The effect of pre- and after-treatment of sevoflurane on central ischemia tolerance and the underlying mechanisms

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In recent years, with continuous research efforts targeted at studying the effects of pre- and after-treatment of inhaled anesthetics, significant progress has been made regarding the common clinical use of low concentrations of inhaled sevoflurane and its effect on induced central ischemia tolerance by pre- and post-treatment. In this study, we collected, analyzed, classified, and summarized recent literature regarding the effect of sevoflurane on central ischemia tolerance and its related mechanisms. In addition, we provide a theoretical basis for the clinical application of sevoflurane to protect the central nervous system and other important organs against ischemic injury.

Keywords: Central Nervous System; Ischemia; Sevoflurane; Tolerance.

INTRODUCTION

In recent years, the inhaled anesthetic sevoflurane has been widely used for general anesthesia and sedation, especially for the induction and maintenance of general anesthesia in children during surgeries. In addition to its anesthetic properties, pre- and after-treatment with sevoflurane may be useful for the treatment of cerebral ischemic injury and related diseases. Evidence suggests that sevoflurane administration either prior to or after surgery can provide tolerance to ischemia both directly and indirectly, but the effects of pre- and post-treatment and the mechanisms underlying these effects are not exactly the same [1]. In this paper, we review the effect of sevoflurane on central ischemia tolerance and the underlying mechanisms.

THE EFFECT OF SEVOFLURANE PRE-TREATMENT ON ISCHEMIA TOLERANCE

Cerebral ischemia pre-processing refers to the ability of brain tissue to tolerate severe ischemia, which would normally be fatal, but is a self-protection phenomenon of the brain against ischemia. A recent study has shown that sevoflurane pre-conditioning can produce tolerance to ischemia. Using various central nervous system (CNS)

damage models, this tolerance effect as a result of pre-treatment has been confirmed by studies in neuro-science, histopathology, immunohistochemistry, molecular biology, and behavioral science. For example, Chen et al. used a Sprague-Dawley (SD) rat model of middle cerebral artery occlusion (MCAO) to show that pre-treatment with 2.7% sevoflurane for 45 min significantly reduced neurological deficit scores and decreased cerebral infarction volume [2]. Previous reports have shown that 2% sevoflurane pre-treatment for 60 min significantly improved nerve function in SD rats after MCAO and reduced the cerebral infarction volume, alleviating neuronal apoptosis [3]. Hu et al. also found that 2.4% sevoflurane pre-treatment for 60 min effectively improved spatial learning and memory ability in a focal cerebral ischemia animal model [4]. Yang et al. not only confirmed that sevoflurane pre-conditioning induced brain ischemic tolerance, but also observed that 2.5% sevoflurane treatment for 60 min over 5 consecutive days significantly improved neural function in C57BL/6 mice after MCAO and alleviated neuronal apoptosis [5]. Bedirli et al. also confirmed that 2% sevoflurane pre-treatment for 60 min relieved the inflammatory response induced by cerebral ischemia, reduced the extent of lipid peroxidation and tissue damage, and regulated apoptosis-related protein expression, thus diminishing neuronal apoptosis. In a rat model of whole cerebral ischemia [6], Wang et al. showed that 4% sevoflurane pre-treatment for 15 min improved neural structure and function, as did 2% sevoflurane pre-treatment for 1 h [7]. Furthermore, Li et al. employed a spinal cord ischemia/reperfusion injury model and showed that 2.4% sevoflurane pre-conditioning inhibited microglial activation, alleviated neuronal apoptosis caused by inflammatory reactions, and promoted the recovery of motor function in injured animals [8]. However, the effect of sevoflurane pre-treatment may only be observed in adult animals, as it has been shown that 2% sevoflurane induced hippocampal neuronal apoptosis in rats at puberty, and transiently affected the ability of young rats to form memories in response to noxious stimuli,

although it did not cause a decline in spatial memory [9]. In summary, concentrations of 2% to 4% sevoflurane for pre-treatment for periods of 60 min or less induced tolerance to ischemia in adult rodent models of focal cerebral ischemia, whole brain cerebral ischemia, and spinal cord reperfusion injury.

