Review

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Progression in the study of protective effect of microRNAs against sevoflurane-induced postoperative cognitive dysfunction and potential mechanisms

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Abstract: As one of the volatile anaesthetic drugs commonly used in clinical anaesthesia, sevoflurane is extensively used in general anaesthesia surgery because of its rapid induction, hemodynamic stability, and rapid metabolism. However, postoperative cognitive dysfunction (POCD) is the most prevalent complications of its clinical application. Neuroinflammation and neuronal apoptosis are currently believed to be the primary mechanisms responsible for the development of cognitive dysfunction. MicroRNAs (miRNAs) can negatively regulate the expression of target genes, thereby influencing neurological and cognitive processes. Therefore, the effects and potential mechanisms of miRNAs on cognitive function may provide new ideas for the prevention and treatment of sevoflurane-induced POCD, a topic of intense research interest at the moment. The mechanisms involved in sevoflurane-induced POCD, the regulation of miRNAs expression by sevoflurane, and the effects of miRNAs on target genes and downstream signalling pathways were reviewed in order to obtain a comprehensive understanding of the effects of miRNAs on cognitive function.

Keywords: microRNAs; sevoflurane; cognitive dysfunction; neuroinflammation; neuronal apoptosis

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Introduction

Sevoflurane is a popular inhalation anaesthetic for patients of all ages because of its rapid onset of action, rapid induction, rapid clearance, low blood gas partition coefficient, low airway irritation, haemodynamic stability, and excellent controllability. Sevoflurane may exert its anaesthetic properties by activating inhibitory ion channels and inhibiting excitatory ion channels, thereby reducing neuronal excitability. POCD is a complication of the central nervous system that occurs predominantly after anaesthesia, and is characterized by impaired cognitive abilities, such as diminished attention, impaired memory, and diminished information processing. Age is major risk factor linked to the development of POCD. Many studies have shown that POCD occurs most frequently in elderly patients after anaesthesia. The inability of older adults with POCD to perform daily tasks and live independently has a severe impact on patients' quality of life and prolongs hospital stays. Moreover, patients with POCD have an increased mortality rate. Even though anaesthetics are widely perceived as safe, complications resulting from them have garnered significant attention. POCD is predominantly caused by inhalational general anaesthetics. Sevoflurane increases the incidence of POCD and induces neurotoxicity and cognitive impairment. A study shown that elderly mice are at greater risk of POCD than younger mice [1]. Current studies indicate that inhalation anaesthesia can induce neurotoxicity and cognitive impairment leading to POCD in the elderly.

Mechanisms involved in the induction of POCD by sevoflurane

In elderly patients, Anaesthesia based on sevoflurane increases POCD incidence significantly. This may be a consequence of the underlying diseases of the elderly. First, aging increases the risk of respiratory, cardiovascular, urinary, and neurological disorders; second, there are substantial differences in pharmacokinetics and pharmacodynamics between elderly and younger individuals, with sevoflurane remaining in the bloodstream for longer durations as organ function declines. Many hypotheses have been proposed for the pathogenesis of POCD induced by sevoflurane, including neuroinflammation, microglia activation, neuronal apoptosis, neurotransmitter changes, autophagy dysfunction, reduced neurotropic factors, oxidative stress, increased β-amyloid (Aβ) concentrations, and impaired blood-brain barrier. The most frequently cited mechanisms associated with POCD are neuroinflammation and neuronal apoptosis.

Neuroinflammation

Neuroinflammation is essential to cognitive processes. Neuroinflammation induces by sevoflurane is a significant contributor to cognitive deficits. Sevoflurane-induced anaesthesia is associated with disruption of the balance between neuroinflammation and neuronal function in the elderly. Pro-inflammatory cytokines and activated microglia are two characteristics of CNS inflammation.

Neuronal microglia are immune cells that reside in the nervous system, and their activation is the defining characteristic of neuroinflammation and POCD develops as a result of their activation. Normally, microglia are in a quiescent state, but under pathological conditions, they become activated. Microglia have two distinct activation states, classical activation (M1) characterized by the promotion of inflammation and production of reactive oxygen species, and alternative activation and acquired inactivation (M2) characterized by anti-inflammatory function. Sevoflurane induces classical activation of M1 in microglia, which results in an increase in pro-inflammatory cytokine production but a decrease in alternative activation and acquired inactivation (M2), thereby diminishing anti-inflammatory and tissue repair functions. When microglia are activated, they simultaneously induce the expression of nuclear factor, release inflammatory factors and induce neuronal apoptosis. Sevoflurane inhalation induces cognitive dysfunction by activating microglia, increasing neuroinflammation in the hippocampus, and up regulating TNF-α, IL-6 and IL-1β [2] (Figure 1).

