

Review Article

Bing Chen, Minqiu Lin, Simiao Chen, Weiyan Chen, Jingmei Song, Yuyan Zhang*

Mechanism underlying sevoflurane-induced protection in cerebral ischemia–reperfusion injury

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Abstract: Cerebral ischemia is an extremely complex disease that can be caused by a variety of factors. Cerebral ischemia can cause great harm to human body. Sevoflurane is a volatile anesthetic that is frequently used in clinic, and has a lot of advantages, such as quick induction of general anesthesia, quick anesthesia recovery, no respiratory tract irritation, muscle relaxation, and small cycle effect. The mechanism of sevoflurane preconditioning or post-treatment induction is poorly understood. The purpose of this study was to illustrate the mechanism underlying sevoflurane-induced protection in cerebral ischemia–reperfusion injury and also provide theoretical guidance for future research.

Keywords: sevoflurane, volatile anesthetic, protection mechanism, cerebral ischemia, reperfusion injury, regeneration

Abbreviations

Akt	protein kinase B
EAA	excitatory amino acid
IL-1 β	interleukin-1 β
iNOS	inducible nitric oxide synthase
Nrf2	nuclear factor-erythroid 2-related factor 2
TGF- β 2	transforming growth factor- β 2
TNF- α	tumor necrosis factor- α

1 Introduction

Sevoflurane is a generally used inhalational anesthetic in clinic that can induce ischemia tolerance both *in vivo* and *in vitro* [1,2]. It is the most commonly used general anesthetic in pediatric populations and is widely used as general anesthesia in Japan, the United States, and Europe. Sevoflurane was listed in China in 2005 and has been widely used in surgery [3].

Cerebral ischemia is characterized by obstruction of blood flow to the brain and is the leading cause of death and chronic disability worldwide [4]. Cerebrovascular disease may lead to cerebral ischemia, which is caused by damage to brain tissue. Cerebral ischemia is not only the cause of high mortality and disability but also a great concern for human health [5]. Since the etiology of cerebral ischemia is complex and the treatment is hard, there are no effective drugs available for treatment [6]. There are three main pathological types of cerebral ischemia [7]: ischemic stroke [8], primary intra-cerebral hemorrhage [9], and subarachnoid hemorrhage [6]. The main reason for ischemia–reperfusion injury is not the ischemia itself, but the excess free radicals that attack cells in this part of the tissue recovering from the obstruction of the blood supply. Cerebral ischemia–reperfusion injury mainly involves free radical formation in excess, toxic effects mediated by excitatory amino acid (EAA), increase

* **Corresponding author: Yuyan Zhang**, College of Life Science, Zhejiang Chinese Medical University, 548 Binwen Road, Binjiang District, Zhejiang Province, Hangzhou 310053, China, e-mail: yannoo7376@sina.com, tel: +86-137-58244937

Bing Chen: College of Life Science, Zhejiang Chinese Medical University, 548 Binwen Road, Binjiang District, Zhejiang Province, Hangzhou 310053, China, e-mail: chenbing0607@sina.com

Minqiu Lin: College of Life Science, Zhejiang Chinese Medical University, 548 Binwen Road, Binjiang District, Zhejiang Province, Hangzhou 310053, China, e-mail: linminqiu1009@163.com

Simiao Chen: College of Life Science, Zhejiang Chinese Medical University, 548 Binwen Road, Binjiang District, Zhejiang Province, Hangzhou 310053, China, e-mail: simiaochen1@outlook.com

Weiyan Chen: Basic Medical Sciences, Zhejiang Chinese Medical University, 548 Binwen Road, Binjiang District, Zhejiang Province, Hangzhou 310053, China, e-mail: chenweiyan19@sina.com

Jingmei Song: Basic Medical Sciences, Zhejiang Chinese Medical University, 548 Binwen Road, Binjiang District, Zhejiang Province, Hangzhou 310053, China, e-mail: songjm201906@126.com

in blood glucose levels, calcium ion overload in the cell, and damage to nerve function and inflammation [10].

