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Anaesthesia and brain development: a review of propofol-induced neurotoxicity in pediatric populations

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Review

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Abstract

With the advancement of medical technology, there are increasing opportunities for new-borns, infants, and pregnant women to be exposed to general anaesthesia. Propofol is commonly used for the induction of anaesthesia, maintenance of general intravenous anaesthesia and sedation of intensive-care children. Many previous studies have found that propofol has organ-protective effects, but growing evidence suggests that propofol interferes with brain development, affecting learning and cognitive function. The purpose of this review is to summarize the latest progress in understanding the neurotoxicity of propofol. Evidence from case studies and clinical studies suggests that propofol has neurotoxicity on the developing brain. We classify the findings on propofol-induced neurotoxicity based on its damage mechanism. We end by summarizing the current protective strategies against propofol neurotoxicity. Fully understanding the neurotoxic mechanisms of propofol can help us use it at a reasonable dosage, reduce its side effects, and increase patient safety.

Introduction

With the continuous improvement of surgical and medical technology, the number of general anesthesia procedures for new-borns, young children and pregnant women is increasing. Studies have found that many anesthetics cause nerve damage and learning and memory impairment.[1–4] Therefore, more attention has been paid to the safety of anesthetics.

Propofol is commonly used in clinical anesthesia and postoperative intensive care because of such advantages as its rapid and stable onset, easy control of anesthesia depth, rapid recovery of patients, complete recovery of brain function, and low incidence of postoperative nausea and vomiting. The mechanism of propofol's anesthetic effect is that it acts on synapses to release gamma-aminobutyric acid (GABA) from the prominent anterior membrane and binds with the postsynaptic GABA-A receptor to enhance the transport activity of chloride ion channels, increasing chloride ion influx, neuronal hyperpolarization, and postsynaptic inhibition, which ultimately lead to a decrease in central excitability. In addition, propofol can block the N-methyl-D-aspartate glutamate receptor to produce anesthetic effects.[5] However, studies have found that the effect of propofol on neuronal hyperpolarization causes abnormal changes in immature neurons.[6]

The rapid development period of the human brain refers to the period from 3 months of embryo development to 2 ~ 3 years after birth. During this period, young children have normal physiological reflexes, such as the sucking reflex and holding reflex, and they can understand pictures and arithmetic approximately 2 years after birth.[7] In the period of rapid development, the blood–brain barrier is not yet fully developed, and synapses grow rapidly. The neurotransmitters produced have different effects than they do on the mature brain. At this time, the brain is very sensitive to changes in the internal or external environment, which is due to the large number of physiological and biochemical changes occurring in the brain during development from the immature to the mature state. Propofol easily passes through the blood–brain barrier and produces anesthetic effects in the brain. Therefore, the use of propofol during rapid development can affect the development of the brain.[8,9]

At present, in vivo and in vitro experiments have shown that propofol is neurotoxic to the developing brain, can cause damage to developing nerve cells, and can interfere with the learning and memory function of animals.[10–12] In case reports and clinical studies, it was found that children under propofol anesthesia experience neuromuscular damage, resulting in various changes, such as tendon hyperreflexia, muscle weakness, visual memory impairment, and cognitive impairment.[13] Due to the neurotoxicity of propofol found in both laboratory and clinical studies, the safety of propofol anesthesia in pregnant women and children has received widespread attention. Many signal pathways of propofol-induced brain injury during development have been explored, but the mechanism of propofol neurotoxicity is still unclear. In addition, there are relatively few prevention methods for propofol neurotoxicity, and its effect

is not obvious. The purpose of this review is to summarize the recent research on the neurotoxicity of propofol to the developing brain. We also summarize the protective measures against propofol neurotoxicity to support the development of new drugs and measures to reduce the damage of propofol to the developing brain.

The clinical study on neurotoxicity of propofol to developing brain

In 1992, a report was published on neurological sequelae after long-term infusion of propofol, which was also the first case in which propofol was thought to have neurotoxicity. The child was 4 years old and was hospitalized due to wheezing secondary to upper respiratory virus infection. After 4 days of continuous infusion of propofol in the ICU, the child had epileptic seizures and slight convulsions. The child could open his eyes but was weak and unresponsive. After stopping propofol for 7 days, the child developed excessive tendon reflex and ankle clonus, normal muscle tension and ataxia while walking. Another child, aged 2.5 years, was hospitalized with severe laryngotracheal bronchitis. The child was sedated with propofol at a speed of 100 mg/h. After continuous infusion for 44 h, the child had muscle weakness, slight convulsions of the hands and feet, and dance movement of the arms.[14] In 2009, three infants developed convulsions with similar clinical features 23–30 h after propofol infusion. During the follow-up period, the investigators found that these patients had progressive microcephaly (with normal head circumference at birth), and 2 of them had developmental impairment with cognitive and behavioral impairment, as well as bilateral symmetric white matter abnormalities on brain magnetic resonance imaging.[15] In 2014, Millar *et al.* selected 58 children aged 5–14 who needed daytime dental surgery and randomly used isoflurane or propofol anesthesia to compare the effects of the two anesthetics on postoperative cognitive impairment. In the propofol group, the initial blood target concentration was 5 μg/ml, and the end-expiratory concentration of isoflurane was maintained at 1 mac. The following symptoms occurred after operation: (1) The postoperative reaction time of both groups was prolonged, and the control of consciousness and movement was impaired but recovered 24 h later. (2) Visual memory impairment was found in the two groups after operation and after 24 h, and cognitive impairment was found after operation. (3) Delayed language recall disorder also appeared in the propofol group.[13] These cases and clinical trials show that propofol may affect the function of the developing brain and disrupt the nervous system. Therefore, in 2016, the US Food and Drug Administration issued a statement that exposure of children under the age of three or women in late pregnancy to anesthetics, including propofol, for more than 3 h or in repeated exposures may lead to brain developmental defects in the child.[16]