TNF-α, IL-1β, and IL-6 are significantly elevated in sevoflurane-induced brains. Increased IL-1β levels are associated with intense neuroinflammation changes that result in neuronal death in the brain [3]. NF-κB protein is widely expressed in mammals and is involved in the regulation of inflammatory factors and the promotion of inflammatory responses. Prolonged anaesthesia can activate the NF-κB inflammatory pathway, leading to increased neuroinflammation and cognitive impairment. According to one study, sevoflurane activated the NF-κB pathway, increasing the expression of NF-κB p65, TNF-α, IL-1β, and IL-6 [4].

Neuronal apoptosis

Neuronal viability and function are diminished in individuals with cognitive impairment. Sevoflurane induces apoptosis and inflammatory responses by decreasing cell viability and exacerbating neurotoxicity. Sevoflurane-induced apoptosis leads to cognitive dysfunction [5]. There is a close relationship

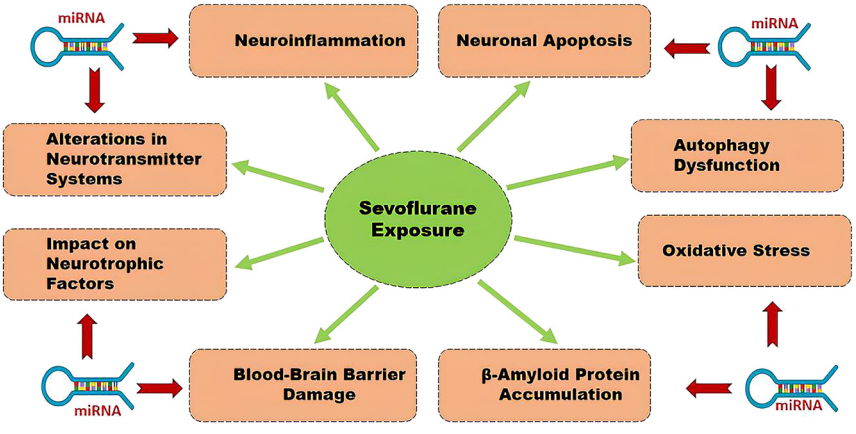

Figure 1: A summary diagram illustrating the main effects of sevoflurane.

between apoptosis and the level of expression of apoptotic protein factors. Following exposure to sevoflurane, the expression of pro-apoptotic proteins Bax and caspase-3 significantly increased, whereas the expression of anti-apoptotic proteins Bcl-2 and Bcl-xL decreased [4]. Unbalanced apoptotic factors may also contribute to cognitive dysfunction; for example, sevoflurane anaesthesia may cause cognitive deficits by upsetting the equilibrium between Bcl-xL and caspase-9 expression [1]. In addition to apoptotic factors, sevoflurane has been shown to induce endoplasmic reticulum stress via activation of IP3R and promote hippocampal neuronal apoptosis via cytoplasmic calcium accumulation [6]. Activation of the NF-κB pathway is also one of the mechanisms by which sevoflurane induces neuronal apoptosis, and neuronal morphology and synaptic integrity are impaired as a result of repeated exposure to sevoflurane.

Alterations in neurotransmitter systems

The effect of sevoflurane on neurotransmitters may have caused POCD. Sevoflurane anaesthesia inhibits acetylcholine (ACh) release and decreases acetylcholine receptor expression in the hippocampus. Sevoflurane induces abnormal expression of SP1 and α7nAChR in the hippocampus of rodents [5], promotes inflammatory responses and apoptosis, and impairs cognitive performance. Sevoflurane can also have pro-inflammatory effects by inhibiting cholinergic neurotransmission. Sevoflurane probably modifies the equilibrium between inflammatory and anti-inflammatory responses and promote neuroinflammation by inhibiting cholinergic anti-inflammatory pathways. Cholinergic 7nAChR agonists can also activate microglia, inhibit macrophage activity, and suppress NF-κB activation, enhancing cognitive function [7]. This suggests that neurotransmitter changes may also contribute to cognitive dysfunction by causing neuroinflammation.