In this study, sevoflurane was extensively used in various stages of cerebral ischemia–reperfusion injury. Both sevoflurane preconditioning and postprocessing can alleviate cerebral ischemia–reperfusion injury to a certain extent, especially sevoflurane has a significant effect in the regeneration and repair of nerve cells [11] and down-regulation of the expression of inflammatory factors, sevoflurane has a significant effect. Previous researchers have found that sevoflurane pretreatment may delay the protection of focal cerebral ischemia–reperfusion injury by reducing the levels of tumor necrosis factor (TNF- α) and interleukin-1 (IL-1 β) [12,13]. Recently, a study [14] has found that sevoflurane pretreatment up-regulates the expression of transforming growth factor- β 2 (TGF- β 2), vascular endothelial growth factor-A, and CD34, as well as the phosphorylation level of Smad3. TGF- β 2 inhibitor treatment can inhibit the expression of TGF- β 2, vascular endothelial growth factor-A and CD34, and the phosphorylation level of Smad3, which suggests that sevoflurane pretreatment can alleviate brain injury in rats with ischemia–reperfusion injury by activating TGF- β 2/Smad3 signaling pathway. Sevoflurane postprocessing also has a considerable protective effect on cerebral ischemia–reperfusion injury in rat brain tissue [15,16], and its mechanism may be to reduce the release of inflammatory factors, reduce inflammation and oxidative stress response, thus inhibiting apoptosis. In addition, sevoflurane post-processing can significantly improve the learning and memory impairment and the degree of cerebral infarction in cerebral ischemia–reperfusion injury in rats [17].

2 Properties of sevoflurane

2.1 Physicochemical properties of sevoflurane

The chemical name of sevoflurane is 1,1,1,3,3,3-hexafluoro-2-(fluorine methoxy)propane. The chemical structure is given in Figure 1.

The molecular formula of sevoflurane is $C_4H_7F_7O$. It is a colorless and aromatic liquid that is volatile and non-flammable and is stable in heat and strong acids. Sevoflurane causes no irritation to the respiratory tract. The effect of sevoflurane on hemodynamics and autonomic respiration was also small. The blood/gas distribution coefficient of

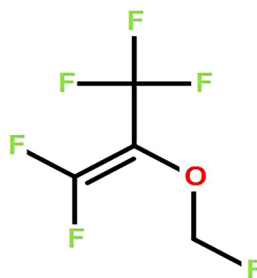


Figure 1: Chemical structure of sevoflurane.

sevoflurane is 0.69 and it has a low boiling point (58.6°C) with a relative molecular weight of 200.05 [18].

2.2 Physiological disposition and metabolic process *in vivo* of sevoflurane

Sevoflurane, in gas form, enters the bloodstream through the alveolar absorption, via blood circulation, into the brain. The produced effect is based on the quantity effect. The drug works through the processes of gas-blood and blood-brain, which transfers alveolar gas through the blood to brain tissue. After inhaling, sevoflurane plays a role in the nervous system.

With the advantages of fast onset, good circulation stability, high safety, and less adverse reactions, sevoflurane is used in the anesthesia induction of craniocerebral surgery [19]. The study has shown that [20] in patients undergoing craniotomy for acute intracranial hemorrhage, compared with total intravenous anesthesia, levels of serum C-reactive protein, serum S-100 β and neuron-specific enolase, inflammation-related factors and intracranial pressure of the patients with 1–2% sevoflurane combined with intravenous anesthesia were significantly decreased, which suggested that sevoflurane could inhibit the inflammatory reaction, and had brain-protective effect. Additionally, in the non-cardiac surgery of elderly patients with coronary heart disease, sevoflurane has little effect on the patient's hemodynamics and myocardial damage. It can effectively improve cardiac function, reduce the incidence of adverse reactions, and has high safety performance [21].

There are two ways to expel sevoflurane from the body. Most of the sevoflurane can be discharged directly through the lungs. A small fraction of sevoflurane needs to be bio-converted and excreted via the kidney. Since liposoluble sevoflurane cannot be excreted through urine, it is obligatory to produce water-soluble hexafluoro-2-propanol which oxidizes to inorganic fluoride ions with the help of cytochrome P450-2E1 in the liver [3].

2.3 Inhalation and induction methods of sevoflurane

Sevoflurane inhalation induction is commonly used in two clinical methods, that is lung capacity breathing induction and tidal volume breathing induction. The lung capacity breathing induction method is the one where the patients are induced with maximal inhalation and breathlessness; when patients cannot tolerate breathlessness, then again deep inhalation and breathlessness. The tidal volume breathing induction method allows the patient to breathe normally [22].