The mechanism of propofol on brain damage during development

The function of neurons determines the function of the central nervous system. Damaged neurons cause functional disorders of the central nervous system, and neurons in development are more vulnerable to the influence of the internal and external environment. It was found that the motor skill learning of adult mice was impaired by multiple intraperitoneal injections of propofol in new-born mice, accompanied by a decrease in the number of vertebral neurons and a weakening of the activity of the cortical motor area.[17] At present, research on propofol in the developing brain is mainly about the injury and death of neurons, and specific mechanistic research mainly involves the following aspects:

Mitochondrial damage pathway

Mitochondria are the main organelles for oxidative energy supply, which convert glucose into adenosine triphosphate (ATP) through oxidative phosphorylation. Studies have shown that when SH-SY5Y nerve cells were treated with 2% propofol for 48 h, the number of mitochondria decreased, the oxygen consumption of cells decreased, the respiratory rate decreased by 35%, the activity of cytochrome C decreased, and the release of ATP decreased. These phenomena indicate that propofol damages mitochondria and impairs mitochondrial function in mature neurons.[18] Propofol also affects neurons in the development stage. In 7-day-old SD rats injected with 100 mg/kg propofol, it was found by electron microscopy that the mitochondria of neurons were swollen, some mitochondrial inner membranes were broken, mitochondrial cristae were loose or even broken, matrix density was reduced, and ATP production was reduced.[19] Propofol not only damages the mitochondria of developing neurons but also induces mitochondrial deformation, vacuolation and swelling and reduces the mitochondrial membrane potential of neural stem cells, which ultimately leads to their proliferation, differentiation and apoptosis.[20] Mitochondrial damage is involved in propofol-induced developmental neurotoxicity and could be an important target for further studies of propofol-induced developmental neurotoxicity.

Oxidative stress pathway

The production and clearance of reactive oxygen species are dynamically balanced in the normal body. Once the balance is broken by endogenous or exogenous stimulation, a large amount of reactive oxygen species (ROS) will be produced, which cause oxidative stress. Oxidative stress leads to neutrophil inflammatory infiltration, increased protease secretion and the production of a large number of oxidative intermediates, which eventually damage cellular proteins, lipids and nucleic acids. Many neurological diseases and injuries are related to oxidative stress, such as Alzheimer's disease, Huntington's disease, Parkinson's disease and cerebral ischemia–reperfusion injury.[21–24] Some studies have found that anesthetics can cause an increase in ROS, mitochondrial damage and neuronal apoptosis.[25] Primary hippocampal neurons were isolated from neonatal SD rats and treated with 20 μM propofol for 6 h. ROS production by these cells increased, which promoted the production of the apoptotic proteins cleaved caspase3 and Bax and reduced the expression of the B-cell lymphoma-2 (Bcl-2) protein. TUNEL staining showed that the number of apoptotic neurons increased.[26] Both superoxide dismutase (SOD) and malondialdehyde (MDA) can be detected as indicators of oxidative stress. When oxidative stress occurs, the release of SOD, an oxygen free radical scavenging enzyme, decreases, causing lipid peroxidation and producing the harmful substance MDA. After exposing hippocampal neurons of neonatal rats to propofol, ROS and MDA increased and SOD decreased.[27] These results suggest that oxidative stress is involved in the process by which propofol damages developing neurons.

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Calcium overload process

Calcium ions (Ca^{2+}) are an important component of the human body and a significant second messenger in cells, which is critical in the central nervous system. The balance of calcium is very important to maintaining normal nervous system function.[28] An imbalance in calcium homeostasis can lead to neuronal damage. The endoplasmic reticulum is the main source of calcium ion release in neurons, maintaining the balance of Ca^{2+} within them through recovery and release. In the mitochondrial matrix, an appropriate amount of Ca^{2+} can regulate the process of oxidative phosphorylation, but excessive Ca^{2+} will hinder mitochondrial respiration and eventually lead to cell damage. Sevoflurane can cause an increase in Ca^{2+} in primary hippocampal neurons of rats and then cause apoptosis.[29] The same effect has been found for propofol. The primary neurons of E17 Wistar rats were exposed to the therapeutic dose of propofol, and the calcium concentration and cell survival rate were measured at 3, 7 and 13 days in vitro (DIV). The results showed that the concentration of Ca^{2+} and the number of apoptotic neurons treated with propofol increased on DIV 3 and 7, but not 13, under therapeutic concentrations of propofol in primary cultured neurons obtained from E17 Wistar rats.[30] In mouse embryonic fibroblasts, it was also found that propofol caused a large outflow of Ca^{2+} in the endoplasmic reticulum and thus cell death.[31] Therefore, calcium overload is closely related to the neurotoxicity of propofol. These findings may provide a new way to alleviate the developmental neurotoxicity caused by propofol by correcting the dysregulation of calcium concentration.