Impact on neurotrophic factors

Neurotrophic factors are a group of proteins that regulate the development, differentiation, survival, and repair of nerve cells. NGF and BDNF are neurotrophic proteins. Both play an important function in neuronal survival, learning, and memory. Sevoflurane modulates the BDNF/TrkB signalling pathway via the NMDA receptor/Ca2+/calpain pathway, resulting in the down regulation of BDNF expression and the onset of POCD [8]. Sevoflurane anaesthesia not only inhibits BDNF expression, but also significantly reduces nerve growth factor (NGF) levels by disrupting NGF synthetic pathway, which is crucial for maintaining the integrity and function of basal forebrain cholinergic neurons (BFCNs). One study found that exposure to sevoflurane inhibited the synthesis of NGF and caused the degeneration of BFCNs, leading to cognitive impairment [9].

Autophagy dysfunction

There is a possibility that sevoflurane-induced defects in mitochondrial autophagy are linked to neuronal cell autophagic injury. According to studies, impaired autophagy of hippocampal neurons following sevoflurane anaesthesia may result in cognitive impairment. It has been shown that activating autophagy reduces neurotoxicity and protects neuronal cells, and it has been discovered that echinacoside increases the expression of FOXO1 in the hippocampus and the expression of autophagy-related proteins, thereby activating cellular autophagy and reducing cognitive dysfunction [10]. Therefore, dysfunctional autophagy may be a potential mechanism for POCD, and autophagy activation may reverse cognitive impairment.

Oxidative stress

POCD is closely associated with neuroinflammation, and oxidative stress is a significant contributor. Neuroinflammation is a major source of reactive oxygen species (ROS), and the excess ROS generated can disrupt biomolecules and alter cellular function, thus promoting inflammation. Mitochondrial autophagy is one of the self-limiting systems that protects tissues and organs from excessive inflammation and promotes tissue repair. Increasing mitochondrial autophagy eliminates more damaged and dysfunctional mitochondria and helps reduce excessive ROS production. Consequently, mitigating oxidative stress through mitochondrial autophagy is also a potential cognitive dysfunction treatment.

Damage to the blood-brain barrier

Studies have demonstrated that sevoflurane anaesthesia substantially increases the blood-brain barrier's permeability. Inflammatory factors interact with the impaired blood-brain barrier, and increases in pro-inflammatory cytokines can induce blood-brain barrier disruption and increase permeability, aggravating neuroinflammation.

β-amyloid protein (Aβ)

In addition to the aforementioned pathogenesis, sevoflurane can impact cognitive function through additional mechanisms. Exposure to sevoflurane, for instance, substantially increases the accumulation of Aβ in the hippocampus, and research indicates that short-term alterations in Aβ can induce inflammation in the brain, resulting in cognitive dysfunction [11]. miRNAs, 18–25 nucleotides in length, negatively regulate gene expression by specifically binding to the 3′-UTR of target mRNAs and inhibiting the transcriptional translation of target mRNAs, thereby influencing cell differentiation, proliferation, and apoptosis. Because miRNAs are intimately associated with cognitive processes, it is crucial to identify miRNAs implicated in anaesthesia induction-related miRNAs and to understand their functions and molecular mechanisms.

Numerous studies have demonstrated that sevoflurane-induced neurological damage and cognitive dysfunction are associated with miRNAs. For example, down regulation of miR-143-3p [12] and miR-125b-5p [13] can up regulate LIMK1 expression, inhibiting the sevoflurane-induced apoptosis and inflammatory response in the rat hippocampus and ameliorating the POCD. In addition, sevoflurane has the ability to affect the expression of microRNAs. Sevoflurane can up regulate the expression of miR-96 while inhibiting IGF1R, leading to accelerated apoptosis of hippocampal neurons and cognitive dysfunction [14]. Moreover, numerous studies have demonstrated the close association between microRNAs and cognitive function. MiR-124 [15], miR-584-5p [16], miR-410-3p [17], miRNA-140-3p [18], miR-146a [19], and miRNA-384-3p [20] can all affect cognitive function by modulating downstream signaling pathways. Therefore, microRNAs appear to be viable therapeutic targets for the prevention of POCD. Numerous potential mechanisms exist by which miRNAs affect cognitive function, but the following two are now widely accepted: first, miRNAs inhibit neuroinflammation by regulating the expression of inflammatory factors; and second, miRNAs promote neuronal function and inhibit neuronal apoptosis, thereby alleviating sevoflurane-induced POCD.

