The role of sevoflurane in postoperative cognitive dysfunction

Sevoflurane, a 200 dalton chemical molecule, is an inhalation anesthetic used for induction and maintenance of general anesthesia, which is used by a specially calibrated volatilizer.[1] As with all inhalation anesthetics, sevoflurane can cause dose-related cardiorespiratory hypofunction. Nausea and vomiting are the most common postoperative adverse effects, and other frequent adverse effects include hypotension, bradycardia, and cough.[2] Relatively rare adverse effects include elevation of aspartate aminotransferases and acute renal failure.[3] However, there are few reports of neurological effects after surgery, particularly postoperative cognitive dysfunction (POCD).

POCD is a central nervous system complication that occurs after surgery, especially in the elderly, manifested as changes in personality, social skills, cognitive abilities and skills, and degeneration of intellectual functions such as memory and concentration decline.[4] The pathogenesis of POCD mainly involves neuroinflammatory response caused by microglial activation, calcium overload-induced mitochondrial damage, and neuronal apoptosis due to oxidative stress,[5,6] all of which affect hippocampal function, resulting in a series of cognitive dysfunction.

Therefore, we attempt to elucidate the mechanism, related signaling pathways, and molecular regulation of sevoflurane-induced POCD based on existing literature reports. This will help to identify possible treatments to reduce the incidence of POCD and improve the prognosis of POCD, thereby optimizing the sevoflurane anesthesia program, reducing patient discomfort, and improving the quality of life of patients.

Mechanism and molecular regulation of sevoflurane-induced POCD: The mechanism of sevoflurane-induced POCD is still not well understood, and researchers explore its related molecular and pathway changes mainly through basic experiments, and the mechanism is mostly close to neuroinflammation and neuronal apoptosis (**Table 1** and **Figure 1**). After treating elderly mice with sevoflurane, Chai et al.[7] found that the level of acidic leucine-rich nuclear phosphoprotein-32A protein increased, which inhibited the acetylation of histones H3K18 and H3K14, thereby preventing H3K18 and H3K14 from binding to GluN2B and GluN2A promoters, causing a decrease in synapse-related protein expression, and finally leading to POCD. It can be seen that the integrity and plasticity of neuronal synaptic function are of great significance in POCD. He et al.[8] found that after treatment with sevoflurane, methyltransferase-like 3 phosphorylation in hippocampal tissue may be inactivated by inhibiting the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, resulting in perturbation in m6A (N6-methyladenosine) RNA methylation, which causes pathogenesis in POCD. Sleep disorders can aggravate the occurrence of POCD. Shen et al.[9] found that after sevoflurane was used to treat sleep-deprived rats, the level of salt-induced kinase 3 in the brain tissue increased, which made the levels of phosphorylation- and total-tau rise, and the level of acetylation decreased, thereby causing POCD. It can be seen that this pathophysiological process involves the salt-induced kinase 3 signaling pathway. In mouse hippocampal primary neuronal experiments, Zhu and Ma[10] found that the levels of inflammatory indicators interleukin-6, interleukin-10 and tumor necrosis factor-α increased after treating neurons with sevoflurane. The mechanism was that sevoflurane activated Hoxa5, thereby upregulating long non-coding RNA Gm5106 and directly targeting the anti-inflammatory molecule miRNA-27-3p. Similarly, Cheng et al.[11] found that in SH-SY5Y cells, sevoflurane intervention caused elevated acyl-coenzyme A synthetase long chain family member 4 expression. Downregulation of acyl-coenzyme A synthetase long chain family member 4 alleviates sevoflurane-induced ferroptotic cell death, and in-depth exploration shows that acyl-coenzyme A synthetase long chain family member 4 is involved in sevoflurane-induced ferroptotic cell death through the adenosine

Table 1: The mechanism of POCD induced by sevoflurane

Author	Year	Experimental subject	Pathway
Chen et al.[16]	2020	Aged rats H4 cells	Mitophagy pathway
Cheng et al.[11]	2021	SH-SY5Y cells	AMPK/mTOR pathway
Ge et al.[12]	2021	C57BL/6 male	Bcl2/Bax pathway
He and Wang[8]	2021	Aging C57BL/6 mice	MAPK/ERK pathway
Shen et al.[9]	2021	Aged Sprague-Dawley rats	Salt-induced kinase 3 pathway
Zhao et al.[14]	2021	Mice	NF-κB signaling pathway
Zhao et al.[13]	2021	Aging male C57BL/6 mice Primary hippocampal neurons of C57BL/6 mice	Ferroptosis pathway
Zhu and Ma[10]	2021	Primary hippocampal neurons of C57BL/6 mice	Hoxa5/Gm5106/miR-27b-3p pathway
Chai et al.[7]	2022	Aging C57BL/6 mice	C/EBPβ-ANP32A pathway
Wei et al.[15]	2022	Aged Sprague-Dawley rats	NF-κB signaling pathway

