# Protective effects of sevoflurane in cerebral ischemia reperfusion injury: a narrative review

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## Abstract

Ischemia/reperfusion (I/R) injury is a phenomenon that the reperfusion of ischemic organs or tissues aggravates their damage, which poses a serious health threat and economic burden to the world. I/R gives rise to a series of physiological and pathological world, including inflammatory response, oxidative stress, brain edema, blood-brain barrier destruction, and neuronal death. Therefore, finding effective treatment measures is extremely important to the recovery of I/R patients and the improvement of long-term quality of life. Sevoflurane is an important volatile anesthetic which has been reported to reduce myocardial I/R damage and infarct size. Sevoflurane also has anti-inflammatory and neuroprotective effects. As reported sevoflurane treatment could reduce nerve function injury, cerebral infarction volume and the level of inflammatory factors. At the same time, there is evidence that sevoflurane can reduce neuron apoptosis and antioxidant stress. The protective effect of sevoflurane in brain injury has been proved to be existed in several aspects, so that a comprehensive understanding of its neuroprotective effect is helpful to exploit new treatment paths for I/R, provide clinicians with new clinical treatment decisions, contribute to the effective treatment of I/R patients and the improvement of quality of life after I/R healing.

**Key words:** central nervous system; cerebral blood flow; cerebral ischemia-reperfusion injury; inflammatory response; inhalant anesthetic; microglia; neuroprotection; sevoflurane

**doi:** 10.4103/2045-9912.318860
**How to cite this article:** Liang TY, Peng SY, Ma M, Li HY, Wang Z, Chen G. Protective effects of sevoflurane in cerebral ischemia reperfusion injury: a narrative review. Med Gas Res 2021;11(4):152-154.
**Funding:** This work was supported by Suzhou Youth Science and Technology Project, China (No. KJXW 2017029).

## Introduction

Cerebral ischemia/reperfusion (I/R) injury can cause the most common stroke-related death and disability worldwide and has a poor prognosis.[1,2] Prompt ischemia-reperfusion can prevent severe neurological defects and death. However, it may further exacerbate neuron death and neurological dysfunction.[3] Due to blocked cerebral arteries and inadequate blood supply, I/R in the brain leads to complex pathophysiological processes leading to further I/R injury.[4] In addition, autophagy and inflammation emerge after I/R contribute to further damages to the neuron death and cell death.[5] In the process of cerebral I/R, there are a large number of inflammatory factors in the ischemic focus.[6,7] While restoring blood flow to ischemic organs is critical to preventing irreversible tissue damage, reperfusion itself may lead to local and systemic inflammatory responses that may increase tissue damage beyond that caused by ischemia alone.[8] I/R injury is characterized by oxidation products, complement activation, leukocyte-endothelial cell adhesion, platelets-leukocyte aggregation, increased microtubule permeability, and decreased endothelium-dependent diastolic function. The most severe I/R damage can lead to multiple organ dysfunction or death.[9]

Sevoflurane is an inhaled anesthetic widely used in surgery.[10] Sevoflurane has the activity of anti-oxidative stress and anti-inflammation, and can protect organs from the damage caused by stress.[11] It is now recognized that sevoflurane is a safe inhaled anesthetic and has the advantages of inducing rapid and rapid resuscitation as an anesthetic inducer.[12] Existing studies have indicated that sevoflurane preconditioning for neurological protection is a double-edged sword for patients with neurological defects. For one thing, sevoflurane can relieve the inflammatory response,[13] reducing cell death, the activation of innate immune cells. For another thing, sevoflurane can inhibit the release of related cytokines, increase cognitive dysfunction and amplify brain damage.[14] However, the mechanism of sevoflurane's function after I/R has not been fully studied. This paper presents a comprehensive description of several existing mechanisms, which is conducive to the full understanding of sevoflurane. More importantly, it is helpful for clinicians to grasp the use of sevoflurane and promote the safe and effective use of sevoflurane in clinical practice.