Inflammatory factors

The main feature of neuroinflammation is the overexpression of pro-inflammatory factors caused by glial cell activation or immune cell infiltration and the suppression of anti-inflammatory factor expression.[32] In the brain, glial cells are divided into microglia, astrocytes and oligodendrocytes. Microglia are the main neuro-immune cells and the first sensor of pathophysiological changes. They are very important for monitoring and defense, and trigger signaling cascades. When experiencing trauma or brain disease, microglia are stimulated and activated, polarized to become M1-activated microglia, and secrete proinflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, thereby stimulating the deterioration characteristic of neurological diseases.[33–35] Inflammatory factors are also important in the process of propofol-induced neurotoxicity. Wang *et al.* exposed Sprague–Dawley rats (SD rats) and PC12 cells to propofol. Propofol caused nerve cell damage in the brains of rats by increasing proinflammatory factors, including IL-1β, IL-6, IL-17, and IL-18, which was also found in vitro.[36] After neonatal rats were exposed to propofol, TNF-α expression levels were found to be elevated in the cerebrospinal fluid, hippocampus and prefrontal cortex, resulting in neuronal damage.[37] Propofol can produce inflammatory effects in the hippocampus of the developing brain by enhancing astrogliosis activation (as measured by GFAP level) and increasing the levels of neuronal nitric oxide synthase (nNOS) and the proinflammatory cytokines IL-6 and TNF-α.[38] The Fas ligand/Fas death receptor pathway, as an inflammatory mediator in central nervous system pathology, is also involved in the neurotoxicity of propofol. This pathway leads to the activation of Caspase-8 and Caspase-9 through the mediated exogenous and Bcl-2-dependent endogenous apoptosis pathways, respectively, to result in neurodevelopmental abnormalities.[39] The above results indicate that neuroinflammation may be involved in the neurotoxicity of propofol, providing meaningful insights for finding therapeutic targets in neuroinflammatory signaling cascades.

Noncoding RNA

In mammals, more than 80% of DNA is transcribed, but less than 2% of RNA is transcribed into proteins, and the rest are RNAs without coding ability. Among all human organs, the central nervous system has the highest content of noncoding RNA.[40] Noncoding RNAs play an important role in brain neurodevelopment and neurological diseases.[41] microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) have been found to be involved in the neurotoxicity process of propofol.[42,43]

MicroRNAs (miRNAs) are endogenous noncoding RNA molecules with a length of approximately 22 nucleotides that regulate cellular processes by inhibiting the translation of messenger RNAs.[44] MiRNAs have become a research hotspot on the neurotoxicity of anesthetics in recent years. So far, more than 40 miRNAs have been found to be involved in the neurotoxicity process of anesthetics.[45] The expression of miR-363-3p and miR-34a in SH-SY5Y cells was dysregulated after propofol treatment, resulting in a decrease in the cell survival rate.[46,47] Propofol can cause neuronal injury during brain development by causing an imbalance of miRNA expression.[10,27,48] Zhu *et al.* exposed hippocampal neurons of neonatal rats to 50 μM propofol for 6 h. PCR showed that after propofol treatment, the expression of miR-455-3p decreased and the expression of its target protein EphA4 increased, leading to a decrease in neuronal proliferation and an increase in apoptosis.[49]

Long noncoding RNAs (lncRNAs), with a length of more than 200 nucleotides, lack an open reading frame.[50] Studies have shown that lncRNAs participate in many biological processes, including neurodevelopment and neurological diseases.[51,52] Transcription of the lncRNA called HOX antisense RNA (HOTAIR) is involved in nervous system diseases and is related to sevoflurane-mediated brain dysfunction.[53,54] It was found that the miR-455-3p/NLRP1 axis regulated by HOTAIR was also involved in the neurotoxicity of propofol.[55] The lncRNA BNDF-AS can reverse the expression of brain-derived neurotrophic factor (BDNF). Xu *et al.* found that the expression of BDNF-AS decreased after propofol treatment in neurons, and reversing this BDNF-AS change reduced the apoptosis induced by propofol.[43] In addition, recent studies have found that neonatal animals with high levels of lncRNA LCRF are more vulnerable to nervous system damage caused by propofol.[56]

The effect of propofol on the fine structure and functional integrity of nerve cells

Most studies on the neurotoxicity of propofol focus on the apoptosis of nerve cells, but some experiments show that the amount of apoptosis caused by propofol accounts for only 1% - 2% of the neural cortex, while 50% of the synapses of hippocampal neurons are lost immediately after anesthesia exposure, and the number of synapses continue to decrease by 10% in the following three months.[57] The occurrence of cognition and consciousness depends on the neuronal circuitries formed between the synapses of nerve cells, and synapse creation coincides with the peak time of brain development. At this time, exposure to general anesthetics can cause serious and persistent ultrastructural abnormalities of the neuropil.[58] Xu *et al.* confirmed that propofol affects the formation of synapses during development through the mTOR pathway and affects cognitive function.[59] In the process of neural