Note: AMPK: Adenosine 3'-monophosphate-activated protein kinase; ANP32A: acidic leucine-rich nuclear phosphoprotein-32A; C/EBPβ: CAAT/enhancer binding protein-β; ERK: extracellular signal-regulated kinase; HOXA5: Homeobox A5; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa-B; POCD: postoperative cognitive dysfunction.

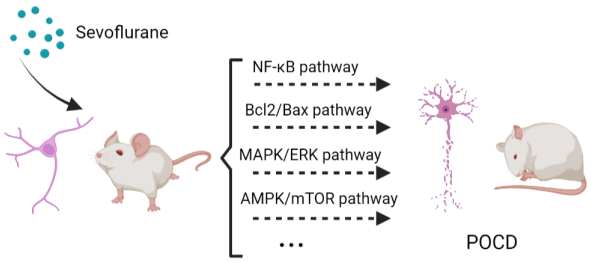

Figure 1: Mechanism of sevoflurane-induced POCD.
Note: Created with BioRender.com. AMPK: Adenosine 3'-monophosphate-activated protein kinase; ERK: extracellular signal-regulated kinase; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa-B; POCD: postoperative cognitive dysfunction.

3'-monophosphate-activated protein kinase/mammalian target of rapamycin pathway.[11] In a study related to ferroptotic cell death, Ge et al.[12] treated old mice with sevoflurane, and iron overload occurred in mouse brain tissue, resulting in oxidative stress and mitochondrial dysfunction, which in turn led to glucose metabolism disorders. At the same time, sevoflurane also inhibits oxygen uptake and glucose absorption. In this way, the cross-dysfunction of iron and glucose causes apoptosis of cortical and hippocampal neurons through the Bcl/Bax pathway.[12] Mind bomb-2 is also an important molecule involved in ferroptotic cell death, which significantly rises in mouse hippocampal tissues after treatment with sevoflurane. Knockdown of mind bomb-2 expression reduces neuronal death and ferroptotic cell death by the fact that lowering mind bomb-2 levels reduces binding to glutathione peroxidase 4, thereby reducing glutathione peroxidase 4 degradation and enhancing glutathione peroxidase 4 stability.[13] MicroRNAs also play an important role in the pathogenesis of sevoflurane-induced POCD, particularly in relation to the nuclear factor kappa-B (NF-κB) pathway. Zhao et al.[14] found that miR-124, which had the effect of preventing apoptosis and inflammatory response through the NF-κB signaling pathway, was inhibited in hippocampal neurons after the intervention of sevoflurane in mice. However, another microRNA has an exacerbating effect on the sevoflurane-induced inflammatory response. Wei et al.[15] found that miR-182-5p, which could be released by plasma exosomes, rose in the rat POCD model. Inhibition of plasma exosomes and miR-182-5p could relieve learning and memory impairment, reduce the level of inflammatory factors, upregulate neurotrophic factors, and inhibit NF-κB pathway.[15] In addition, studies have shown that mitochondrial autophagy is also involved in the pathogenesis of POCD, and sevoflurane treatment can inhibit mitochondrial oxidative respiratory chain and autophagy flow, which will cause changes in mitochondrial morphology and affect mitochondrial autophagy function, thereby causing cognition-related disorders.[16]

In a neonatal rat experiment, Zhu et al.[17] found that USP1-associated factor 1 inhibits the degradation of NOD-like receptor protein 3 through the ubiquitin-proteasome pathway, which can aggravate sevoflurane-induced POCD. Therefore, downregulation of USP1-associated factor 1 reduces cognitive impairment. Mao et al.[18] conducted a study using wild-type C57BL/6 mice and protrophic factor knockout mice treated with sevoflurane. The study revealed that the presence of multi-acting proteins can worsen sevoflurane-induced learning dysfunction. However, the knockout of multi-acting proteins and the use of multi-acting protein receptor inhibitors can help mitigate sevoflurane-induced neuroinflammation as well as cognitive and learning dysfunction. This suggests that pleiotrophin plays a detrimental role in the pathogenesis of POCD. However, in a separate study,[19] researchers aimed to create an aged rat model of POCD using sevoflurane anesthesia. They found that overexpression of C1q/tumor necrosis factor-related protein-3 had beneficial effects such as inhibiting cell apoptosis, reducing inflammation, minimizing brain tissue damage, and improving cognitive impairment. These effects were achieved by regulating two key pathways: adenosine triphosphate-activated protein kinase/SIRT1 and phosphoinositol 3-kinase/AKT.[19] Studies have shown that miR-140-3p can negatively target DNA methyltransferase-1 to reduce 5-hydroxytryptamine receptor 2A promoter methylation, which upregulates 5-hydroxytryptamine receptor 2A expression and activates the extracellular signal-regulated kinase/Nrf2 pathway, thereby improving neuronal survival and reducing sevoflurane-induced POCD.[20] In addition, long non-coding RNA Rian can also play a protective role in neurons by regulating the miR-143-3p/LIM domain kinase 1 axis.[21] It can be seen that the molecular regulation involved in sevoflurane-induced POCD is very extensive. Therefore, it is also important and urgent to select the appropriate target to manage POCD.