2.4 Sevoflurane was used in combination with different drugs

Sevoflurane is administered via a mixture of sevoflurane and oxygen or oxygen–nitrous oxide. The anesthetic concentration of sevoflurane is 8% [23]. Nitric oxide is a gas anesthetic used in clinic. The anesthetic effect of the drug itself is low; however, its combination with other volatile drugs can reduce the anesthetic minimum alveolar concentration, and thus exert a beneficial effect [24]. Sevoflurane can also be administered with oxygen or oxygen–nitrous oxide, after the amount of intravenous anesthesia necessary for sleep is reached. The administration of narcotic drugs is usually performed with oxygen or oxygen–nitrous oxide. In the case of patients, the minimum effective concentration is used to maintain the anesthetic status below 4.0%. The medication is usually stopped three minutes before the end of the operation [25].

The use of propofol after inhalation of sevoflurane can ensure rapid reach of anesthetic depth and the inhibition of cough and spasm. Propofol is a general anesthetic drug with a short duration and no excitatory effects. It can inhibit the appearance of the myotonic phenomenon.

2.5 Sevoflurane for anesthesia

Since children are in the developmental stage, heart rate changes, respiratory depression, body temperature instability, and wakefulness delay are prone to occur during anesthesia. This needs to be carefully considered while selecting an anesthetic. A multicenter study involving comparison of sevoflurane and halothane anesthesia in 428 children showed that sevoflurane groups were induced to be stable without coughing, breath holding, excitement, laryngospasm, bronchial spasm, increased

respiratory exudates, vomiting, and other adverse reactions [26]. For adults, Thwaites et al. [27] compared 8% sevoflurane and propofol-induced cystoscopy in adult patients. The results showed that the induction time required for sevoflurane was longer than propofol; but the rate of apnea caused by propofol was significantly higher than that of sevoflurane, and the apnea duration caused by propofol was longer than that of sevoflurane.

2.6 Effect of abnormal blood pressure on sevoflurane

The minimum alveolar concentration with a relatively stable value is used to evaluate the efficacy of inhalation anesthetics. In an animal experiment [28], the minimum alveolar concentration of sevoflurane in the normotensive group and hemorrhagic hypotension group was measured by tail clamping method and the results showed that hemorrhagic hypotension could reduce the minimum alveolar concentration of sevoflurane. However, preventive use of sevoflurane combined with inhaled sevoflurane to maintain the status of anesthesia has a better effect on stabilizing blood pressure, cerebral blood flow, and intracranial pressure in patients with hypertensive intracranial aneurysms undergoing interventional surgery [29]. In addition, in the operation of elderly hypertension patients, sevoflurane anesthesia can maintain the depth of anesthesia, and extubation under deep anesthesia can better inhibit cardiovascular response [30,31]. This suggests that hypertension has little effect on the use of sevoflurane.

2.7 Sevoflurane's protection mechanism on cerebral ischemia–reperfusion injury

2.7.1 Reduction of cell damage caused by free radicals

The body's oxidation/antioxidant system is in dynamic balance under normal conditions. However, in ischemia and hypoxia, the production of free radicals and the oxidative defense system become imbalanced in the body, which is an important pathophysiological basis closely related to cerebral ischemia–reperfusion injury [32].

Brain cells are extremely vulnerable to oxygen-free radical damage due to their high metabolic activity, rapid production of active oxygen metabolites, high content of unsaturated fatty acids, and low antioxidant capacity. Free radicals have strong chemical activity, by which they can react with nucleic acids, proteins, carbohydrates, and other substances, leading to dysfunction or even death of brain cells [33]. Inflammation results in

