

Review

Research Progress of Hippocampal Dopamine System Changes in Perioperative Neurocognitive Disorders

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Abstract

Perioperative neurocognitive disorders (PND) are a cognitive impairment that occurs after anesthesia, especially in elderly patients and significantly affects their quality of life. The hippocampus, as a critical region for cognitive function and an important location in PND research, has recently attracted increasing attention. However, in the hippocampus the impact of anesthesia and its underlying mechanisms remain unclear. This review focuses on investigation of the effects of anesthesia on the hippocampal dopamine (DA) system and explores its potential association with PND. Through comprehensive review of existing studies, it was found that anesthesia affects the hippocampus through various pathways involved in metabolism, synaptic plasticity and oxygenation. Anesthesia may also influence the DA neurotransmitter system in the brain which plays a role in emotions, rewards, learning and memory functions. Specifically, anesthesia may participate in the pathogenesis of PND by affecting the DA system within the hippocampus. Future studies should explore the molecular mechanisms of these effects through techniques such as neuroimaging to study real-time effects to improve animal models to better simulate clinical observations. For clinical application, it is recommended that physicians exercise caution when selecting and managing anesthetic drugs by adopting comprehensive cognitive assessment methods to reduce post-anesthesia cognitive risk. Overall, this review provides a better understanding of the relationship between the hippocampal DA system and perioperative neurocognitive function and provides valuable guidance for prevention and treatment strategies for PND.

Keywords: perioperative neurocognitive disorders; hippocampus; dopamine; anesthesia; sevoflurane; isoflurane

1. Introduction

Perioperative neurocognitive disorders (PND) refer to a new cognitive disorder after anesthesia, involving one or more cognitive domains such as orientation, memory, calculation, attention, language, executive function, reasoning and visuospatial function [1]. The incidence of PND in elderly patients aged ≥ 60 years has increased to ~12.0–23.8% [2]. It is a common complication after anesthesia and leads to prolonged hospital stay, increased complications, decreased independence and quality of life and even increased risk of long-term death [2]. In clinical practice, PND have become the main factor endangering the postoperative recovery of elderly patients and brings a significant burden to patients and their families [3].

The hippocampus has been widely recognized as the main brain area in the formation of cognitive function and it has become a focus of study in cognition-related impairment. Currently, increasing attention is being directed towards PND, with a growing research focus on the hippocampus in related research. As a common medical method, anesthesia is widely used in surgery and other medical procedures. Studies have found that the structure of the hippocampus is damaged after anesthesia, which leads

to cognitive dysfunction [4]. Currently, it is believed that the main cause of PND is neuroinflammatory reaction. In related experiments, the authors of this review have found that the use of anesthetic drugs leads to the activation of microglia and astrocytes in brain tissue, thus producing related inflammatory factors and causing the occurrence of PND [5]. In further studies, they have found that the anesthetic process mainly leads to the release of Interleukin-1 β (IL-1 β), Tumour Necrosis Factor alpha (TNF- α) and other related inflammatory factors from astrocytes and microglia in the hippocampus, resulting in PND [6,7].

Although the research on the relationship between PND and neuroinflammation is comprehensive, the authors have also found a close correlation between PND and neuronal inhibition. Isaeva *et al.* [8] have found that the use of inhaled anesthetics such as isoflurane inhibits neuronal activity in the CA3 region of the hippocampus. There is also a large body of research that has found that anesthesia not only affects the tissue structure of the hippocampus, but also its neurotransmitter release and reuptake [9–11]. Among recent studies, it has been observed that the neurotransmitter dopamine (DA), which is the primary focus here, plays a crucial role [12]. The release of DA is closely linked to



the reward mechanism, regulating positive reinforcement of behavior and motivation formation [13]. It plays a key role in motor control, sending synaptic signals to the caudate and putamen of the dorsal striatum via the substantia nigra pathway, helping to maintain coordinated and fluid movements [14]. Additionally, DA is also involved in the process of learning and memory. Therefore, the DA nervous system provides a key pathway for regulating mood, reward and motivation and may also have an impact on cognitive function during anesthesia. Consequently, this review concentrates on a pivotal and persuasive theme: the correlation between an impaired hippocampal DA system and perioperative neurocognitive impairment. Existing research and literature on the impact of anesthesia on the hippocampal DA system, is aimed at investigating its potential contribution to PND. This exploration underscores the significance of the hippocampus and DA in the realm of anesthesia and their role in cognitive dysfunction, thus aiming to advance understanding of the intricate relationship between anesthesia technology and brain function.