miRNAs suppress inflammatory responses to protect cognitive function

Sevoflurane can induce microglial activation and increased expression of inflammatory factors, thereby aggravating neuroinflammation, one of the principal mechanisms underlying POCD. Numerous studies have demonstrated that modulating miRNAs can ameliorate cognitive dysfunction by reducing the inflammatory response; for example, down regulation of miR-125b-5p [13] and miR-143-3p [12] can up regulate LIMK1 expression to suppress inflammatory responses in rat hippocampal cells, protecting against sevoflurane-induced cognitive dysfunction. miR-124 protects against sevoflurane-induced cognitive dysfunction by modulating the NF-κB signalling pathway and inhibits IL-1β, IL-6 and TNF-α expression in hippocampal neurons to ameliorate sevoflurane-induced cognitive deficits [15]. The NF-κB signalling pathway is a key inflammatory response-inducing pathway and one of the distal pathways on which miRNAs act. According to studies [19], MiR-146a modulates hippocampal neuroinflammation and improves cognitive decline by inhibiting the IRAK1/TRAF6/NF-κB pathway. In addition to the classical NF-κB signalling pathway to regulate inflammation levels, miRNAs can also regulate the expression and release of inflammatory factors via other pathways. Microglia activation is also a target for inducing inflammatory responses, studies have shown that increasing miR-124 and decreasing VAMP3 expression regulates microglia activation and subsequent inflammatory responses [21]. Studies have demonstrated that overexpression of miR-128-3p can suppress elevated levels of inflammatory factors [22]. Nevertheless, the specific protective mechanisms and pathways are not yet known. In conclusion, modulating microRNA levels can affect the expression of relevant inflammatory factors, thereby ameliorating the cognitive dysfunction induced by sevoflurane (Table 1).

Table 1: Summary of key findings on miRNAs and their effects.

miRNA	Effect	Pathway/target	Impact on POCD
miR-125b-5p	Upregulates LIMK1, reduces inflammation	LIMK1, NF-κB	Reduces neuroinflammation
miR-143-3p	Upregulates LIMK1, reduces inflammation	LIMK1, NF-κB	Reduces neuroinflammation
miR-124	Inhibits IL-1β, IL-6, and TNF-α	NF-κB, inflammatory cytokines	Alleviates cognitive deficits
miR-96	Accelerates apoptosis by inhibiting IGF1R	IGF1R, apoptosis pathways	Enhances neurotoxicity and apoptosis
miR-410-3p	Regulates PI3K/Akt pathway	PI3K/Akt, apoptosis pathways	Reduces neuronal apoptosis
miR-584-5p	Targets BDNF and regulates apoptosis	BDNF, caspase3	Modulates neuronal apoptosis

miRNAs inhibit apoptosis to improve cognitive function

In addition to sevoflurane-induced POCD, which is associated with microglia activation and elevated levels of inflammatory factors, another significant mechanism is neuronal cell apoptosis. Sevoflurane decreases Bcl-2 levels and increases Bax and caspase-3 expression levels, causing an increase in hippocampal neuronal apoptosis, which impairs learning and memory. After sevoflurane exposure, miR-96 [14] expression is up regulated and miRNA-384-3p [20] and MiR-128-3p [22] expression is down regulated, enhancing neurotoxicity and promoting apoptosis. miRNAs have numerous targets and pathways involved in neuronal apoptosis, for example, miRNA-1297 inhibits neuronal apoptosis by targeting PTEN proteins and inhibiting the Akt/GSK3b signalling pathway [23] and miR-584-5p can target BDNF and regulate Caspase3 and BDNF/TrkB signalling pathway [16] are involved in neuronal apoptosis.

There are also studies showing that microRNA modulation can prevent neuronal apoptosis and ameliorate cognitive dysfunction. miR-124 [15] and miR-410-3p [17] inhibit apoptosis by decreasing expression of caspase-3 and Bax and increasing expression of Bcl-2. Numerous studies have shown that modulating the expression levels of related miRNAs can modulate downstream targets, affect the activation of related signalling pathways, and elicit subsequent apoptotic responses. For example, down regulation of miR-125b-5p increases LIMK1 expression [13], miR-410-3p targets the PI3K/Akt signalling pathway of CXCR5 [17], microRNA- 140-3p targets DNMT1 to activate the HTR2A/ERK/Nrf2 signalling pathway [18], and miRNA-384-3p inhibits Aak1 kinase [22],which inhibits sevoflurane anaesthesia-induced apoptosis in neuronal apoptosis. Neurotrophic factor levels also can affect neuronal cell activity.

For example, miR-584-5p [16] can negatively regulate BDNF to decrease neurotrophic factor levels, thereby reducing neuronal cell activity and function, down-regulation of miR-133 could increase GDNF expression, inhibit neuronal apoptosis and reduce the toxic effects of sevoflurane on neuronal cells [24], but up-regulation of miR-133 could increase GDNF expression, inhibit neuronal apoptosis, and reduce neuronal cell toxicity.