compounding inducible nitric oxide synthase (iNOS) and existing EEA, both of which lead to an increase in NO synthesis. Nitric oxide radicals can strengthen lipid peroxidation, which induces injury in cytomembrane and increase permeability, which can damage the brain tissues directly. In the heart and cerebral ischemia–reperfusion injury models, inhaled anesthetics can eliminate nitric oxide and a wide range of free radicals, such as peroxides and NO, both of which exert their biological effects by activating guanylate cyclase that plays a protective role [34]. Sevoflurane postconditioning can significantly inhibit the upregulation of nitric oxide synthase (iNOS), induced by cerebral ischemia [35]. Superoxide and oxygen free radicals released during ischemia and reperfusion can induce lipid peroxidation in the cell membrane causing irreversible damage to the cells. Malonic dialdehyde is the main metabolite of this process, and its concentration positively correlated with the extent to which cells are attacked and damaged by free radicals. Superoxide dismutase plays the role of oxygen radical scavenger in the body, and its activity levels represent the body's ability to scavenge oxygen free radicals. Therefore, inhibiting the excessive release of free radicals and increasing the activity of superoxide dismutase can play a role in brain protection. Allouchiche had found that Sevoflurane post-treatment can increase superoxide dismutase and catalase activity after cerebral ischemia–reperfusion injury, reduce malonic dialdehyde concentration, and exert neuroprotective effects [36]. Thus, it can provide palliative care for the brain injury. The protection mechanism is related to controlling iNOS and superoxide dismutase. It was showed previously that in the cerebral ischemia model, inhaled anesthetic plays a protective role by eliminating oxygen free radicals, such as NO, peroxide, and ONNO[−] [34]. Moreover, sevoflurane pretreatment can increase the nuclear translocation of nuclear factor-erythroid 2-related factor 2 (Nrf2), and then up-regulate endogenous antioxidation [37]. Post-treatment administration may involve Akt/Nrf2 pathway, significantly increase the expression of phosphorylated protein kinase B (Akt), oxidoreductase 1, Nrf2, thereby reducing the level of oxidative stress and playing a neuroprotective role [38].

2.7.2 Decreased calcium ion content in cells

Neonatal brain injury occurs at about one in every 4,000 live births [39]. However, the mechanism of sevoflurane preconditioning-induced neuroprotection is poorly understood [40]. Calcium ions play an important role in nerve

cell activity and signal transduction. Cerebral ischemia leads to energy deficiency, calcium pump dysfunction, mitochondrial damage, and cell membrane depolarization. It can also promote the release of glutamate by the vesicles and activate *N*-methyl-D-aspartate receptor, calpain1, and Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), which causes excitotoxicity of neurons, which increases calcium influx and induce apoptosis [41]. Suction sevoflurane has two mechanisms to decrease calcium ion concentration in the cells. One of them is the activated GABAA receptor, which is located in the post-synaptic vesicles and can extend and increase the conduction of the receptor to the chloride ions, open long-time channels, and inhibit synaptic excitability to reduce the internal flow of calcium ions. The other one is activated ATP-sensitive potassium channel, KATP. These channels are inhibited by ATP and activated under energy-depleted conditions. They also can be activated by volatile anesthetics [42]. The opening of these channels produces an outward current. This current can maintain the mitochondrial membrane potential and reduce the opening of mitochondrial permeability transition pore to inhibit cell injury and death [43,44]. The consequence is reduced calcium ions in the internal flow and calcium ions overload.

2.7.3 Alleviate the toxic effect by EAA

Glutamate accumulating outside the nerve cells is observed in the ischemia and hypoxia, with insufficient blood supply to the brain tissue. Glutamic acid stimulates α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate-receptor and *N*-methyl-D-aspartate to excessive excitability and both of them can activate calcium ions and calcium-dependent proteases, causing cytoskeleton destruction, free radical damage, and ionic equilibrium disorder [45]. It seems that the toxicity of EAAs is the originator of all these consequences [45,46]. Previous studies found that sevoflurane can reduce the concentration of glutamic acid by microdialysis [47]. Another experiment demonstrated that the protection mechanism of cerebral ischemia may be related to glutamate transporter by pre-treatment of sevoflurane [48]. The results of the microdialysis study showed that sevoflurane pre-conditioning could reduce the concentration of glutamic acid in cerebral ischemia rats. About 2.5 and 4% of sevoflurane decreased the release of glutamate caused by the depolarization of the synaptic membrane in the neurons of the cerebral frontal cortex of the isolated brain, and the degree of inhibition was 45 and 55%, respectively [47]. Sevoflurane activated protein kinase C kinase by acting directly on the catalytic area and the

regulatory region of the protein kinase C. The activation of the latter can enhance the transport function of the glutamic acid transporter in the presynaptic membrane neuron and reduce the concentration of excitatory neurotransmitter glutamic acid in the brain [49].