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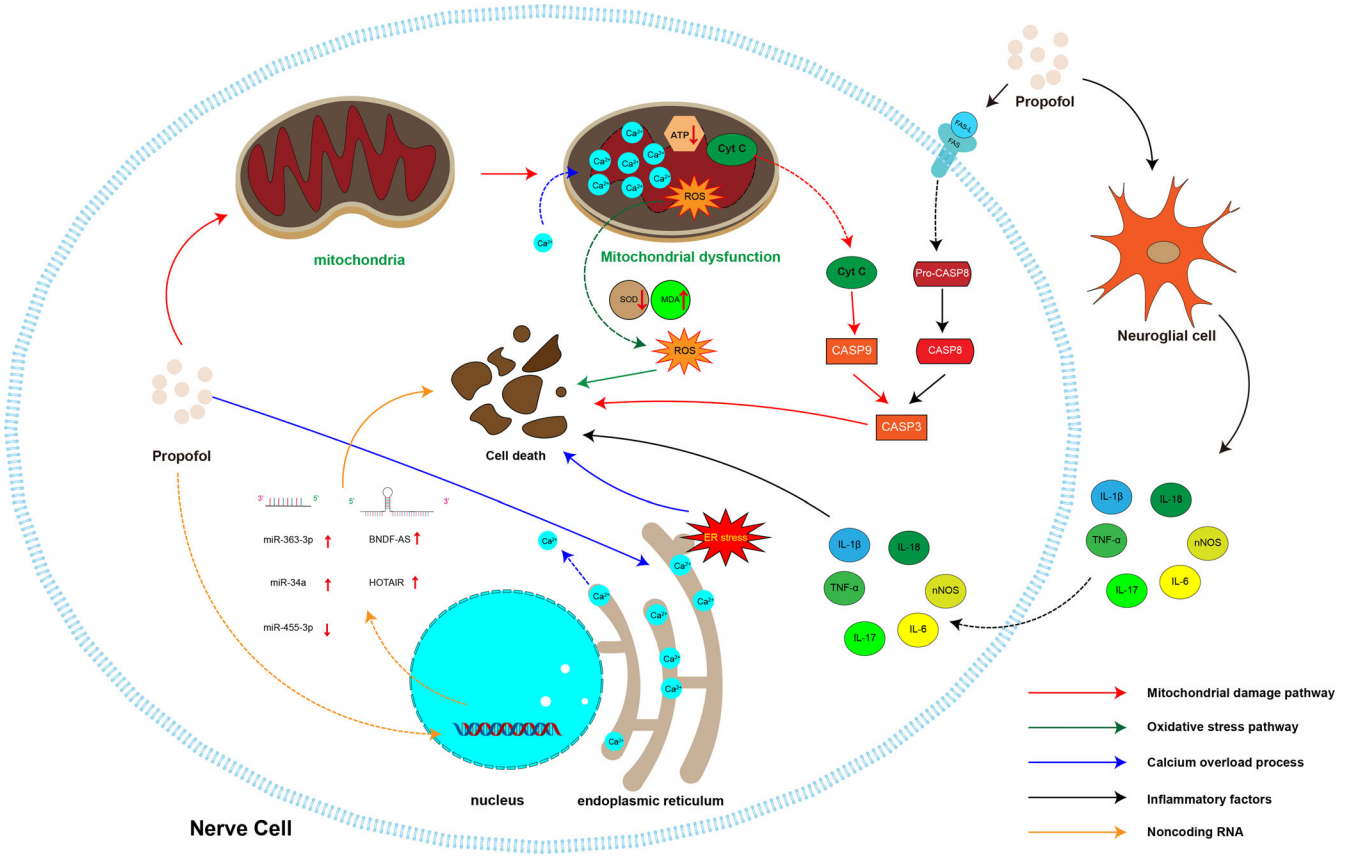

Figure 1. Schematic diagram of the processes by which propofol leads to neuronal death: through mitochondrial damage, oxidative stress, calcium overload, inflammatory factors and noncoding RNA pathways. Cyt C, cytochrome C; ATP, adenosine triphosphate; SOD, superoxide dismutase; MDA, malondialdehyde; ROS, reactive oxygen species; nNOS, neuronal nitric oxide synthase; TNF-α, tumor necrosis factor-α (TNF-α); IL-1β, interleukin-1β; fasL, fas ligand; Ca^{2+} calcium ion; CASP8, caspase-8.

development, the growth of neurons is determined by the morphology of their growth cones and axonal transport. Propofol collapses the growth cones of neurons in new-born mice by activating RhoA and affects the axonal transport of the neurotrophic factor brain-derived neurotrophic factor (BDNF), resulting in the impairment of cognitive function in mice.[60] Milanovic *et al.* found that exposure to propofol can cause damage to neural synaptic function and structure in the developing brain and can cause long-term cognitive function changes by interfering with brain plasticity changes.[61] The fine structure and functional integrity of nerve cells as affected by propofol are worth exploring in depth.

The effect of propofol on neural stem cells

Neural stem cells mainly exist in the subventricular area of the lateral ventricle of the brain and the subgranular area of the dentate gyrus of the hippocampus. Neural stem cells are key to neural development because they are numerous in the developing brain and have the ability to proliferate, differentiate and migrate.[62,63] Human induced pluripotent stem cell (hiPSC)-derived neural progenitor cells were exposed to 20 μM, 50 μM, 100 μM and 300 μM propofol for 6 or 24 h, and 20 μM or 50 μM propofol treatment for 6 h had no significant effect on neural progenitor cells, but when the concentration of propofol was 100 μM and 300 μM, the survival rate of neural progenitor cells decreased significantly. When treated with 50 μM propofol for 24 h, the neural progenitor cells also had a significantly decreased survival rate, which indicates that long-term or high concentration propofol exposure will induce apoptosis of neural progenitor cells.[64] Jiang *et al.* isolated neural stem cells from the rat embryonic hippocampus and exposed them to 112 μM propofol for 6 h, which weakened their proliferation and migration. In addition, neuronal marker β-Tubulin III protein expression decreased, indicating that propofol inhibits the neurogenesis of neural stem cells.[65] Propofol not only reduces the survival rate of neural stem cells and causes their apoptosis but also inhibits the proliferation of neural stem cells. A mechanistic study confirmed that propofol inhibits the proliferation of neural stem cells through the Ca2+-PKCα-ERK1/2 signal pathway.[66]

Neural stem cells can differentiate into a variety of neural cells, including neurons, astrocytes and oligodendrocytes. Studies have clarified that the excessive production of glial cells is the pathophysiological basis of many neurological diseases. The excessive production of astrocytes leads to synaptic dysfunction and abnormal cerebrovascular function during neural development, resulting in impaired learning and memory and behavioral disorders.[67,68] The use of propofol during brain development can make neural stem cells more inclined to differentiate into astrocytes, reduce the differentiation of neurons and hinder the neurogenesis of neural stem cells.[69,70] Cao *et al.* confirmed that when rat neural stem cells were cultured with 50 μM propofol for 6 h, the cell cycle stagnated, and astrocyte differentiation increased. The mechanism was that propofol interfered with neural stem cell differentiation through the microRNA-124-3p–specificity protein 1–cyclin-dependent kinase inhibitor 1B signaling pathway.[71] The

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above studies show that propofol induces apoptosis and impairs proliferation, differentiation and migration of neural stem cells to cause neurotoxicity, which may explain much of the propofol-induced learning and memory impairment in children. These results suggest that propofol should be used more cautiously in pregnant women and early new-borns.