Currently, there are many types of anesthetic drugs used clinically, among which the inhalation anesthetic drugs, propofol and opioids are the main ones. For example, sevoflurane affects Ca^{2+} currents to reduce transmission at cholinergic synapses, thereby affecting mood and cognitive ability [15]; ketamine suppresses Long Term Potentiation (LTP) by acting on N-methyl-D-aspartate (NMDA) receptors [16]. There are also studies that show propofol interacts with the Brain-derived neurotrophic factor-tyrosine kinase B-cyclic-AMP response binding protein (BDNF-TrkB-CREB) signaling pathway through NMDA receptors, impairing the learning and memory function of rats, resulting in PND [17]. Additionally, Tian *et al.* [18] have found that opioids such as fentanyl alter synaptic plasticity in the hippocampus, thereby triggering PND.

2. The Effect of Anesthesia on the Hippocampus

As an intervention, anesthesia not only triggers an inflammatory response and the release of inflammatory factors affecting hippocampal function but also induces neuronal apoptosis and alters the hippocampal volume. Primarily, anesthesia may influence the metabolic activity of hippocampal tissue cells, causing shifts in energy metabolism. For instance, isoflurane, a commonly used inhaled anesthetic in clinical practice, has been demonstrated to impact the metabolomics of the hippocampus by elevating glutamate and lactate levels in this region [19]. Beyond direct metabolic impact, anesthesia also exerts an indirect influence on hippocampal metabolic processes through modulation of cellular gene expression, consequently influencing hippocampal function [20,21]. Experiments have shown that inhalation of sevoflurane causes oxidative stress, increases the apoptosis of hippocampal neurons and signifi-

cantly reduces the expression of BDNF, resulting in learning and memory disorders [22]. Peng *et al.* [23] discovered in mouse hippocampal neurons that sevoflurane alters mRNA expression levels by inhibiting the acetylcholine receptor (mAChR-M). Further, during prolonged anesthesia, anesthetics may impact learning and memory processes by inhibiting synaptic plasticity, synaptic transmission, and weakening neuronal activity [24–26]. Numerous experimental studies have confirmed that narcotic drugs partially influence nerve conduction function in the hippocampus by altering synapses before and after anesthesia [9–11]. For example, Khodaei *et al.* [26] found in animal experiments that sevoflurane anesthesia inhibited postsynaptic excitatory neuronal current amplitude. Anesthesia also affects the physiological state of the hippocampus by influencing brain oxygenation. In clinical anesthesia, anesthetics reduce brain tissue oxygen saturation, which impairs the health of brain cells and impairs their related functions [27]. Additionally, anesthesia can cause an inflammatory response in the body, which affects the function of the hippocampus. Firstly, the inflammatory response induced by anesthesia can be achieved by promoting the expression of inflammatory factors. Useinovic *et al.* [28] found that after sevoflurane anesthesia, expression of the Nucleotide-binding domain leucine-rich repeat protein-1 (*NLRP1*) and Nucleotide-binding domain leucine-rich repeat protein-3 (*NLRP3*) genes were stimulated in the hippocampus of mice and simultaneously up-regulated gene expression, resulting in a large production of inflammatory factors such as IL-1 β and IL-18. Similarly, Lin's team [29] used isoflurane for anesthesia-related experiments and verified that isoflurane stimulated the expression of TNF- α and IL-6 in the hippocampus of mice by Western blot and other detection methods. In the case of signal transduction pathways, anesthetic drugs can activate relevant signal pathways and cells to release a large number of cytokines to produce inflammatory responses, leading to hippocampal dysfunction and thus perioperative neurocognitive impairment [29]. For example, the nuclear factor kappa-B (NF- κ B) signaling pathway, which has attracted significant research attention, is enhanced by inhaled anesthetics such as sevoflurane and isoflurane, activating microglia in the hippocampus and releasing a large amount of NF- κ B, resulting in an inflammatory response in the hippocampus. Furthermore, such inflammatory factors inhibit the expression of the inhibitory pathway of inflammatory factors through a negative feedback regulation mechanism. Simultaneously, they activate the complement system, exacerbating the inflammatory response [30–33]. In terms of inflammatory factor damage, the hippocampal CA1 region is critical for cognition and overactivated microglia and neuroinflammation produces neurotoxic responses that lead to synaptic dysfunction, thus PND [34]. However, some studies have found that inflammatory factors produced after anesthesia do not cause significant functional changes in the hippocampus [35]. In addition to the