2.7.4 Relieve inflammation and high blood glucose

Hyperglycemia is not only an important independent risk factor for cerebral ischemia, but also causes poor prognosis in patients with ischemic stroke. The inflammatory correlation factor of hyperglycemia plays an important role in cerebral ischemia–reperfusion injury, and the damage to endothelial cells directly leads to functional impairment of brain neurons [50]. Cytokines have a dual functions. One is neurotrophs and the other is neurovirulence. However, when the cytokines are superfluous, it mainly results in the neurovirulence function [51]. One of the main mechanisms of ischemia–reperfusion injury is an excessive inflammatory response. TNF- α and IL-1 β are the main inflammatory factors in the process of immune and inflammatory reactions, which can induce the expression of intercellular adhesion molecules and aggregation of neutrophils, activating endothelial cells to produce various cytokines. Recent studies have shown that NF- κ B is also present in brain vascular endothelial cells, nerve cells, and glial cells, which are specifically activated when the central nervous system is ischemic. Cerebral ischemic–reperfusion injury induces over-expression of pro-inflammatory factors, such as TNF- α , IL-1, and IL-6 through the expression of activated NF- κ B, thereby causing inflammatory damage of nerve cells [52]. Studies have shown that pretreatment with sevoflurane effectively inhibits nuclear translocation and activation of NF- κ B, thereby significantly reducing the release of inflammatory factors, such as TNF- α and IL-1 by inhibiting the overexpression of many genes associated with inflammatory responses [53]. Previous experiments have shown that the combination of sevoflurane pre-treatment and post-treatment indicates that sevoflurane can reduce TNF- α in serum [54].

2.7.5 Inhibit cell apoptosis

Apoptosis is an important cause of cerebral ischemia–reperfusion injury. Apoptosis is irreversible especially in nerve cells. Therefore, inhibition of apoptosis is critical. The number of apoptotic cells in functional nerve cells at different time points after cerebral ischemia and

reperfusion in adult rats showed that the number of apoptotic cells in the sevoflurane preconditioning group was significantly lower than that of the control group at 3–7 days of recovery period [55]. Classical apoptotic pathways include intracellular pathways and extracellular pathways. The intracellular pathways involved in apoptosis are mainly divided into caspase-dependent and caspase-independent signaling pathways.

Studies have confirmed that sevoflurane postconditioning can regulate the expression of caspase-3, thus, inhibiting neuronal apoptosis. The extracellular pathway closely related to apoptosis is mainly the Bcl-2 family, of which Bcl-2 is the most important anti-apoptotic factor, while Bax has a pro-apoptotic effect. The balance between pro-apoptotic and anti-apoptotic members affects the induction of apoptosis. When brain damage, such as cerebral ischemia, occurs, the apoptotic protein Bax and the anti-apoptotic protein Bcl-2 can migrate from the cytoplasm to the mitochondria. This Bax-mediated mitochondrial apoptotic pathway plays an important role in neuronal damage. Research shows that sevoflurane postconditioning can also suppress apoptosis, protect nerve function, and induce the expression of antiapoptotic protein Bcl-2, while downregulating the expression of apoptotic protein P53 and Bax [56]. Previous research showed that sevoflurane post-treatment can significantly reduce the expression of TLR4 protein and TRAF6 protein and their mRNAs in brain tissue [57].

2.7.6 Regulate cerebral blood flow

Cerebral blood flow is not kept under control due to continuous pressure changes after cerebral ischemia–reperfusion. Sevoflurane can significantly ameliorate cerebral blood flow by dilating the blood vessels and increasing the cerebral blood flow in a dose-dependent manner. Studies have shown that when 8% sevoflurane is inhaled, the mean velocity of cerebral blood flow increases markedly [58]. Bundgaard et al. showed that 1.5 to 2.5% sevoflurane can increase cerebral blood flow and reduce cerebral vascular resistance in a concentration-dependent manner [59]. Reinsfelt et al. believed that sevoflurane has a certain effect on the regulation and metabolism of cerebral blood flow during cardiopulmonary bypass. However, the use of sevoflurane has not yet reached a consensus on the regulation of cerebral blood flow. Therefore, whether the changes in cerebral blood flow can explain the neuroprotective effects of sevoflurane is not yet clear [60]. Cerebral blood flow autoregulation refers to the process in which cerebral parenchymal

blood vessels maintain constant cerebral blood flow and normal brain function through various mechanisms when blood pressure changes [61]. When sevoflurane of approximately one minimum alveolar concentration is inhaled, it can effectively reduce the range of cerebral blood flow autoregulation. But it does not demonstrate the connection between the reduction in cerebral blood flow autoregulation and injury of cerebral ischemia [62]. It has been found that sevoflurane combined anesthesia can control the concentration of amino acids (reduce the toxic injury of amino acids) and maintain the normal hemodynamics of cerebrovascular by regulating cerebral blood flow autoregulation [63].