Prevention of propofol neurotoxicity

At present, there are many studies on propofol in developmental brain injury, and the prevention of propofol-induced developmental brain neurotoxicity has also become an important issue. Dexmedetomidine, an α^2 adrenoceptor agonist, is commonly used in the clinic for sedation, analgesia and anti-anxiety.[72] Dexmedetomidine can attenuate propofol-induced apoptosis of hippocampal neurons and astrocytes and inhibit the proliferation of cells in the dentate gyrus through the glycogen synthesis kinase-3 β (GSK-3 β)–collapsin response mediator protein-2 ($Crmp^2$) signal pathway and the cyclin-dependent kinase 5 (Cdk5)–$Crmp^2$ signal pathway.[73] Another study found that exposure to propofol during childhood significantly increased the escape latency, hippocampal neuronal apoptosis, and synaptic ultrastructural changes in adult rats. However, the neurotoxicity of propofol was significantly reduced by pretreatment with dexmedetomidine: pretreatment of young rats with dexmedetomidine attenuated the potential induced long-term neurotoxicity in their developing hippocampus.[74] Clobenpropit, a histamine H3 receptor antagonist, can also reduce the damage done by propofol to hippocampal neurons in neonatal mice through the PI3K–Akt pathway.[75]

Neurotrophic factors mainly include nerve growth factor (NGF), BDNF, neurotrophic factor-3 (NT-3) and NT-4/5, which are similar in structure and belong to the same gene family. Neurotrophic factors can mediate the self-healing of the brain after traumatic injury or stroke and improve motor function.[76] Studies have shown that overexpression of the transcriptional inhibitor RE-1 silencing transcription factor can reduce the damage caused by propofol to the mouse neuronal HT-22 cell line by upregulating BDNF production.[77] Li *et al.* showed that 25 ng/ml NGF can improve the survival rate of neurons by reducing the production of the apoptotic protein Bax caused by propofol in developing hippocampal neurons.[78]

Xenon is a rare inert gas with anesthetic effects that can reduce neuronal damage.[79] One study found that when xenon and propofol were administered at the same time, xenon reduced the damage of propofol to neural stem cells, reduced the differentiation of astrocytes, and effectively blocked the reduction of neuronal differentiation caused by propofol.[80] So far, there are many studies on protective measures against propofol neurotoxicity, but their clinical efficacy and safety are still unknown. Further research is needed on propofol-protective measures.

Conclusion

In conclusion, both cellular and animal experiments have proven the neurotoxicity of propofol, especially in the critical period of brain development. These studies tell us that children need to be more cautiously treated with propofol. This review describes the neurotoxic mechanisms of propofol, which include mitochondrial damage, activation of the oxidative stress pathway, calcium overload, release of inflammatory factors, interference with noncoding RNA expression and changes in the microstructure of nerve cells, and summarizes the current protective measures against propofol neurotoxicity (Fig. 1). We found that the neurotoxicity of propofol needs further exploration. First, due to ethical requirements, trials cannot be conducted directly on children, and there is no evidence to prove the clinical relevance of these cell models and animal models, so these studies have been limited. In addition, because each patient has different tolerance to propofol, whether patients will have neurotoxicity and clinical symptoms of neurotoxicity are inconsistent at the same dose. It is difficult to observe whether propofol causes developmental brain injury. Finally, in clinical anesthesia, propofol is not used alone, but in combination with other drugs, and we cannot determine whether developmental brain injury is caused only by propofol.

There are many noteworthy shortcomings of the studies that have been done so far, but these limitations provide guidance for our future research. First, although we cannot directly conduct experiments in children or pregnant women, human embryonic stem cells are pluripotent stem cell lines derived from the internal cell clusters of early embryos, theoretically capable of differentiating into any type of neural cell in the brain. We can simulate the development of the brain by regulating the differentiation of embryonic stem cells, serving as a bridge between laboratory and clinical research. Second, with the advancement of medical imaging, it has been found that nerve activation is accompanied by changes in haemodynamics and oxidative metabolism, which can be observed by blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI). In the developing brain, the neurotoxicity of propofol is accompanied by a decrease in the functional connectivity of nerve cells, which leads to the weakening of signal transmission. We can analyze the changes in brain information flow through fMRI technology to see whether nerve cell function is abnormal and thereby observe the neurotoxicity of propofol to the developing brain. Finally, in future research, we should establish animal models to compare the neurocognitive development of propofol in combination with other anesthetics and propofol alone and explore whether the combination of anesthetics reduces or exacerbates the neurotoxicity of propofol.

The contribution of our review is to clarify that the neurotoxicity of propofol is due to various pathological effects. By gaining a more comprehensive understanding of the neurotoxic effects of propofol, we will have the ability to better apply it in clinical practice and increase the safety of pediatric anesthesia.

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References

1. Zhang W, Liu Q, Ma C, *et al.* Propofol induces the apoptosis of neural stem cells via microRNA-9-5p / chemokine CXC receptor 4 signaling pathway. *Bioengineered.* 2022; 13(1), 1062–1072.
2. Xintong Z, Jinghua Z, Tian C, Qi W, Wenhan L, Li G. Ketamine exerts neurotoxic effects on the offspring of pregnant rats via the Wnt/β-catenin pathway. *Environ Sci Pollut R Int.* 2020; 27(1), 305–314.