Mechanisms regulating the expression of miRNAs

miRNAs are members of the non-coding RNA family that inhibit the function of downstream signalling by binding to the 3′-UTR of target mRNAs. Long-stranded non-coding RNAs (LncRNAs) operate as microRNA sponges that affect the expression of microRNA target mRNAs via a ceRNA regulatory mechanism that competitively binds to miRNAs, which is a popular topic in the field of inflammatory disease research. LncRNAs inhibits cognitive function by sponging miRNAs to inhibit inflammatory responses, oxidative stress, and apoptotic pathways, thereby exerting a neuroprotective effect on POCD. Similar investigations have identified the regulation of inflammatory responses by lncRNAs, LncRNA 4344/miR-138-5p/NLRP3 [25] and LncRNA GAS5/miR-137/TCF4 pathways are closely associated with neuroinflammation [1, 26]. Studys suggests that the lncRNA CDKN2B-AS1/miR-133/GDNF [24], LncRNA Peg13/microRNA-128-3p/Sox13 [27], and lncRNA Rian/miR-143-3p/LIMK1 [12] pathways mitigate sevoflurane toxicity and neural cell injury.

In addition to the LncRNA/miRNA/mRNA regulatory mechanism, circular RNA (circRNA) is another endogenous mechanism for regulating miRNA expression. The circRNA-associated ceRNA network may contribute to the occurrence of POCD by regulating multiple pathways, including the PKC pathway, the Wnt pathway, the VEGF pathway, the glycolipid metabolic pathway, and other neurological functional processes. The up regulation of mm9-circ-009789 and mm9-circ-004229 may serve as a substrate for mmu-miR-298-5P, which regulates the expression of Prkcb, Zbtb4, and Syngap1 and correlates with the development of POCD [1]. Similar research [28] discovered that neuronal cell apoptosis mediated by circRIMS2/miR-186/BDNF improved vascular cognitive impairment. A further study constructed a circRNA-miRNA-mRNA triple regulatory network and concluded that may be biomarkers and therapeutic targets for the diagnosis of POCD [29]. In conclusion, these investigations offer novel insights into the treatment of inflammatory responses and neurotoxicity induced by sevoflurane.

miRNAs regulate downstream signalling pathways

Sevoflurane-induced cognitive dysfunction is caused by multiple mechanisms. POCD induced by sevoflurane may involve the Rap1 signalling pathway, PI3K-Akt signalling pathway, ecm-receptor interaction, phospholipase D signalling pathway, cGMP-PKG signalling pathway, miRNAs-GABAergic delivery pathway and Wnt signalling pathway.

There are also numerous downstream pathways of microRNAs; for instance, miR-182-5p [13] and miR-146a [19] can regulate the NF-κB signalling pathway to influence the release of inflammatory factors. In addition to the NF-κB signalling pathway, the PI3K/Akt pathway regulated by miR-410-3p [17],

the BDNF/TrkB pathway regulated by microRNA-188-3p [16] and the microRNA-140-3p HTR2A/ERK/Nrf2 pathway [18] are all associated with neural function and activity. In conclusion, the effect of microRNAs on signalling pathways is a crucial aspect of their neuroprotective effects research.

Drugs related to improving cognitive dysfunction

Cognitive dysfunction following surgery is one of the most common adverse effects of sevoflurane anaesthetics, which are widely utilized in clinical settings. According to pharmacological studies, inhibiting inflammatory responses and apoptosis can ameliorate the cognitive impairment brought on by sevoflurane. This will be the primary focus of our future research into the sevoflurane-induced relief of POCD. There are currently a variety of medications that improve cognitive function.

Several studies have demonstrated that resveratrol, cistanches, carnosol, luteolin, hesperidin, and honokiol, ampelopsin], and cucurbitacin E ameliorate cognitive dysfunction by inhibiting the inflammatory response and inhibiting neuronal apoptosis. Also, echinacoside, rapamycin, and luteolin have been found to enhance cognitive function by mediating autophagy [30–32]. Echinacoside, rapamycin, and luteolin enhance cognitive function by mediating autophagy, a cellular process that clears damaged cells and proteins, thus supporting cognitive health and reducing neurodegenerative changes. Echinacoside, derived from Echinacea, and luteolin, a flavonoid from various plants, both improve cognitive function through their neuroprotective and anti-inflammatory effects. Rapamycin, an mTOR inhibitor, further supports cognitive health by enhancing autophagy and reducing neuroinflammation. Additionally, dexmedetomidine, an alpha-2 adrenergic agonist, attenuates post-operative cognitive dysfunction by modulating miRNAs that regulate DNA damage, neuroinflammation, and neuronal apoptosis, thereby offering a multifaceted approach to mitigating cognitive impairment [10, 33].