THE EFFECT OF SEVOFLURANE AFTER-TREATMENT ON ISCHEMIA TOLERANCE

In 2013, Zhu et al. found that sevoflurane after-treatment had certain protective effects on damaged myocardium [10]. The effect of sevoflurane after-treatment on ischemic tolerance has received increasing attention and recognition in recent years. Li et al. used the MCAO model to study the effect of sevoflurane inhalation after-treatment on cerebral ischemic tolerance; treatment with 2.6% sevoflurane for 60 min immediately after reperfusion injury significantly reduced neurologic deficit scores, decreased cerebral infarction volume, and resulted in lower levels of oxidative stress, thus exerting a neuroprotective effect [11]. Yu and Jia found that 2.5% sevoflurane after-treatment for periods ranging from 30 min to 24 h administered immediately after 90 min of local ischemia and reperfusion, improved neurological function scores and significantly reduced cerebral infarction volume [12]. Jeon et al. used an SD rat model of bilateral common carotid artery occlusion in which 2.5% sevoflurane was administered twice after reperfusion, 5 min per treatment, with a 5-min processing interval. By the 7th day after treatment, sevoflurane after-treatment had clearly reduced apoptosis in the hippocampal Cornu Ammonis 1 (CA1) area and improved nerve function scores [13]. Wang et al. also studied the protective effect of different concentrations of sevoflurane against focal cerebral ischemic injury and found that minimum alveolar concentrations (MAC) of 1.0 and 1.5 administered for 30 min immediately after reperfusion increased the neurologic deficit score, reduced cerebral infarction volume and brain edema, and significantly

improved learning and memory ability. The mechanism for these effects of sevoflurane post-treatment involved the regulation of apoptosis-related protein expression to reduce apoptosis and protect the brain [14]. Peng et al. used an in vitro oxygen and glucose deprivation model, and found that providing oxygen during 60 min of 2%, 4%, and 6% sevoflurane after-treatments significantly reduced hippocampal neuron damage in a concentration-dependent manner [15]. A study by Deng et al. further found that after exposure to an electromagnetic pulse, 2% and 4% sevoflurane after-treatments for 20 min protected SD rats from electromagnetic radiation damage in the cerebral cortex by promoting nerve cell survival; in vitro experiments further confirmed that the tolerance effect was related to inhibition of neural apoptosis and a reduction in oxidative stress levels. In summary, concentrations of 6% sevoflurane or less with after-treatment times for less than 60 min exerted dose-dependent protective effects in adult rodent models of focal cerebral ischemia and whole brain ischemia, after electromagnetic pulse radiation and in an in vitro model of oxygen and glucose deprivation [16].

It is worth noting that the post-treatment effect of sevoflurane occurs after damage has been induced and before behavioral intervention. Perioperative application of sevoflurane can not only cause a general anesthesia effect but may also produce tolerance to ischemia and achieve the goal of reducing brain injury.

THE EFFECT OF SEVOFLURANE PRE-TREATMENT AND POST-TREATMENT ON MECHANISMS OF ISCHEMIC TOLERANCE

Sevoflurane has been widely used for clinical anesthesia, but the mechanism underlying its effect on ischemic tolerance is still being explored. In recent years, research results have suggested that the mechanisms controlling sevoflurane-induced ischemic tolerance may be related to regulation of cerebral blood flow [17], inhibition of apoptosis, relief of antioxidant stresses,

inhibition of excitatory toxins, activation of mitochondrial ATP-sensitive potassium channels, and stimulation of phosphatidylinositol 3-kinase/protein kinase signaling pathways.