Management of sevoflurane-induced POCD: At present, there is no mature treatment for POCD, and the reported treatment methods are limited to animal experiments. We hope that the approach compiled will provide guidance and ideas for further treatment options. Peng et al.[22] found that cistanche, a Chinese herbal medicine, can play a role of antioxidant, anti-inflammatory, anti-apoptotic and anti-microglial activation by activating the PPAR signaling pathway, thereby alleviating sevoflurane-induced neuroinflammation and improving hippocampus-dependent memory loss. Chikusetsu saponin IVa, another active ingredient derived from traditional Chinese medicine, could alleviate neurological dysfunction by inhibiting the NOD-like receptor protein 3/caspase-1 pathway to reduce apoptosis and neuroinflammation.[23] Carnosol, extracted from rosemary, can also reduce sevoflurane-induced neuroinflammation, prevent microglial activation, and inhibit apoptosis, mainly by regulating the NF-κB pathway.[24] In the rat POCD model, Wei et al.[25] found that dexmedetomidine, a clinically commonly used sedative, promotes neuroactivity and reduces apoptosis by upregulating miR-129 levels that targets inhibition of Toll-like receptor 4 and NF-κB p65 phosphorylation. Glucagon-like peptide 1 analog liraglutide, a new type of hypoglycemic drug, has been found to improve spatial learning and memory ability of aged rats after sevoflurane anesthesia, and play an anti-apoptotic and anti-inflammatory effect in hippocampal tissue, thereby reducing cognitive dysfunction.[26] In a study investigating the effects of different doses of vitamin D on POCD, Zhang et al.[27] found that high levels of vitamin D can improve cognitive dysfunction after sevoflurane anesthesia by enhancing hippocampal cholinergic activity and reducing the expression of inflammatory factors. A study has also shown that sevoflurane can reduce cyclic adenosine monophosphate levels, block protein kinase A-cyclic adenosine monophosphate-response element binding protein, mitogen-activated protein kinase/extracellular signal-regulated kinase pathways, increase apoptosis and reactive oxygen species to induce cognitive impairment.[28] Thus, roflumilast, a phosphodiesterase 4 inhibitor, maintains normal levels of cyclic adenosine monophosphate as well as the activity of the above signaling pathways, thereby improving rat neurological function.[28] Necroptosis, which is related to calcium overload, also plays a role in the pathogenesis of POCD in aged rats. The use of necrostatin-1, an inhibitor of necroptosis, can improve neuroprotective effects of cognitive function by increasing BDNF pathway activity and inhibiting necroptosis-related pathways.[29] In addition, it has been reported that electro-acupuncture pretreatment can alleviate sevoflurane-induced cognitive dysfunction, and its mechanism mainly lies in inhibiting calcium overload and reducing mitochondrial damage and neuronal apoptosis of hippocampal neurons.[30] Similarly, atmospheric normobaric hyperoxia preconditioning can also reduce sevoflurane-induced apoptosis of hippocampal neurons, thereby improving POCD.[31] Intestinal dysbacteriosis can increase the permeability of the blood-brain barrier in aged mice after sevoflurane surgery, thus inducing POCD. Lactobacillus may reduce the blood-brain barrier permeability to protect neurological function.[32]

Conclusion: POCD induced by sevoflurane is clinically common, especially in elderly patients. Cognitive dysfunction will adversely affect the normal life of these patients. We have found that the pathogenesis of POCD lies mainly in neuroinflammation, apoptosis, and hippocampal dysfunction, but current treatments

are still very limited or limited to animal experiments. Thus, we hope that these experiments may provide some guidance and new ideas for clinical treatment and give helps to these patients.

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