## Mechanisms of Sevoflurane

Existing studies have shown that sevoflurane is a vasodilator, and *in vitro* and *in vivo* experiments have shown that sevoflurane can effectively protect neurons following cerebral ischemia through several pathways. Although its protective effect has been an issue of concern, the mechanism of sevoflurane remains to be further studied. Signal transduction pathway is the main way for cells to transmit information. At present, several signal transduction pathways for sevoflurane to play a neuroprotective role have been discovered, such as Janus kinase-signal transducer and activator of transcription pathway,[15] Toll like receptor 4/nuclear factor-κB pathway,[16]

TWIK-related $K^+$ channel 1 channel,[17] phosphoinositide 3-kinase/Akt signaling pathway,[18] Akt signaling pathway,[19] protein kinase B/nuclear factor-erythroid 2-related factor 2 pathway.[20] Through these signaling pathways, sevoflurane reduces inflammation, activates glial cells, inhibits neuronal apoptosis, and protects damaged brain tissue.

### Sevoflurane attenuates the inflammatory response

It is widely known that sevoflurane has the benefits of anti-inflammatory and neuroprotection. In 2004, Nader et al.[21] pointed out that volatile anesthetics, such as sevoflurane, could attenuate the inflammatory response, in their report, the inhalation of sevoflurane could reduce the expression of inflammatory factors of tumor necrosis factor-α and interleukin-1β in plasma. *In vivo* studies have also shown that sevoflurane post-treatment can reduce the inflammatory response in the cerebral infarction area and reduce the concentration of serum pro-inflammatory cytokines in rats after cerebral I/R injury.[16] It has been reported that sevoflurane treatment can enhance the barrier function of the brain, protect the vascular endothelial integrity, and maintain the cell junction protein arrangement, which effectively increases cerebral blood flow, and also enhances the anti-inflammatory ability of the body.[22] Numerous subsequent studies have shown that sevoflurane has an anti-inflammatory effect to protect damaged brain tissue after I/R by reducing the production of inflammatory factors through various pathways. This is the key step in the recovery of patients with cerebral I/R injury.[16,18]

### Sevoflurane helps macrophages/microglia perform immune function

Microglia and macrophages are the most effective central nervous system damage repair and regeneration regulators and undertake an important character in innate immunity and acquired immunity.[23] After I/R, the activated microglia not only release neurotrophic factors, but also secrete a variety of pro-inflammatory cytokines, nitric oxide and other factors that can aggravate the injury.[24] In case of I/R, infiltration and migration of microglia to the spinal cord is associated with damage to the vasculature, caused by substances released by activated microglia, matrix metalloproteinases. The researchers found that sevoflurane pretreatment prevented an increase in the number of harmful microglia in the spinal cord of rats with I/R damage.[25] Current studies also suggest that sevoflurane preconditioning may affect motor function by inhibiting microglial cell infiltration and migration of injured neurons, and sevoflurane preconditioning inhibits the production of pro-inflammatory chemokines and cytokines and neuronal cell apoptosis after spinal cord I/R.[25] However, there is increasing evidence that microglia/macrophages have dual functions, one is to amplify ischemic damage by releasing proinflammatory neurotoxins, and the other is to support brain recovery after stroke by removing cell debris and secreting nutrient factors.[26,27] It was found that after sevoflurane administration, reactive microglia/macrophages began to accumulate in and around the lesion site on the 3rd day after stroke, showing a highly branched form and rapid response.[25,28] The phagocytosing microglia/macrophages with amoeboid morphology have been confirmed to promote neural survival by clearing potential toxic debris and reducing subsequent secondary brain damage.[29] After sevoflurane pretreatment, its derivative microglia/macrophages rapidly transformed into amoebia-like morphology on the third day after I/R injury and accumulated in the infarcted cortex and striatum, indicating that sevoflurane improves the phagocytic efficiency by increasing the phagocytic capacity of each cell. Compared with the control group, the number of phagocytes in the infarction area of sevoflurane pretreatment group increased significantly on the 5th day after injury, indicating that sevoflurane pretreatment could collect more phagocytes and enhance their phagocytic ability.[30]

