing kinase 1 (PINK1) and Parkin and deacetylate them to promote mitophagy, and upregulating SIRT3 activity can prevent neuronal degeneration in Parkinson's disease models [9]. Tyagi et al. found increased IL-1β levels and microglial activation in the brain tissue of SIRT3−/− mice. SIRT3−/− mice show poor remote memory and the number of neurons in brain tissue [10]. Furthermore, SIRT3 has been demonstrated to influence inflammatory responses linked to mitochondria [11]. However, The function of SIRT3 in POCD in old mice is poorly understood. Thus, we think that by controlling mitochondrial oxidative stress in the mouse hippocampal tissue, SIRT3 may mitigate the effects of postoperative cognitive function. Our current

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goal is to ascertain how SIRT3 affects anesthesia-induced cognitive function in older mice and the underlying molecular underpinnings of this effect.

## 2. Materials and methods

### 2.1. Experimental animals

This experiment selected 30 C57BL/6 mice(15 males and 15 females) aged 18 months and weighing 10-15 g. The mice were all from Shanghai Slack Experimental Animal Co., Ltd. (Shanghai, China). There were 5 mice per cage, with free access to food and water at 22-25°C, with a 12-h light/dark cycle.

The SIRT3 overexpression vector (AAV-SIRT3) was constructed with adeno-associated virus (AAV). The rAAV-mNeonGreen vector without SIRT3 was used as the control group (AAV-VEH). Viral vector construction was entrusted to OBiO Biotechnology (Shanghai, China).

### 2.2. Group grouping and administration of mice

3 groups of thirty C57BL/6 mice each were created at random: (1) Control group: the mice were given tracheal tubes to inhale 40% oxygen. (2) Anesthesia group: mice were given inhalation of 3% sevoflurane and injection of AAV-VEH (20 μM). (3) SIRT3 group: mice were given inhaled 3% sevoflurane and injected with AAV-SIRT3 (20 μM). The inhalation time of oxygen and sevoflurane was 3 h. Adenoviral vectors were injected through the left cerebral ventricle of mice 1 hour before sevoflurane anesthesia. On the third day after anesthesia induction, 5 mice from each group were sacrificed, and hippocampal tissue was collected. The remaining mice were continued to be fed for 1 week for cognitive performance.

### 2.3. Open field test, OFT

We measured the mice's capacity for locomotor activity at various times using OFT. Provide a 40×40×40 cm square arena and allow the mice to roam freely in the arena for 5 minutes. The entire range of the mice within the arena is tracked and recorded. Before each test, the site must be disinfected with 75% ethanol.

### 2.4. Morris water maze experiment

Mice were subjected to spatial acquisition training 5 days before sevoflurane anesthesia. Divide the pool into 4 areas, put the mice from any position in the pool, and train the mice to find the platform within 60 seconds. The platform was removed one day before anesthesia, and the rodents were put in the same position in the pool. The time it took for the mice to get to the stage (i.e., the escape latency) was recorded and calculated. At the same time, statistics were collected and evaluated for the time the mice passed through the original platform and stayed in the original platform area. Learning and memory functions in mice.

### 2.5. Real-Time PCR

The entire RNA was taken out of hippocampal tissue cells and transcribed into cDNA using TRIpure total RNA extraction reagent and reverse transcriptase (Shanghai Keaibo Biotechnology, Shanghai, China). Prepare a mixture of cDNA template, specific gene primers and diluted 2×Plus SYBR, and use the PCR mixture to perform real-time quantitative PCR. PCR results were normalized by GAPDH, and gene expression levels were detected by the $2^{-\Delta\Delta CT}$ method.

### 2.6. Western blot

Use lysis solution to process hippocampal tissue and extract protein components in the tissue. Electrophoresis was used to separate the proteins, which were then moved to cellulose membranes. After 5% skim milk was used to block the membrane, SIRT3 (1:1000), TNF-α, IL-1β, and IL-6 primary antibody solutions (1:3000, GeneTex, Irvine, CA, USA) were added and left overnight to incubate. As an internal control, GAPDH (1:5000, Abcam, Cambridge, MA, USA) primary antibody solution was utilized. After applying HRP-conjugated secondary antibody (1:5000; Cell Signaling Technology, Danvers, MA, USA) solution to the membrane, an enhanced chemiluminescence detection kit (Thermo Fisher, Waltham, MA, USA) was used to identify the membrane. The inside of the membrane was measured using Image J software.