1. Cerebral blood flow regulation

Research by Bundgaard et al. suggests that in surgical operations to remove brain tumors, inhaled sevoflurane at 1.5% (0.7 MAC) to 2.5% (1.3 MAC) can increase cerebral blood flow and reduce cerebral vascular resistance in a dose-dependent manner [18]. However, Zhang et al. found that sevoflurane post-treatment reduced cerebral blood supply after ischemic damage [19]. Reinsfeh and colleagues believe that sevoflurane affects extracorporeal circulation to regulate cerebral blood flow and metabolism [20]. Due to contradictory reports, there is not yet a consensus on the effect of sevoflurane on cerebral blood flow regulation . Therefore, whether cerebral blood flow changes can explain the cerebral protective effect of sevoflurane is unclear.

2. Anti-apoptotic mechanisms

Several reports have confirmed that sevoflurane pre-processing or post-treatment has an anti-apoptotic effect. These studies have focused not only on specific markers of apoptosis and cell morphology analysis, but also on apoptosis pathways and related molecules.

Classical apoptotic pathways include intracellular and extracellular pathways. Intracellular pathways related to cell apoptosis consist of caspase-dependent and caspase-independent signaling pathways. It has been confirmed that sevoflurane pre- and post-treatment can control caspase 3, as well as the expression of activated caspase 3, leading to the reduction of apoptosis of neurons after cerebral ischemic injury [7]. Li et al. has recently found that sevoflurane pre-processing can inhibit phosphorylation of astrocyte differentiation-related genes, thus inhibiting the expression of activated caspase 3, alleviating neuronal apoptosis, and inducing ischemic tolerance [2]. These experiments on the mechanisms by which sevoflurane pre-processing affects ischemic

tolerance provides a new theoretical basis for understanding targets of cerebral ischemia/reperfusion injury.

Closely associated with cell apoptosis are extracellular pathways. These pathways are mainly associated with the Bcl-2 family, in which Bcl-2 is the main anti-apoptotic factor and Bax promotes apoptosis; the balance between pro-apoptotic and anti-apoptotic members regulates apoptosis [21]. After brain injury produces ischemia, the apoptosis protein Bax and anti-apoptotic protein Bcl-2 migrate from the cytoplasm into the mitochondria, where their distribution is consistent with the release of cytochrome C and caspase-9. Thus Bax, mediated by the mitochondrial apoptosis pathway in injured neurons, plays an important role [22]. It is reported that 2.5% sevoflurane post-treatment has a protective effect against whole cerebral ischemic injury in rats, which is achieved by increasing Bcl-2 protein levels. Post-treatment with sevoflurane combined with albumin can strengthen the effect of sevoflurane on ischemic tolerance [13]. In addition, sevoflurane post-treatment can also increase Bcl-2 protein and mRNA levels, and reduce Bax protein and mRNA expression, thus promoting tolerance to ischemia [23]. Sevoflurane post-treatment can reduce the number of apoptotic cells after cerebral ischemic injury by raising Bcl-2 protein levels and decreasing Bax protein levels, thus inhibiting apoptosis. Preliminary results from our current study show that sevoflurane can reduce the expression of Bax, increase Bcl-2 expression, and diminish electromagnetic pulse radiation−induced mitochondria damage and apoptosis in rat cortical neurons. This suggests that sevoflurane can regulate the mitochondrial apoptosis pathway mediated by Bax and play a protective role in the CNS [16].

3. Anti-oxidant stress mechanisms

After severe injury, the CNS produces large numbers of oxygen free radicals. If these free radicals produced are not completely removed by the body due to their large numbers, it will lead to oxidation, specifically, lipid peroxidation, which may induce serious CNS injury [24]. Yang et al. reported that sevoflurane pre-processing increased the activity of antioxidant enzymes after cerebral ischemia/reperfusion to provide nerve protection in a dose-dependent manner [25]. Wang et al. found that sevoflurane post-treatment can increase spinal cord superoxide dismutase numbers, catalase activity after ischemia/reperfusion injury, and reduce malondialdehyde content, thus playing a role in CNS protection [26].