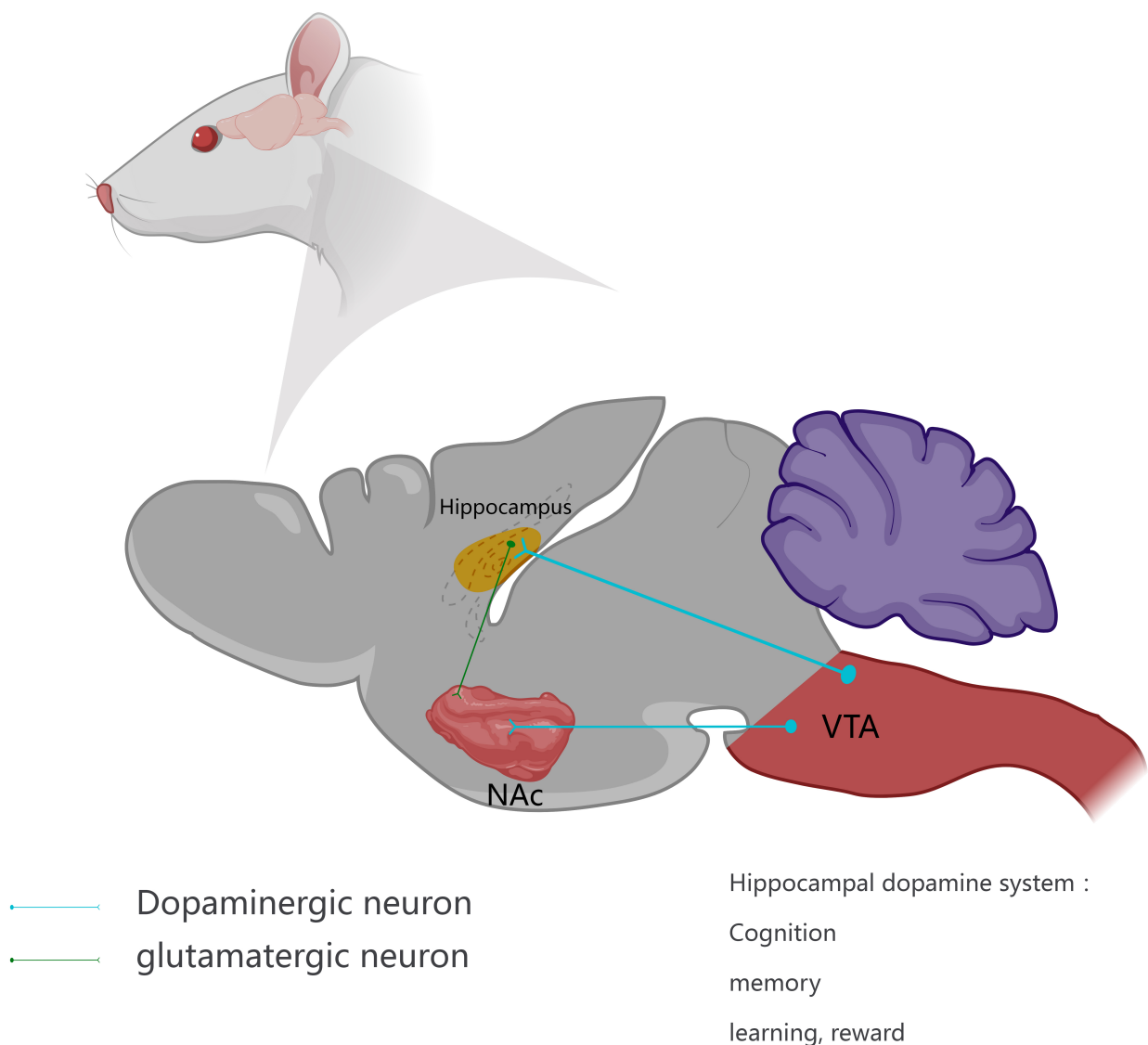


Fig. 1. The hippocampal dopamine system. The dopamine nervous system in the hippocampus mainly comes from the ventral tegmental area (VTA), and there are abundant nerves between the two. At the same time, DA-binding DA receptors (DAR) are also present in the nucleus accumbens (NAc) (ventral striatum), receiving innervation from DAergic pathways in the VTA and dense innervation from glutamatergic neurons in the hippocampus to release dopamine (DA) in response to reward-related stimuli. Thus, DAergic pathways control cognition, memory and learning, and reward. The diagram was meticulously crafted and designed in-house, using [Medpeer.cn](https://www.medpeer.cn).

above-mentioned influencing factors, other factors related to the effect of anesthesia on hippocampus in recent years are summarized (Table 1) [4,23,36–39].

3. Effects of Anesthesia on Dopamine

Anesthesia impairs concentration and executive ability. It manifests, for example, as decreased ability to assign and perform tasks, poor concentration and prolonged reaction time. Cognitive dysfunction caused by anesthesia can be divided into long and short-term cognitive impairment according to the duration of the effect. Karaman *et al.* [40] performed water maze experiments on rats anesthetized by sevoflurane and found it to cause obvious defects in

short-term spatial learning ability and short-term memory. Additionally, a prospective study of 46 patients undergoing general anesthesia in clinical studies showed that repeated exposure to general anesthesia can lead to short-term postoperative cognitive impairment [41]. In clinical trials, Linassi *et al.* [42] conducted Montreal Cognitive Assessment (MoCA) and Trail Making Test B (TMT-B) tests on 151 adult patients undergoing elective cardiac surgery; results showed that isoflurane caused long-term cognitive dysfunction. As a critical neurotransmitter in the central nervous system, DA plays a pivotal role in several key functions, including emotion, reward, motor control, learning and memory. The release of DA is closely linked to the reward mechanism and regulates the positive reinforcement