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3. Zhang W, Chen Y, Qin J, *et al.* Prolonged sevoflurane exposure causes abnormal synapse development and dysregulates beta-neurexin and neuroligins in the hippocampus in neonatal rats. *J Affect Disorders*. 2022; 312, 22–29.
4. Zuo C, Ma J, Pan Y, *et al.* Isoflurane and sevoflurane induce cognitive impairment in neonatal rats by inhibiting neural stem cell development through microglial activation, neuroinflammation, and suppression of VEGFR2 signaling pathway. *Neurotox Res*. 2022; 40(3), 775–790.
5. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature*. 1994; 367(6464), 607–614.
6. Tagawa T, Sakuraba S, Mizoguchi A. In reply: is propofol more neurotoxic in the developing brain? *J Anesth*. 2015; 29(2), 314–314.
7. Jiang W, Duong T, de Lanerolle N. The neuropathology of hyperthermic seizures in the rat. *Epilepsia*. 1999; 40(1), 5–19.
8. Jevtovictodorovic V, Hartman RE, Izumi Y, *et al.* Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci*. 2003; 23(3), 876–882.
9. Olney JW, Ikonomidou C, Mosinger JL, Frierdich G. MK-801 prevents hypobaric-ischemic neuronal degeneration in infant rat brain. *J Neurosci*. 1989; 9(5), 1701–1704.
10. Zhang Z, Xu Y, Chi S, Cui L. MicroRNA-582-5p reduces propofol-induced apoptosis in developing neurons by targeting ROCK1. *Curr Neurovasc Res*. 2020; 17(2), 140–146.
11. Huang J, Jing S, Chen X, *et al.* Propofol administration during early postnatal life suppresses hippocampal neurogenesis. *Mol Neurobiol*. 2016; 53(2), 1031–1044.
12. Xiong M, Li J, Alhashem HM, Tilak V, Bekker A. Propofol exposure in pregnant rats induces neurotoxicity and persistent learning deficit in the offspring. *Brain Sci*. 2014; 4(2), 356–375.
13. Millar K, Bowman AW, Burns D, *et al.* Children's cognitive recovery after day-case general anesthesia: a randomized trial of propofol or isoflurane for dental procedures. *Pediatr Anesth*. 2014; 24(2), 201–207.
14. Lanigan C, *et al.* M. Neurological sequelae in children after prolonged propofol infusion. *Anaesthesia*. 1992; 47(9), 810–1.
15. Meyer P, Langlois C, So?Te S, *et al.* Unexpected neurological sequelae following propofol anesthesia in infants: three case reports. *Brain Dev-JPN*. 2010; 32(10), 872–878.
16. Olutoye O, Baker B, Belfort M, Olutoye O. Food and drug administration warning on anesthesia and brain development: implications for obstetric and fetal surgery. *Am J Obstet Gynecol*. 2018; 218(1), 98–102.
17. Zhou H, Xie Z, Brambrink AM, Yang G. Behavioural impairments after exposure of neonatal mice to propofol are accompanied by reductions in neuronal activity in cortical circuitry. *Brit J Anaesth*. 2021; 126(6), 1141–1156.
18. Qin J, Li Y, Wang K. Propofol induces impairment of mitochondrial biogenesis through inhibiting the expression of peroxisome proliferator-activated receptor-gamma coactivator-1alpha. *J Cell Biochem*. 2019; 120(10), 18288–18297.
19. Xiao F, Lv J, Liang YB, *et al.* The expression of glucose transporters and mitochondrial division and fusion proteins in rats exposed to hypoxic preconditioning to attenuate propofol neurotoxicity. *Int J Neurosci*. 2020; 130(2), 161–169.
20. Liang C, Sun M, Zhong J, Miao C, Han X. The role of Pink1-mediated mitochondrial pathway in propofol-induced developmental neurotoxicity. *Neurochem Res*. 2021; 7(9), 1–12.
21. Liu X, Shirley etal. REST and stress resistance in ageing and Alzheimer's disease. *Nature*. 2016; 507, 448.
22. Crotty GF, Ascherio A, Schwarzschild MA. Targeting urate to reduce oxidative stress in Parkinson disease. *Experiment Neurol*. 2017; 298, 210–224.
23. Ma AS, Reverter-Branchat G, Tamarit J, Ferrer I, Ros J, abiscol EC. Proteomic and oxidative stress analysis in human brain samples of Huntington disease. *Free Radical Bio Med*. 2008; 45(5), 667–678.
24. Araceli DR, Patricia VA, Antonio MN, *et al.* Metallothionein-II inhibits lipid peroxidation and improves functional recovery after transient brain ischemia and reperfusion in rats. *Oxidative Med Cell Longev*. 2014; 2014, 436429.