In addition to natural herbal components for the preventive treatment of sevoflurane-induced cognitive dysfunction, dexmedetomidine attenuates POCD by modulating miRNA inhibition of DNA damage, neuroinflammation, and neuronal apoptosis [34]. At present, many drugs and their potential mechanisms for the prevention of cognitive dysfunction have been studied, and the effect of miRNAs on POCD is gradually being discovered. Acetylcholinesterase inhibitors like donepezil and rivastigmine work by increasing acetylcholine levels in

Table 2: Summary of drugs investigated for ameliorating postoperative cognitive dysfunction (POCD).

Drug	Mechanism of action	Clinical trial status
Resveratrol	Anti-inflammatory, antioxidant; inhibits neuroinflammation and oxidative stress	Clinical trials in progress for cognitive function in various conditions
Cistanches	Improves cognitive function through anti-inflammatory and antioxidant effects	Limited clinical evidence; further studies needed
Carnosol	Reduces oxidative stress and inflammation, promotes neuroprotection	Preclinical studies; clinical trials needed
Luteolin	Anti-inflammatory, antioxidant; enhances cognitive function by modulating neuroinflammation	Clinical trials in progress for cognitive decline and neurodegenerative diseases
Hesperidin	Antioxidant, anti-inflammatory; protects neurons from oxidative stress	Clinical trials in progress for neuroprotection
Honokiol	Anti-inflammatory, neuroprotective; modulates neurotransmitter systems	Clinical trials in progress for neurodegenerative diseases
Ampelopsin	Antioxidant, anti-inflammatory; improves cognitive function	Preclinical studies; further clinical research needed
Cucurbitacin E	Anti-inflammatory, neuroprotective; modulates cell signaling pathways	Preclinical studies; clinical trials needed
Echinacoside	Enhances autophagy, neuroprotective, anti-inflammatory	Clinical trials in progress for cognitive function
Rapamycin	mTOR inhibitor; enhances autophagy, reduces neuroinflammation	Clinical trials in progress for cognitive decline and neurodegenerative diseases
Dexmedetomidine	Modulates miRNAs, reduces neuroinflammation and neuronal apoptosis	Clinical trials in progress for postoperative cognitive dysfunction
Donepezil	Acetylcholinesterase inhibitor; increases acetylcholine levels	Widely used; approved for Alzheimer's disease
Rivastigmine	Acetylcholinesterase inhibitor; increases acetylcholine levels	Approved for Alzheimer's disease; clinical trials for other conditions
Memantine	NMDA receptor antagonist; regulates glutamate activity	Approved for Alzheimer's disease
Ginkgo biloba	Antioxidant, improves blood flow, reduces oxidative stress	Mixed evidence; some clinical trials show benefits
Curcumin	Anti-inflammatory, antioxidant; modulates various signaling pathways	Clinical trials in progress for cognitive decline and neurodegenerative diseases

the brain, which can improve memory and cognitive function in conditions such as Alzheimer's disease. NMDA receptor antagonists such as memantine help to regulate glutamate activity, potentially protecting neurons from excitotoxicity associated with cognitive decline. Neuroprotective agents like ginkgo biloba and curcumin have shown promise in reducing oxidative stress and inflammation, which are implicated in cognitive dysfunction. Additionally, emerging research is exploring the role of anti-inflammatory drugs and hormonal therapies in modulating neuroinflammation and supporting cognitive health [35]. Thus, it seems that the prevention and treatment of POCD by pharmaceutical active ingredients through miRNAs will become a research hotspot (Table 2).

Conclusions

This study highlights the potential of microRNAs (miRNAs) in mitigating sevoflurane-induced postoperative cognitive dysfunction (POCD) by targeting key mechanisms such as neuroinflammation and neuronal apoptosis. Findings reveal that miRNAs like miR-125b-5p, miR-143-3p, and miR-124 can modulate critical signaling pathways, including NF-κB and PI3K/Akt, to reduce cognitive impairments associated with sevoflurane. Future research should focus on elucidating the precise molecular mechanisms of miRNAs, developing miRNA-based therapies, identifying biomarkers for early detection, and exploring combination therapies to enhance cognitive protection and recovery.