### Other mechanisms that sevoflurane protects central nervous system

Sevoflurane has attracted more and more attention in clinical application as an inhaled anesthetic in recent years.[31] Existing studies have revealed that sevoflurane can reduce the release of excitatory neurotransmitters such as catechol and glutamine caused by cerebral ischemia injury and relieved the re-stimulation to neurons.[32] After cerebral I/R, the production of reactive oxygen species increases dramatically, which is exceeding the endogenous antioxidant system and leading to oxidative stress. The brain is particularly vulnerable to oxidative stress because it consumes a lot of oxygen, rich in polyunsaturated fatty acids and low levels of endogenous antioxidants.[33] Sevoflurane can reduce the release of free radicals, showing antioxidant properties.[34] Sevoflurane can also inhibit the voltage-gated calcium channel and protein kinase C in the presynaptic membrane of neurons, up-regulate the hippocampal anti-apoptotic proteins Bcl-2 and murine double minute-2, and inhibit the expression of ischemia-mediated apoptotic activating protein Bax, thus protecting the central nervous system (**Table 1**).[35]

## Future and Prospect

Although the molecular mechanism of sevoflurane to protect injured brain tissue has not been fully elucidated, its application value has been paid more and more attention, including improving cerebral blood flow, inhibiting inflammatory response, reducing infarct area, etc. It is expected that sevoflurane will be widely used in the treatment and recovery of clinical patients.

**Author contributions**
Manuscript drafting: TYL and SYP; manuscript writing: HYL and MM; manuscript revision: ZW and GC. All the authors read and approved the final version of the manuscript for publication.
**Conflicts of interest**
The authors have no conflicts of interests to declare.
**Financial support**
This work was supported by Suzhou Youth Science and Technology Project, China (No. KJXW 2017029).

**Table 1: Neuroprotective effects of sevoflurane and the related mechanisms**

| Disease | Intervention | Model animal/cell | Result |
|---|---|---|---|
| MCAO | On 4 consecutive days before MCAO, the rats inhaled a mixture of sevoflurane, oxygen and air. | Rat | Sevoflurane preconditioning can alleviate cerebral I/R injury and promote the repair of damaged brain tissue. |
| OGDR | Sevoflurane preconditioning: 2.5% sevoflurane with 5% $CO_2$/95% air for 30 min, repeating for 3 times, with 15 min washout after each exposure. | Neuron | Sevoflurane preconditioning alleviated cell injury in OGDR model, which is manifested in increased cell vitality, decreased lactate dehydrogenase release and decreased apoptosis rate after sevoflurane treatment. |
| MCAO | The sevoflurane post-conditioning: 2% sevoflurane was infused for 15 min before reperfusion. | Rat | Sevoflurane post-conditioning can decrease the level of inflammatory response the concentration of proinflammatory cytokines. |
| MCAO | Sevoflurane treatment group was given 2% sevoflurane for 15 min before reperfusion | Rat | Sevoflurane treatment could decrease the percentage of cerebral infarction volume, contents of inflammation factors in brain tissue and the apoptotic index of brain tissue after I/R injury. |
| MCAO | Rats were administered with 1.2% sevoflurane + 98.8% $O_2$ in a sealed chamber for 60 min on 4 consecutive days. | Rat | Sevoflurane preconditioning had positive effects on macrophages/microglia. |

Note: I/R: Ischemia/reperfusion; MCAO: middle cerebral artery occlusion; OGDR: oxygen-glucose deprivation/ reperfusion.



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*Date of submission: April 9, 2020*
*Date of decision: April 21, 2020*
*Date of acceptance: April 27, 2020*
*Date of web publication:*