25. Zhang Y, Dong Y, Wu X, *et al.* The mitochondrial pathway of anesthetic isoflurane-induced apoptosis. *J Biol Chem*. 2010; 285(6), 4025–4037.
26. Liang C, Du F, Cang J, Xue Z. Pink1 attenuates propofol-induced apoptosis and oxidative stress in developing neurons. *J Anesth*. 2018; 32(1), 62–69.
27. Tang F, Zhao L, Yu Q, *et al.* Upregulation of miR-215 attenuates propofol-induced apoptosis and oxidative stress in developing neurons by targeting LATS2. *Mol Med*. 2020; 26(1), 38.
28. Wei H, Xie Z. Anesthesia, calcium homeostasis and Alzheimer's disease. *Curr Alzheimer Res*. 2009; 6(1), 30–35.
29. Zhu X, Yao Y, Guo M, Li J, Lin D. Sevoflurane increases intracellular calcium to induce mitochondrial injury and neuroapoptosis. *Toxicol Lett*. 2021; 336, 11–20.
30. Satoshi S, Tomotaka M, Jun K. Intravenous anesthetic-induced calcium dysregulation and neurotoxic shift with age during development in primary cultured neurons. *NeuroToxicology*. 2018; 69, S0161813X1830322X–.
31. Xu ZD, Wang Y, Liang G, *et al.* Propofol affects mouse embryonic fibroblast survival and proliferation in vitro via ATG5- and calcium-dependent regulation of autophagy. *Acta Pharmacol Sin*. 2020; 41(3), 303–310.
32. Peng X, Li C, Yu W, Liu S, Qi S. Propofol attenuates hypoxia-induced inflammation in BV2 microglia by inhibiting oxidative stress and NF- κ B/ Hif-1 α signaling. *Biomed Res Int*. 2020; 2020, 1–11.
33. Liu J, Li Y, Xia X, *et al.* Propofol reduces microglia activation and neurotoxicity through inhibition of extracellular vesicle release. *J Neuroimmunol*. 2019; 333, 476962.
34. Jiang P, Jiang Q, Yan Y, Hou Z, Luo D. Propofol ameliorates neuropathic pain and neuroinflammation through PPAR γ up-regulation to block Wnt/ β-catenin pathway. *Neurol Res*. 2020; 43(1), 1–7.
35. Wang S, Fu X, Duan R, *et al.* TREML2The Alzheimer's disease-associated gene modulates inflammation by regulating microglia polarization and NLRP3 inflammasome activation. *Neural Regen Res*. 2023; 18(2), 434–438.
36. Wang M, Suo L, Yang S, Zhang W. CircRNA 001372 reduces inflammation in propofol-induced neuroinflammation and neural apoptosis through PIK3CA/Akt/NF-κB by miRNA-148b-3p. *J Invest Surg*. 2021; 34(11), 1167–1177.
37. Chen B, Deng X, Wang B, Liu H. Etanercept, an inhibitor of TNF-a, prevents propofol-induced neurotoxicity in the developing brain. *Int J Dev Neurosci*. 2016; 55(1), 91–100.
38. Yang Y, Yi J, Pan M, Hu B, Duan H. Edaravone alleviated propofol-induced neural injury in developing rats by BDNF/TrkB pathway. *J Cell Mol Med*. 2021; 25(11), 4974–4987.
39. Milanovic D, Pesic V, Loncarevic-Vasiljkovic N, *et al.* The fas ligand/Fas death receptor pathways contribute to propofol-induced apoptosis and neuroinflammation in the brain of neonatal rats. *Neurotox Res*. 2016; 30(3), 434–452.
40. Mehta SL, Chokkalla AK, Vemuganti R. Noncoding RNA crosstalk in brain health and diseases. *Neurochem Int*. 2021; 149, 105139.
41. Ang CE, Trevino AE, Chang HY. Diverse lncRNA mechanisms in brain development and disease. *Curr Opin Genet Dev*. 2020; 65, 42–46.
42. Xiu M, Luan H, Gu X, Liu C, Xu D. MicroRNA-17-5p protects against propofol anesthesia-induced neurotoxicity and autophagy impairment via targeting BCL2L11. *Comput Math Method M*. 2022; 2022, 6018037–11.
43. Xu Y, Luo Y, Cao. J, etal, lncRNA BDNF-AS attenuates propofol-induced apoptosis in HT22 cells by modulating the BDNF/TrkB pathway. *Mol Neurobiol*. 2022; 59(6), 3504–3511.
44. He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet*. 2004; 5(7), 522–531.
45. Bahmad HF, Darwish B, Dargham KB, Machmouchi R, Chamaa F. Role of MicroRNAs in anesthesia-induced neurotoxicity in animal models and neuronal cultures: a systematic review. *Neurotox Res*. 2020; 37(3), 479–490.
46. Li GF, Li ZB, Zhuang SJ, Li GC. Inhibition of microRNA-34a protects against propofol anesthesia-induced neurotoxicity and cognitive dysfunction via the MAPK/ERK signaling pathway. *Neurosci Lett*. 2018; 675, 152–159.
47. Yao Y, Zhang J. Propofol induces oxidative stress and apoptosis in vitro via regulating miR-363-3p/CREB signalling axis. *Cell Biochem Funct*. 2020; 38(8), 1119–1128.