Table 1. Effects of anesthesia on the hippocampus.

Influencing factors	Subject	Anesthetic drugs	Medication dosage	Experimental methods	Conclusions	Data sources
Anesthesia temperature	Newborn mice	Propofol	25 mg/kg	Water maze test and Western blot	Hypothermia during anesthesia increases apoptosis rate of hippocampal neurons in neonatal rats	Liu, Wenbo <i>et al.</i> [37]
	Adult rat	Isoflurane	1.50%	The Y-maze test and Western blot experiment	Hypothermia during anesthesia induction leads to cognitive dysfunction in rats	Tan, Wenfei <i>et al.</i> [36]
Types of narcotic drugs	Adult rat	Isoflurane	1.20%	Barnes maze and fear conditioning test, Western blot	Isoflurane increases expression of inflammatory cytokines, which leads to cell damage in the hippocampus and cognitive dysfunction in rats	Lin, Daowei <i>et al.</i> [38]
	Adult rats	Sevoflurane	3%	Reverse Transcription-Polymerase Chain Reaction (RT-PCR)	Sevoflurane can affect the cognitive function of rats by inhibiting the expression of M1 muscarinic acetylcholine receptor (mAChR·M1) mRNA in the hippocampus	Peng, Sheng <i>et al.</i> [23]
	Young rats	Midazolam	10 mg/kg	Immunohistochemical method	Midazolam affects the expression of hippocampal neural stem cells, results in cognitive impairment in mice that can last into adulthood	Doi, Hiroyoshi <i>et al.</i> [39]
Prolonged continuous anesthesia	Adult rats	Propofol	90 mg/kg	Immunofluorescence staining	Prolonged use of propofol produced rapid but transient cognitive impairment	Kim, Jenny L <i>et al.</i> [4]
	Adult rats	Midazolam	8.0 mg/kg	Immunofluorescence staining	Prolonged use of midazolam produced cognitive changes that were delayed by several weeks	Kim, Jenny L <i>et al.</i> [4]
	Adult rats	Dexmedetomidine	0.1 mg/kg	Immunofluorescence staining	Prolonged administration of dexmedetomidine produced cognitive changes that were delayed for several weeks	Kim, Jenny L <i>et al.</i> [4]