In order to determine whether sevoflurane post-conditioning induces the expression of nuclear factor erythroid 2-related factor (Nrf2, a master transcription factor regulating antioxidant defense genes) and hemoxygenase-1 (HO-1, an antioxidant enzyme), and whether protein kinase C (PKC) is involved in Nrf2 activation, in a rat model of transient global cerebral ischemia/reperfusion (I/R) injury. Eighty-six rats were assigned to five groups: sham, control, sevoflurane post-conditioning (two cycles with 2 vol% sevoflurane inhalation for 10 min), chelerythrine (a PKC inhibitor; 5 mg kg (-1) intravenous administration), and sevoflurane post-conditioning plus chelerythrine. The levels of nuclear Nrf2 and cytoplasmic HO-1 were assessed 1 or 7 days after ischemia. The results showed that on day 1, but not day 7, post-ischemia, Nrf2 and HO-1 expression were significantly higher in the sevoflurane post-conditioning group than in the control group. Chelerythrine administration reduced the elevated Nrf2 and HO-1 expression induced by sevoflurane post-conditioning. It was concluded that sevoflurane post-conditioning increased Nrf2/HO-1 expression via PKC signaling in the early phase after transient global cerebral I/R injury, suggesting that activation of antioxidant enzymes may be responsible for sevoflurane post-conditioning-induced neuroprotection in the early phase after cerebral I/R injury [27].

We have also found in previous reports that sevoflurane post-treatment can inhibit the oxidative stress reaction and decrease the extent of electromagnetic pulse radiation damage in rat cerebral cortex neurons.

4. Inhibition of excitatory toxin release

It has been confirmed that excitatory amino acids

(EAA) play an important role in neuronal death induced by CNS injury. EAA are widely present in the mammalian CNS, and in addition to providing excitatory information, may also function as neurotoxins, particularly glutamic acid and aspartic acid. Glucose content is high in the cerebral cortex and hippocampus. Normally, after interaction with their receptors, released EAA are quickly taken up by neurons and glial cells, degraded by enzymes, and rapidly cleared. However, after CNS injury, including cerebral ischemia/reperfusion injury, the release of EAA from nerve and glial cells is increased, while reuptake and inactivation declines. This results in abnormal increases in glutamic and aspartic acid concentrations in the intercellular space which produce cascading reactions leading to cell death [28]. Zhang et al. confirmed that sevoflurane can reduce glutamate excitatory toxicity [29], but also questioned the effect of sevoflurane [30]. Therefore, further investigation is required to determine whether sevoflurane exerts a neuroprotective effect by inhibiting excitatory toxin release.

5. The activation of mitochondrial ATP-sensitive potassium channels

Mitochondrial ATP-sensitive potassium (mitoKATP) channels are present on the inner mitochondrial membrane of many tissues and cells, and play an important role in brain injury. The protective effects of sevoflurane pre-processing are associated with activation of mitoKATP channels, and sevoflurane-induced channel opening promotes ischemic tolerance [31]. Velly et al. found that early sevoflurane pre-treatment for ischemia/reperfusion brain protection had a "threshold effect" and was dose-dependent in a clinically relevant concentration range, and that the mechanism was related to opening of mitoKATP channels [32]. Adamczyk reported that whether sevoflurane was administered as pre-treatment or as after-treatment, it played a neuroprotective role by inducing the opening of mitoKATP channels. A recent study has also pointed out that sevoflurane post-treatment can play a protective role in the CNS via mitoKATP

channels [33], which can be reversed by the mitoKATP inhibitor 5-hydroxydecanoic acid [34].

6. Activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway

It has recently been observed that activation of the PI3K/Akt signaling pathway by inhalation anesthetics promotes resistance to apoptosis and neuronal survival. New discoveries by Chen et al. have shown that sevoflurane pre-treatment can activate the PI3K/Akt signaling pathway and increase the level of phosphorylated glycogen synthase kinase-3B, which also plays a role in CNS protection [1]. Ye et al. confirmed that sevoflurane post-treatment can activate the PI3K/Akt signaling pathway and increase mRNA and protein levels of hypoxia inducible factor-1 alpha and hemoglobin oxidase-1, thus reducing damage to neurons via their neuroprotective effect [35].

7. Anti-inflammatory effects

The anti-inflammatory actions of sevoflurane post-conditioning are suggested as an important mechanism of sevoflurane post-conditioning-induced neuroprotection against cerebral ischemia. A study determined whether the anti-inflammatory effects of sevoflurane post-conditioning were mediated via inhibition of the toll-like receptor (TLR)-4/nuclear factor kappa B (NF-κB) pathway after global transient cerebral ischemia in rats. Forty-five rats were randomly assigned to five groups as follows: (1) control (10 min of ischemia, n = 10); (2) sevoflurane post-conditioning (two periods of sevoflurane inhalation after ischemia for 10 min with a wash period of 10 min, n = 10); (3) resatorvid (intraperitoneal injection of a selective TLR-4 antagonist (3 mg/kg) 30 min before ischemia, n = 10); (4) sevoflurane post-conditioning plus resatorvid (n = 10), and sham (n = 5). The numbers of necrotic and apoptotic cells in the hippocampal CA1 region, the expression levels of TLR-4, NF-κB, cleaved caspase-3, and tumor necrosis factor alpha (TNF-α) in the anterior part of each brain, and the serum levels of TNF-α, interleukin 6 (IL-6), and interleukin 1 beta (IL-1β) were

assessed 1 day after ischemia. The necrotic cell counts and expression levels of TLR-4, NF-κB, caspase-3, and TNF-α in brain tissue as well as serum levels of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) were significantly higher in the control group than in the other groups. These findings suggest that the anti-inflammatory actions of sevoflurane post-conditioning via inactivation of the TLR-4/NF-κB pathway and subsequent reduction in pro-inflammatory cytokine production, in part, contribute to sevoflurane post-conditioning-induced neuroprotection after global transient cerebral ischemia in rats [36].

Another study investigated whether combined administration of celecoxib and sevoflurane after ischemia produces additive neuroprotection against transient global cerebral ischemia in rats. Cerebral ischemia was induced by bilateral common carotid artery occlusion with hemorrhagic hypotension for 8 min. After ischemia, no drugs were administered in the sham (n = 4) and control (n = 10) groups. In the celecoxib group (n = 10), celecoxib 2 mg/kg was administered after reperfusion. In the sevoflurane group (n = 10), after reperfusion, sevoflurane 2.4% was inhaled two times for 5 min each at an interval of 10 min to achieve post-conditioning. In the celecoxib + sevoflurane group (n = 10), administration of celecoxib 2 mg/kg and the sevoflurane after-treatment were performed simultaneously. Necrotic or apoptotic cells were examined in the hippocampus 7 days after ischemia. Serum levels of proinflammatory cytokines including tumor necrosis factor-α and interleukin-1β were measured 2 h, and 3 and 7 days after ischemia. Necrotic or apoptotic cells were observed more frequently in the control group than in the celecoxib or sevoflurane groups 7 days after ischemia (P < 0.05). Cytokine levels were higher in the control group when compared with the celecoxib or sevoflurane groups 2 h after ischemia (P < 0.05). However, the histological outcomes and cytokine levels were similar in all three groups treated with celecoxib or sevoflurane. It was concluded that combined treatment with celecoxib and sevoflurane after global cerebral ischemia has no additive neuroprotective effects

in rats [37].

CONCLUSION

From the discussion, we can conclude that the protective effects of sevoflurane inhalation against CNS damage have been widely confirmed, although specific mechanisms require further investigation. We believe that further study on the neuroprotective effect of sevoflurane and its underlying mechanism will provide a more thorough theoretical basis for its clinical application.

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