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References

1. Zhang M-X, Lin JR, Yang ST, Zou J, Xue Y, Feng CZ, et al. Characterization of circRNA-associated-ceRNA networks involved in the pathogenesis of postoperative cognitive dysfunction in aging mice. Front Aging Neurosci 2022;14:727805.
2. Xu F, Wang Y, Han L, Deng D, Ding Y, Ma L, et al. PEX5R/Trip8b-HCN2 channel regulating neuroinflammation involved in perioperative neurocognitive disorders. Cell Biosci 2022;12:156.
3. Tian Y, Chen K, Liu L, Dong Y, Zhao P, Guo S. Sevoflurane exacerbates Cognitive Impairment Induced by Aβ1–40 in rats through initiating neurotoxicity, Neuroinflammation, and neuronal apoptosis in Rat Hippocampus. Mediat Inflamm 2018;2018:3802324.
4. Huang H, Hu C, Xu L, Zhu X, Zhao L, Min J. The effects of hesperidin on neuronal apoptosis and cognitive impairment in the sevoflurane anesthetized rat are mediated through the PI3/Akt/PTEN and nuclear Factor-κB (NF-κB) signaling pathways. Medical Science Monitor. Int Med J Exp Clin Res 2020;26:e920522–1.
5. Lv G, Wang W, Wang K. Retracted article: silencing SP1 alleviated sevoflurane-induced POCD development via cholinergic anti-inflammatory pathway. Neurochem Res 2020;45:2082–90.
6. Zhang Q, Li Y, Wang X, Yin C, Zhou Q, Guo J, et al. Sevoflurane exposure causes neuronal apoptosis and cognitive dysfunction by inducing ER stress via activation of the inositol 1, 4, 5-trisphosphate receptor. Front Aging Neurosci 2022;14:990679.
7. Huffman WJ, Subramaniyan S, Rodriguiz RM, Wetsel WC, Grill WM, Terrando N. Modulation of neuroinflammation and memory dysfunction using percutaneous vagus nerve stimulation in mice. Brain Stimul 2019;12:19–29.
8. Wang C-m., Chen W, Zhang Y, Lin S, He H. Update on the mechanism and treatment of sevoflurane-induced postoperative cognitive dysfunction. Front Aging Neurosci 2021;13:702231.
9. Xiong L, Duan L, Xu W, Wang Z. Nerve growth factor metabolic dysfunction contributes to sevoflurane-induced cholinergic degeneration and cognitive impairments. Brain Res 2019;1707:107–16.
10. Yang H, Zhao L, Li Q. Echinacoside alleviates sevoflurane-induced cognitive dysfunction by activating FOXO1-mediated autophagy. Int J Dev Neurosci 2022;82:339–48.
11. Xu Y, Dong Y, Wang C, Jiang Q, Chu H, Tian Y. Lovastatin attenuates sevoflurane-induced cognitive disorder in aged rats via reducing Aβ accumulation. Neurochem Int 2021;148:105078.
12. Yu Y, Zhang W, Zhu D, Wang H, Shao H, Zhang Y. LncRNA Rian ameliorates sevoflurane anesthesia-induced cognitive dysfunction through regulation of miR-143-3p/LIMK1 axis. Hum Cell 2021;34:808–18.
13. Xiong J, Wang H, Mu F, Liu Z, Bao Y, Sun Y. miR-125b-5p inhibitor might protect against sevoflurane-induced cognitive impairments by targeting LIMK1. Curr Neurovascular Res 2019;16:382–91.
14. Xu C, Niu JJ, Zhou JF, Wei YS. MicroRNA-96 is responsible for sevoflurane-induced cognitive dysfunction in neonatal rats via inhibiting IGF1R. Brain Res Bull 2019;144:140–8.
15. Zhao Z, Ma L, Li Y, Zhang Q, Wang Y, Tai Y, et al. MiR-124 protects against cognitive dysfunction induced by sevoflurane anesthesia in vivo and in vitro through targeting calpain small subunit 1 via NF-κB signaling pathway. Adv Clin Exp Med 2021;30:701–9.
16. Li Y, Liu L, Tian Y, Zhang J. Rapamycin improves sevoflurane-induced cognitive dysfunction in aged rats by mediating autophagy through the TLR4/MyD88/NF-κB signaling pathway. Mol Med Rep 2019;20:3085–94.