and motivation formation of behaviors [13]. From Donald Hebb's first proposal of homo-synaptic plasticity, to Kandel and Tauc's proposal of the hetero-synaptic rule, to a large number of experiments demonstrating that plasticity is a homeostatic synaptic scaling, increasing evidence suggests that neural plasticity plays a crucial role in brain learning and memory abilities [14,43–46]. DA, as an important neurotransmitter, participates in motivation and stimulus-reward learning processes while also possessing the ability to regulate synaptic plasticity [47]. It also affects the synaptic efficacy of neuronal circuits, enabling them to produce LTP and Long Term Depression (LTD) [48]. Therefore, DA is an indispensable part of learning and memory processes.

Narcotic drugs affect the DA nervous system through a variety of pathways. First, some narcotic drugs may reduce the number of DA neurons. By comparing experimental data, Zhou *et al.* [49] confirmed that due to the neurotoxicity of anesthetic drugs, DA neurons undergo apoptosis during anesthesia, so the function of DA is affected. Second, anesthetics may also disrupt the release of neuronal electrical signals in the DA nervous system [49]. For example, cocaine inhibits the function of neurons by reducing the firing frequency and the number of bursts of neurons, while Bao *et al.* [50] found through clinical studies that sevoflurane reduces the electrical signal release of neurons and is also one of the reasons for inhibiting neurons [51]. He *et al.* [52] also confirmed that the use of anesthetics such as isoflurane to inhibit the discharge of D2-SPNs (spin-projecting neurons expressing d2 type DA receptors) and the broadband oscillation rhythm of the local field potential resulted in the inhibition of DA release. Additionally, anesthetics may also have an effect on DA transporters. Dopamine Transporter (DAT), which removes DA from the synaptic cleft, ensures proper DA function and coordinates spatial and temporal modulation of DA neurotransmission [53]. In related experiments, the use of anesthetics resulted in abnormal DAT function. As a result, the transmission and regulation of DA signaling are affected [53,54]. Taken together, these effects may have multiple impacts on cognitive function, including emotion, learning, memory and movement. Additionally, the effects of anesthesia and DA are also summarized in this review as well as the effects of anesthesia and DA. We provide a summary of recent correlation studies exploring the relationship between anesthesia and DA (Table 2) [51,55–57].

4. Effects of Anesthesia on the Hippocampal Dopamine System

First, the hippocampus receives dopaminergic innervation and DA plays a crucial role in hippocampal-dependent plasticity and related learning and memory processes [12]. In the mammalian central nervous system, the dopaminergic pathway between the ventral tegmental area of the midbrain and the hippocampus in mice is involved in the formation of cognition, memory and learning, reward

and other functions (Fig. 1). Second, a large number of experimental data confirm the existence of DA receptor subtypes in the hippocampus. In the dorsal hippocampus, D1 receptors were significantly expressed in the granule cells of the dentate gyrus. D2 receptors were mainly found in hilar mossy cells [58]. D1/D2 heterodimers were mainly distributed in the dorsal hippocampal hilar region. The ventral hippocampus plays a key role in addiction and other DA-dependent psychiatric disorders [59,60]. DA is a key regulator of memory function in the hippocampus and plays diverse roles in various aspects of memory and cognition [55–60]. The hippocampus is involved in the formation of spatial memory and innovative learning based on synaptic plasticity. In response to novel information and motivational events (rewards), signals at hippocampal CA1 synapses are mediated by DA [61]. Additionally, DA induces the protein synthesis required for late LTP within hippocampal neuron dendrites. In conclusion, the hippocampal DA system as a whole is mainly involved in the formation of cognitive function.