### 2.7. TUNEL dye

The TUNEL apoptosis detection kit (Beyotime Biotech, Shanghai, China) was used to identify cell apoptosis. Paraformaldehyde 4% was used to fix hippocampal tissue for 30 minutes. Triton X-100 (0.1%) was then applied to fixed cell slices, and blocked with endogenous peroxidase blocking solution for 20 min. Use fluorescein-labeled dUTP solution to prepare TUNEL solution and react with the sections for 1 hour. Apoptotic cells were viewed with a fluorescent microscope and numbered. (excitation light wavelength is 450~500 nm).

### 2.8. Enzyme-linked immunosorbent assay (ELISA)

After homogenizing hippocampus tissue, remove the supernatant using low-temperature centrifugation. The contents of SOD and MDA were measured using SOD and MDA detection kits (Shanghai Enzyme Biotech, Shanghai, China). The absorbance was measured using an ELISA meter (BioTek, Biotek Winooski, VT, USA) at a wavelength of 450 nm. Then draw a curve from which the SOD and MDA contents are calculated.

### 2.9. Statistical analysis

For statistical analysis, GraphPad Prism8.0 (GraphPad Software, Inc., La Jolla, CA, USA) was utilized. The data is shown as mean±SD. The unpaired t-test was used to compare the differences between the groups. An unimodal analysis of variance was used for data pertaining to several groups. A difference was deemed significant when $P<0.05$.

## 3. Results

### 3.1. Assessment of cognitive ability in mice

In an assessment of cognitive performance in the mice, we found that sevoflurane anesthesia reduced the distance of movement, whereas AAV-SIRT3 treatment restored mobility (Figure 1A). AAV-SIRT3 decreased escape latency in mice, although halflurane anesthesia enhanced it, according to the Morris water maze test (Figure 1B). Subsequent examination of the data revealed that the number of passes and the amount of time spent in the platform quadrant dropped following three days of sevoflurane inhalation, but SIRT3 overexpression was able to comparatively enhance the number of passes and the amount of time spent in the target quadrant (Figure 1C, 1D). SIRT3 overexpression can alleviate sevoflurane-induced memory

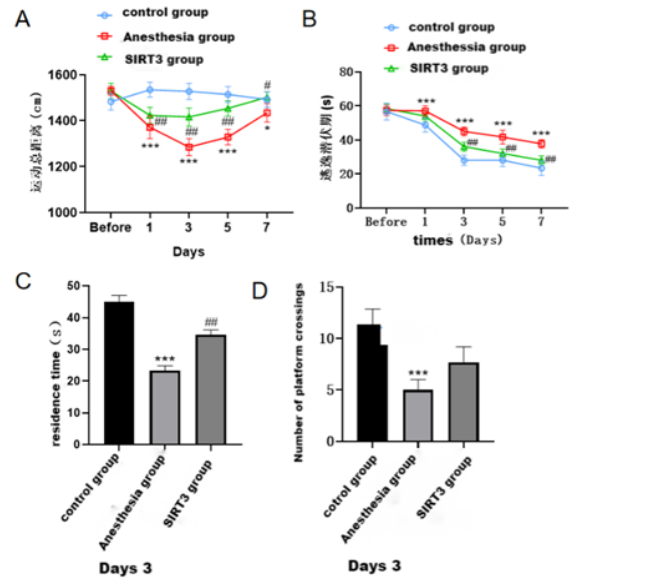


**Fig. 1.** Assessment of Cognitive Function in Mice. (A) movement distance assessment of mice. (B) Evaluation of escape latency in mice. (C) residence time of mice in the target quadrant. (D) number of times mice passed through the target quadrant. ***$P$<0.001, *$P$<0.05, compared with the control group; ##P<0.01, #$P$<0.05, compared with anesthesia group.

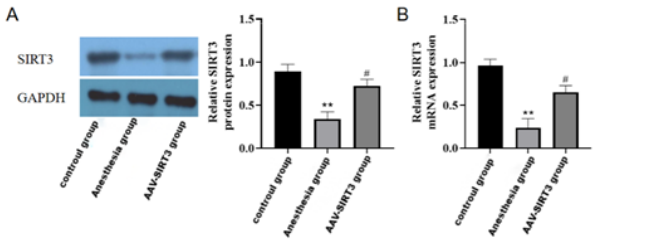


**Fig. 2.** SIRT3 Expression in the Hippocampus. (A) Detection of SIRT3 protein expression. (B) Detection of SIRT3 mRNA expression. **P<0.01, compared with control group; #P<0.05, compared with the anesthesia group.

and learning dysfunction.

### 3.2. SIRT 3 expression in the hippocampus

After three days of inhaling sevoflurane, SIRT3 expression in the hippocampus of mice was measured as shown in Figure 2. When compared to the pre-anesthesia group, the anesthesia group's SIRT3 protein expression was lower. Furthermore, compared to the anesthetic group, the AAV-SIRT3 group had higher SIRT3 protein expression (Figure 2A). PCR assay also showed that inhalation of anesthesia reduced SIRT3 mRNA levels, and AAV-SIRT3 treatment restored the anesthesia-induced decrease in SIRT3 expression (Figure 2B).