17. Su R, Sun P, Zhang D, Xiao W, Feng C, Zhong L. Neuroprotective effect of miR-410-3p against sevoflurane anesthesia-induced cognitive dysfunction in rats through PI3K/Akt signaling pathway via targeting C–X–C motif chemokine receptor 5. Genes Genomics 2019;41:1223–31.
18. Wu Z, Tan J, Lin L, Zhang W, Yuan W. microRNA-140-3p protects hippocampal neuron against pyroptosis to attenuate sevoflurane inhalation-induced post-operative cognitive dysfunction in rats via activation of HTR2A/ERK/Nrf2 axis by targeting DNMT1. Cell Death Discov 2022;8:290.
19. Chen L, Dong R, Lu Y, Zhou Y, Li K, Zhang Z, et al. MicroRNA-146a protects against cognitive decline induced by surgical trauma by suppressing hippocampal neuroinflammation in mice. Brain Behav Immun 2019;78:188–201.
20. Chen Y, Gao X, Pei H. miRNA-384-3p alleviates sevoflurane-induced nerve injury by inhibiting Aak1 kinase in neonatal rats. Brain Behav 2022;12:e2556.
21. Chen Y, Sun J, Chen W, Wu G, Wang Y, Zhu K, et al. miR-124/VAMP3 is a novel therapeutic target for mitigation of surgical trauma-induced microglial activation. Signal Transduct Targeted Ther 2019;4:27.
22. Li D, Sun J, Yu M, Wang Y, Lu Y, Li B. The protective effects of miR-128-3p on sevoflurane-induced progressive neurotoxicity in rats by targeting NOVA1. J Toxicol Sci 2022;47:51–60.
23. Wang Q, Luo J, Sun R, Liu J. MicroRNA-1297 suppressed the Akt/GSK3 β signaling pathway and stimulated neural apoptosis in an in vivo sevoflurane exposure model. J Int Med Res 2021;49: 0300060520982104.
24. Jiang S, Wang C, Zhu J, Huang X. Regulation of glial cell-derived neurotrophic factor in sevoflurane-induced neuronal apoptosis by long non-coding RNA CDKN2B-AS1 as a ceRNA to adsorb miR-133. Am J Tourism Res 2021;13:4760.
25. Feng X, Zhan F, Luo D, Hu J, Wei G, Hua F, et al. LncRNA 4344 promotes NLRP3-related neuroinflammation and cognitive impairment by targeting miR-138-5p. Brain Behav Immun 2021;98:283–98.
26. Zhang C, Chen D, Gu Y, Wang T, Wang C. Effects of LncRNA GAS5/ miR-137 general anesthesia on cognitive function by TCF4 inflammatory bodies in patients undergoing lumbar spinal canal decompression. Medicine 2022;101:e31880.
27. Jiang Y, Wang Y, Sun Y, Jiang H. Long non-coding RNA Peg13 attenuates the sevoflurane toxicity against neural stem cells by sponging microRNA-128-3p to preserve Sox13 expression. PLoS One 2020;15:e0243644.
28. Niu Y, Wan C, Zhang J, Zhang S, Zhao Z, Zhu L, et al. Aerobic exercise improves VCI through circRIMS2/miR-186/BDNF-mediated neuronal apoptosis. Mol Med 2021;27:1–12.
29. Wang W, Huo P, Zhang L, Lv G, Xia Z. Decoding competitive endogenous RNA regulatory network in postoperative cognitive dysfunction. Front Neurosci 2022;16:972918.
30. Zhou Q, Deng Y, Hu X, Xu Y. Resveratrol ameliorates neuronal apoptosis and cognitive impairment by activating the SIRT1/RhoA pathway in rats after anesthesia with sevoflurane. Bosn J Basic Med Sci 2022;22:110–17.
31. Peng S, Li P, Liu P, Yan H, Wang J, Lu W, et al. Cistanches alleviates sevoflurane-induced cognitive dysfunction by regulating PPAR-γ-dependent antioxidant and anti-inflammatory in rats. J Cell Mol Med 2020;24:1345–59.
32. Li Q, Zhang X, Li S, Li W, Teng Y, Zhou Y, et al. Carnosol alleviates sevoflurane-induced cognitive dysfunction by mediating NF-κB pathway in aged rats. Drug Dev Res 2022;83:1342–50.
33. Qiu H, Liu X. Echinacoside improves cognitive impairment by inhibiting Aβ deposition through the PI3K/AKT/Nrf2/PPARγ signaling pathways in APP/PS1 mice. Mol Neurobiol 2022;59:4987–99.
34. Wang Y-L, Zhang Y, Cai D-S. Dexmedetomidine ameliorates postoperative cognitive dysfunction via the microRNA-381-mediated EGR1/p53 axis. Mol Neurobiol 2021;58:5052–66.
35. Fink HA, Jutkowitz E, McCarten JR, Hemmy LS, Butler M, Davila H, et al. Pharmacologic interventions to prevent cognitive decline, mild cognitive impairment, and clinical alzheimer-type dementia: a systematic review. Ann Intern Med 2018;168:39–51.