Anesthesia, as an intervention, may cause PND in patients by affecting the function of hippocampal DA system. As shown in Fig. 2, firstly, the neurons in the ventral CA1 of the hippocampus and the medial prefrontal cortex are regulated by the DA system. DA activates synaptic plasticity in hippocampal neurons after acting on D1-like receptors [62]. During anesthesia, anesthetic drugs may impede the function of DAT and obstruct its transport function, resulting in diminished recovery of DA neurotransmitters. Consequently, this reduction in DA neurotransmitter release may impair synaptic plasticity of ventral CA1 and medial prefrontal cortex neurons [43]. Therefore, the reason for PND due to anesthesia may be the inhibition of synaptic plasticity in the hippocampus by affecting the hippocampal DA system. Secondly, Hu *et al.* [57] found that the use of morphine and other narcotic drugs leads to the abnormal enhancement of NMDA receptor-dominated neurons in the hippocampus and the hippocampal DA D1 receptor plays an important role in the synaptic potentiation induced by morphine. Experiments have also found that DA binds to DA D1-like receptors after morphine treatment, which enhances NMDA current and stimulates cAMP-dependent signaling [57]. Therefore, it is hypothesized here that morphine and other anesthetics promote the release of electrical signals from DA neurons by acting on dopamine D1 receptors, thereby affecting cognitive functions such as emotion, reward, learning and memory. However, this effect may also be achieved through a variety of other mechanisms, including the regulation of neurotransmitters and changes in synaptic plasticity.

In conclusion, by investigating the relationship between the hippocampus, DA and perioperative neurocognitive dysfunction, as well as potential mechanisms, a more comprehensive understanding is gained of the potential impact of anesthesia on cognitive function. This, in turn, of-