https://doi.org/10.1017/S2040174424000059 Published online by Cambridge University Press

48. Mao Z, Wang W, Gong H, Wu Y, Zhang Y, Wang X. Upregulation of miR-496 rescues propofol-induced neurotoxicity by targeting rho associated coiled-coil containing protein kinase 2 (ROCK2) in prefrontal cortical neurons. *Curr Neurovasc Res*. 2020; 17(2), 188–195.
49. Zhu X, Li H, Tian M, Zhou S, He Y, Zhou M. miR-455-3p alleviates propofol-induced neurotoxicity by reducing EphA4 expression in developing neurons. *Biomarkers*. 2020; 25(8), 685–692.
50. Jxcab C, Ypw D, Xin Z, Gxla B, Kuang Z, Czda B. lncRNA Mtss1 promotes inflammatory responses and secondary brain injury after intracerebral hemorrhage by targeting miR-709 in mice. *Brain Res Bull*. 2020; 162, 20–29.
51. Chen J, Wang Y, Zhang X, Li G, Zheng K, Duan C. lncRNA Mtss1 promotes inflammatory responses and secondary brain injury after intracerebral hemorrhage by targeting miR-709 in mice. *Brain Res Bull*. 2020; 162, 20–29.
52. Aliperti V, Skonieczna J, Cerase A. Long non-coding RNA (lncRNA) roles in cell biology, neurodevelopment and neurological disorders. *Non-coding RNA*. 2021; 7(2), 36.
53. Khani-Habibabadi F, Zare L, Sahraian M, Javan M, Behmanesh M. Hotair and Malat1 long noncoding RNAs regulate bdnf expression and oligodendrocyte precursor cell differentiation. *Mol Neurobiol*. 2022; 59(7), 4209–4222.
54. Wang J-Y, Feng Y, Fu Y-H, Liu G-L. Effect of sevoflurane anesthesia on brain is mediated by lncRNA HOTAIR. *J Mol Neurosci*. 2018; 64(3), 346–351.
55. Gong H, Wan X, Zhang Y, Liang S. Downregulation of HOTAIR reduces neuronal pyroptosis by targeting miR-455-3p/NLRP1 axis in propofol-treated neurons in vitro. *Neurochem Res*. 2021; 46(5), 1141–1150.
56. Zeng Z, Yao J, Zhong J, *et al.* The role of the lncRNA-LRCF in propofol-induced oligodendrocyte damage in neonatal mouse. *Neurochem Res*. 2021; 46(4), 778–791.
57. Briner A, Nikonenko I, De Roo M, Dayer A, Muller D, Vutskits L. Developmental stage-dependent persistent impact of propofol anesthesia on dendritic spines in the rat medial prefrontal cortex. *Anesthesiology*. 2011; 115(2), 282–293.
58. Jevtovic-Todorovic V. Developmental synaptogenesis and general anesthesia: a kiss of death? *Curr Pharm Design*. 2012; 18(38), 6225–6231.
59. Xu J, Mathena RP, Xu M, *et al.* Early developmental exposure to general anesthetic agents in primary neuron culture disrupts synapse formation via actions on the mTOR pathway. *Int J Mol Sci*. 2018; 19(8), 2183.
60. Pearn ML, Schilling JM, Jian M, *et al.* Inhibition of RhoA reduces propofol-mediated growth cone collapse, axonal transport impairment, loss of synaptic connectivity, and behavioural deficits. *Br J Anaesth*. 2018; 120(4), 745–760.
61. Milanovic D, Pesic V, Loncarevic-Vasiljkovic N, *et al.* Neonatal propofol anesthesia changes expression of synaptic plasticity proteins and increases stereotypic and anxyolitic behavior in adult rats. *Neurotox Res*. 2017; 32(2), 247–263.
62. Dennis C, Suh L, Rodriguez M, Kril J, Sutherland G. Human adult neurogenesis across the ages: an immunohistochemical study. *Neuropath Appl Neuro*. 2016; 42(7), 621–638.
63. Piermartiri T, Dos Santos B, Barros-Aragão F, Prediger R, Tasca C. Guanosine promotes proliferation in neural stem cells from hippocampus and neurogenesis in adult mice. *Mol Neurobiol*. 2020; 57(9), 3814–3826.
64. Long B, Li S, Xue H, Sun L, Kim DH, Ying L. Effects of propofol treatment in neural progenitors derived from human-induced pluripotent stem cells. *Neural Plast*. 2017; 2017, 9182748–12.
65. Jiang Q, Wang Y, Shi X. Propofol inhibits neurogenesis of rat neural stem cells by upregulating MicroRNA-141-3p. *Stem Cells Dev*. 2017; 26(3), 189–196.
66. Hu Q, Huang L, Zhao C, *et al.* Ca-PKCα-ERK1/2 signaling pathway is involved in the suppressive effect of propofol on proliferation of neural stem cells from the neonatal rat hippocampus. *Brain Res Bull*. 2019; 149, 148–155.
67. Bailey A, Hou H, Song M, *et al.* GFAP expression and social deficits in transgenic mice overexpressing human sAPPα. *Glia*. 2013; 61(9), 1556–1569.
68. Allen J, Oberdorster G, Morris-Schaffer K, *et al.* Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. *Neurotoxicology*. 2017; 59, 140–154.
69. Liang C, Du F, Wang J, Cang J, Xue Z. Propofol regulates neural stem cell proliferation and differentiation via Calmodulin-dependent protein kinase II/AMPK/ATF5 signaling axis. *Anesth Analg*. 2019; 129(2), 608–617.
70. Liu F, Liu S, Patterson T, *et al.* Protective effects of xenon on propofol-induced neurotoxicity in human neural stem cell-derived models. *Mol Neurobiol*. 2020; 57(1), 200–207.
71. Cao J, Li Y, Zeng F, Liu X, Qin Z. Propofol exposure disturbs the differentiation of rodent neural stem cells via an miR-124-3p/Sp1/Cdkn1b axis. *Front Cell Dev Biol*. 2020; 8, 838.
72. Mahmoud M, Mason K. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. *Brit J Anaesth*. 2015; 115(2), 171–182.
73. Li J, Guo M, Liu Y, *et al.* Both GSK-3β/CRMP2 and CDK5/CRMP2 pathways participate in the protection of dexmedetomidine against propofol-induced learning and memory impairment in neonatal rats. *Toxicol Sci*. 2019; 1(1), 1–210.
74. Xiao Y, Zhou L, Tu Y, *et al.* Dexmedetomidine attenuates the propofol-induced long-term neurotoxicity in the developing brain of rats by enhancing the PI3K/Akt signaling pathway. *Neuropsych Dis Treat*. 2018; 14, 2191–2206.
75. He W, Yuan Q, Zhou Q. Histamine H3 receptor antagonist clobenpropit protects propofol-induced apoptosis of hippocampal neurons through PI3K/AKT pathway. *Eur Rev Med Pharmaco*. 2018; 22(22), 8013–8020.
76. Song S, Kong X, Wang B, Sanchez-Ramos J. Recovery from traumatic brain injury following treatment with Δ9-tetrahydrocannabinol is associated with increased expression of granulocyte-colony stimulating factor and other neurotrophic factors. *Cannabis Cannabinoid Res*. 2022; 7(4), 415–423.
77. Liu C, Peng S, Li Q. RE-1 silencing transcription factor alleviates the growth-suppressive effects of propofol on mouse neuronal cells. *Neuroreport*. 2019; 30(15), 1025–1030.
78. Li X, Zhao Z, Huang L, Kang R, Liu X, Dong Z. The anti-apoptotic effect of nerve growth factor on propofol-induced neurotoxicity in hippocampal neurons is Rac1 dependent. *Pharmazie*. 2018; 73(12), 706–710.
79. Maze M, Laitio T. Neuroprotective properties of xenon. *Mol Neurobiol*. 2020; 57(1), 118–124.
80. Ma D, Williamson P, Januszewski A, *et al.* Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. *Anesthesiology*. 2007; 106(4), 746–753.

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