2.7.7 Repair nervous system

When the central nervous system gets damaged, microglia can eliminate cell debris by phagocytosis and accelerate tissue repair. Xu et al. [64] randomly divided the rats into three groups. There were sham operation group (sham group), focal cerebral ischemia–reperfusion group (control group), and sevoflurane pre-treatment + focal cerebral ischemia–reperfusion group (sevo group). The research showed that sevoflurane preconditioning could cause the migration of microglia to the cerebral ischemia region. It also promoted the activation and phagocytosis of microglia. Activated microglia secreted brain-derived neurotrophic factor, providing a nutritious microenvironment for nerve regeneration and repair. Research found that sevoflurane post-treatment, in a dose-dependent

manner, ameliorated the neurological function and abatement of the cerebral infarction region [65]. The study found that the activation of the PI3K/Akt signaling pathway plays an important role in the anti-apoptotic activity of anesthetics and the neuroprotective effects of neuronal survival [66]. Sevoflurane post-treatment upregulates the mRNA and protein levels of heme oxygenase-1 by activating the PI3K/Akt signaling pathway, thereby alleviating neuronal damage by exerting its neuroprotective effects [67]. Previous studies have shown that pretreatment with sevoflurane can alleviate the extent of damage to astrocytes after cerebral ischemia injury, using transmission electron microscopy. Meanwhile, it also proved that sevoflurane pretreatment can reduce the loss of CX-43 protein as shown by immunofluorescence staining and western-blotting [68]. CX-43 protein, extensively located at glial cells, has been shown to repair neurological injury after ischemia [69].

3 Discussion

Sevoflurane is an anesthetic for general use, whose function is to protect heart and brain tissues. But the use of anesthetic preconditioning is limited, as most ischemia episodes are unpredictable [70]. Previous studies showed that sevoflurane at a concentration as low as 1% was effective to induce neuroprotection, suggesting that a subclinical concentration for anesthesia can induce the postconditioning effect [71]. The use of sevoflurane can reduce free radical formation, alleviate toxic effect by EAA, decrease

Table 1: Mechanisms and relevant indicators of sevoflurane in the protection of cerebral ischemia–reperfusion injury

Medical gas	Mechanism of action	Main relevant indicators	Ref.
Sevoflurane	Reduction of cell damage caused by free radicals	Peroxides, NO, ONNO [−]	[34]
		iNOS	[35]
		Superoxide dismutase, catalase, malonic dialdehyde	[36]
		Akt, oxidoreductase 1, Nrf2	[37,38]
	Decreased calcium ion content in cells	N-methyl-D-aspartate receptor, calpain1, Ca ²⁺ /CaMKII	[41]
		GABAA receptor, KATP	[42]
	Alleviate the toxic effect by excitatory amino acid	α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionate-receptor,	[45]
		N-methyl-D-aspartate	
	Relieve inflammation and high blood glucose	Protein kinase C kinase	[49]
		NF- κ B, inflammatory factors (TNF- α , IL-1, etc.)	[53,54]
	Inhibit cell apoptosis	Bcl-2, P53, Bax	[56]
		TLR4, TRAF6	[57]
	Regulate cerebral blood flow	Concentration of amino acids	[63]
	Repair nervous system	Microglia	[64]
		PI3K/Akt, heme oxygenase-1	[65,66]
		CX-43 protein	[68]

calcium ion overload in the cell, mitigate the damage to nerve function, and relieve inflammation (Table 1).

In summary, cerebral ischemia is a complex disease. The cause of cerebral ischemia injury is not clear yet, but elucidating the mechanism will play a guiding role in preventing brain injury and other fatal conditions, such as producing large amounts of oxygen free radicals and inflammatory factors; thus, causing apoptosis in the nervous system after cerebral ischemia–reperfusion [72]. These mechanisms still need to be clarified in future studies.

Sevoflurane is the third generation of inhalable anesthetics. The mechanism of its neuroprotective effects is not yet clear. The current research is at the exploratory stage. To date, many studies have reported that sevoflurane can downregulate the expression of inflammatory factors, but the specific mechanism of sevoflurane on inflammatory factors is not understood. Whether the protection mechanism of sevoflurane preconditioning and postprocessing is different remains to be studied. Furthermore, whether sevoflurane has different protective mechanisms for individuals of different ages and genders remains to be studied.

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