### 3.3. Effect of SIRT 3 on mitochondrial oxidative stress and inflammation in hippocampal tissue

An assessment was conducted on the hippocampal mitochondrial oxidative stress index. SOD levels were substantially lower and MDA levels were significantly higher in the anesthetic group, as Figure 3 illustrates. In contrast, SIRT3 overexpression increased SOD levels and decreased MDA levels (Figure 3A, 3B). After measuring the levels of inflammatory factors, it was discovered that while AAV-SIRT3 therapy decreased the expression of inflammatory factors, the induction of anesthesia increased the production of TNF-α, IL-1β, and IL-6 in the hippocampal regions (Figure 3C).

### 3.4. Effect of SIRT 3 on cell apoptosis in hippocampal tissues

Hippocampal tissue apoptosis was evaluated, and the results are shown in Figure 4. Apoptosis in the anesthetic group is associated with increased Bax and Caspase 3 mRNA expression and dramatically decreased Bcl ~ 2 mRNA expression. In contrast to the anesthetic group, the Bcl-2 expression rose in the group AAV - SIRT3 apoptosis factor mRNA expression of Bax and Caspase 3 declines (Figure 4A). Apoptosis assays showed increased apoptosis in hippocampal cells in the anesthesia group and decreased apoptosis in the AAV-SIRT3 group, in contrast to the group under control (Figure 4B).

## 4. Discussion

Inhalation is frequently employed in medical settings, and existing studies have shown that sevoflurane can cause neurotoxicity in young mice [12]. Sevoflurane is

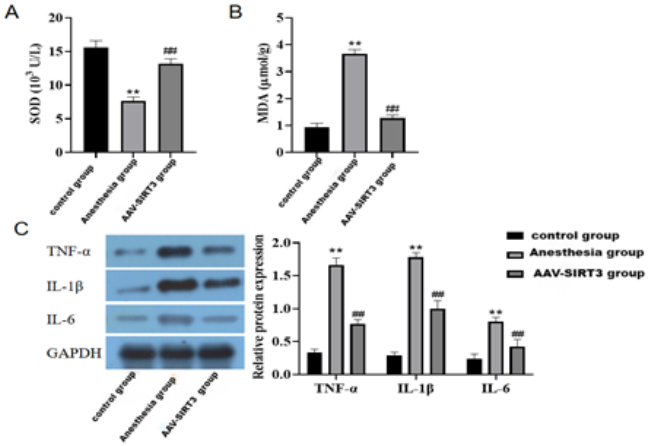


**Fig. 3.** Indicators of mitochondrial oxidative stress and levels of inflammatory factors in the three groups. (A) Detection of SOD level. (B) Detection of MDA levels. (C) Protein expression levels of TNF-α, IL-1β and IL-6. **P<0.01, compared with control group; ##P<0.01, compared with the anesthesia group.

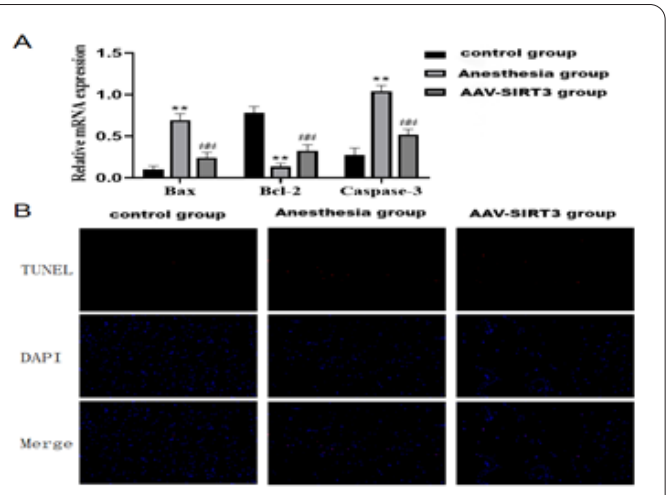


**Fig. 4.** Detection of apoptosis in hippocampal tissues of the three groups. (A) Bax, Bcl-2, Caspase 3 mRNA expression evaluation. (B) TUNEL staining (×200). **$P$<0.01, compared with control group; ##$P$<0.01, compared with the anesthesia group

used in clinical surgical treatment, and it is very easy for elderly surgical patients to develop postoperative cognitive function [13]. Inhalation of the anesthetic sevoflurane can cause learning and memory deficits in animals, as well as escape latency and platform crossing [14]. This study shows that sevoflurane anesthesia can lead to mice's movement distance, autonomous behavior ability, simultaneous escape latency and platform crossing time, and mice's learning and memory abilities, which is consistent with previous studies [14]. However, overexpression of SIRT3 can reduce the escape latency of mice and restore their learning and memory abilities. Therefore, we demonstrated that SIRT3 overexpression can alleviate cognitive function induced by sevoflurane anesthesia, and SIRT3 may have a neuroprotective effect. It has been demonstrated that synaptic plasticity, neuroinflammation, and mitochondrial damage are factors in the pathophysiology of POCD [6]. In the hippocampal regions of aged rats with tibial fractures, Netto et al. observed oxidative damage and reduced activity of the antioxidant enzyme superoxide dismutase (SOD) [15]. The hippocampal CA1 area is essential for cognition because neurotoxic reactions resulting from activated microglia and neuroinflammation cause synaptic function, which in turn leads to cognitive function [16]. The activation of mitochondrial oxidative stress response in hippocampal tissue is closely related to the occurrence of postoperative cognitive function in patients. SIRT3 has recently been demonstrated to play a role in neurodegenerative disorders through controlling mitochondrial damage induced by oxidative stress [9]. For example, Alzheimer's disease (AD) patients' cerebral cortexes exhibit downregulated SIRT3 expression, and SIRT3 function leads to mitochondrial and neuronal damage in AD [17]. In addition, According to reports, SIRT3 overexpression prolongs the lifespan of neurons in primary hippocampal cultures by preventing oxidative stress [18]. This shows that SIRT3 overexpression can counteract brain oxidative stress, which is linked to cognitive decline. Therefore, we speculate that SIRT3 can affect brain cognitive ability by regulating oxidative stress. After anesthesia, we examined the expression level of SIRT1 and discovered that it was significantly expressed, which was in line with the findings of earlier studies [17]. Next, we took measurements of SOD and MDA levels, and we found that the decrease in SOD and the increase in MDA after anesthesia could be improved by overexpression of SIRT3. These results imply that SIRT3 may be necessary for the oxidative stress response in the hippocampus mitochondria of POCD animals. Additionally, this study discovered that the hippocampal tissue of the mice in the anesthetized group had high expression levels of the inflammatory markers TNF-α, IL-1β, and IL-6, and the inflammatory responses caused by mitochondrial oxidative stress were greatly activated, and these inflammatory responses could be overridden by SIRT1. expression is inhibited. Previous research has demonstrated that the NLRP3 inflammasome's activation can enhance mice's microglia's inflammatory response., and the inflammatory response of hippocampal cells is related to cognition in aged mice [19,20]. We speculate that SIRT1 regulates mitochondrial damage in the mouse brain and may also play a role in regulating inflammatory responses. In this work, anesthesia-induced neuroinflammation was lessened by local SIRT3 overexpression in the hippocampus., thus confirming that SIRT1 overexpression can improve the inflammatory response through the mitochondrial damage pathway. Sevoflurane anesthesia inhibits neural stem cells' ability to regenerate themselves and promotes neuronal apoptosis. Sevoflurane anesthesia is neurotoxic [21]. At the same time, massive apoptosis of neuronal cells may lead to brain learning and memory [22]. Previous studies have shown that drug-induced learning and memory in mice can improve cognitive function through neuronal apoptosis [23,24]. This study demonstrates that apoptotic factors are highly expressed in the hippocampal tissue of mice given sevoflurane anesthesia, and that sevoflurane-induced apoptosis in hippocampal tissue cells may be triggered by overexpressing SIRT1. Excessive use of SIRT1 can induce apoptosis in hippocampal tissue, thereby improving cognitive function in mice.

## 5. Conclusions

In summary, this study suggests that SIRT1 overexpression can regulate mitochondrial oxidative stress response, hippocampal tissue inflammatory response and apoptosis, thereby improving induced postoperative cognition. SIRT3 could be a viable target for the diagnosis and therapy of elderly POCD patients.

## Conflict of interests

The author has no conflicts with any step of the article preparation.

## Consent for publications

The author read and approved the final manuscript for publication.

## Ethics approval and consent to participate

This study was approved by the Animal Ethics Committee of Changsha First Hospital Animal Center.

## Informed consent

The authors declare not used any patients in this research.

## Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request

## Authors' contributions

Changzong Dai and Jiandong Deng designed the study and performed the experiments, Changquan Fu and Zhiguo Yi collected the data, Changquan Fu, Zhiguo Yi and Xiaohong Guan analyzed the data, Changzong Dai and Jiandong Deng prepared the manuscript. All authors read and approved the final manuscript.

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