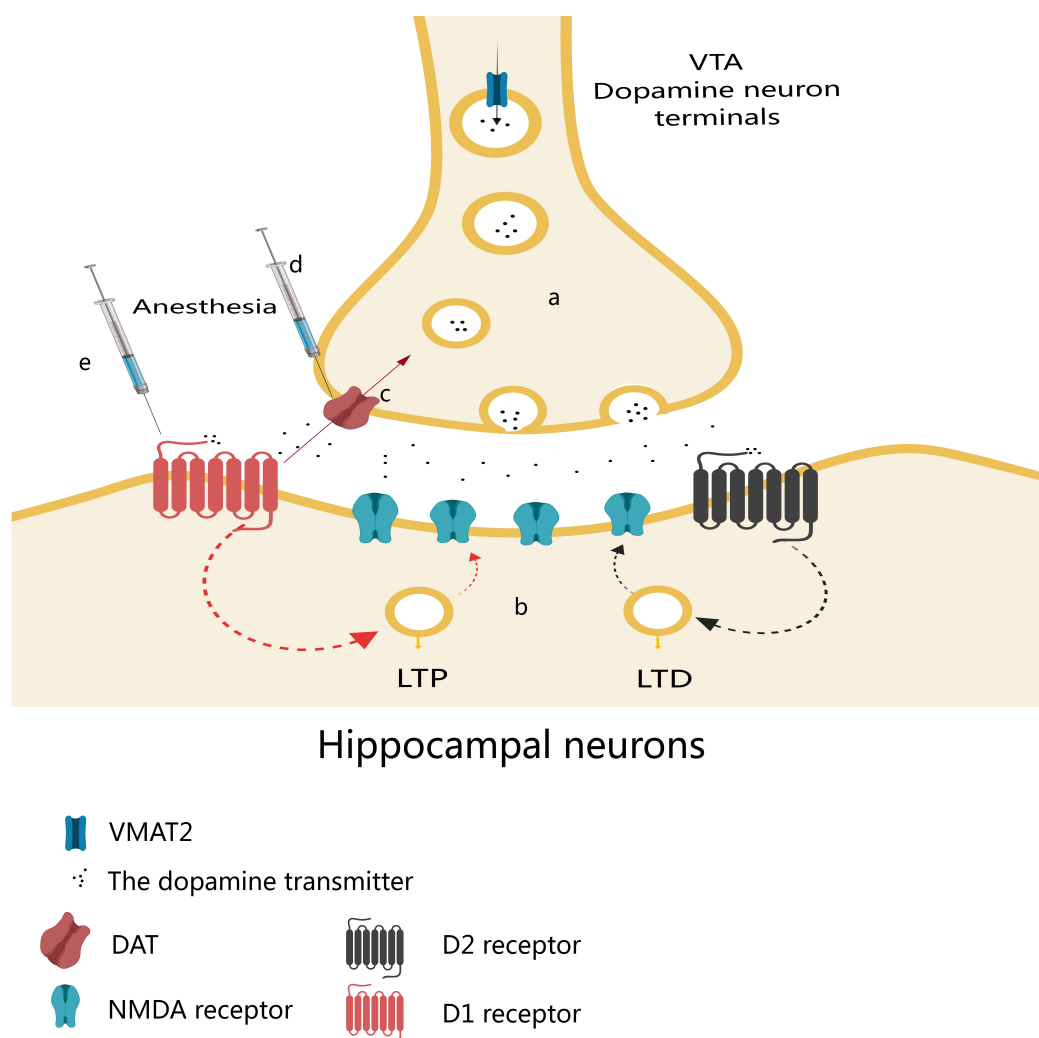


Fig. 2. Effects of narcotic drugs on the hippocampal dopamine system. (a) After dopamine (DA) synthesis, vesicular monoamine transporter 2 (VMAT2) transports DA from the cytoplasm to synaptic vesicles at the synaptic terminal, where it is finally released. (b) Neurons in the ventral hippocampal CA1 (vCA1) and medial prefrontal cortex (mPFC) are regulated by the DA system, which acts on D1-like and D2-like receptors to activate synaptic plasticity—long-term potentiation (LTP) and long-term depression (LTD). (c) DA is transported back to the presynaptic terminals of DA neurons by DA transporter (DAT). (d) During anesthesia, anesthetics may inhibit the function of DAT, block its transport function and reduce the recovery of DA neurotransmitters, thereby reducing their release, resulting in the impairment of synaptic plasticity in vCA1 and mPFC neurons. (e) Anesthetics can lead to abnormal synaptic potentiation of NMDA receptor-dominated neurons in the hippocampus and hippocampal DA D1 receptor (D1R) plays an important role in the synaptic potentiation. DA can bind to hippocampal D1R receptors, enhance NMDA currents, and stimulate cAMP-dependent signaling. VTA, ventral tegmental area; NMDA, N-methyl-D-aspartate; cAMP, cyclic adenosine monophosphate.

fers valuable insights for clinical practice and treatment. Future research should focus on elucidating the mechanisms of action of the effects of anesthesia on the hippocampus and DA system, thereby enhancing the understanding of the relationship between hippocampus, DA, and cognitive function.

5. Future Research Directions and Clinical Applications

First, the mechanism of anesthesia on the hippocampus and the DA system should be further studied along with

the specific signaling pathways, subpathways and related cellular and molecular changes. Second, with the help of advanced neuroimaging techniques, such as positron emission tomography, magnetic resonance imaging and electroencephalography, the real-time effects of anesthesia on the activity of hippocampal DA system are studied, so as to better understand its role in cognitive function [63,64]. Thirdly, better animal models should be designed to better simulate the anesthetic process in clinical practice, so as to study the relationship between hippocampus, DA and cognitive function in experiments.

Table 2. The effects of anesthesia and dopamine.

Pathways of influence	Subject	Anesthetic drugs	Medication dosage	Experimental Methods	Conclusions	Data sources
Neuronal firing	Adult rats	Cocaine	10 mg/kg	Multielectrode array with telemetry recording system	Cocaine increases the firing and burst rates of most DA neurons	Koulchitsky <i>et al.</i> [51]
Dopamine uptake and release	Adult rats	Isoflurane	1.50%	Quick scan cyclic voltammetry	Prolonged use of isoflurane alters DA release and uptake	Brodnik <i>et al.</i> [55]
Dopamine concentration	Middle-aged rats	Sevoflurane	3%	High Performance Liquid Chromatography (HPLC) with electrochemical detector (ECD-300, EICOM)	Isoflurane anesthesia significantly increases extracellular DA concentrations in middle-aged rats	Kimura-Kuroiwa <i>et al.</i> [56]
	Young rats	Sevoflurane	3%	HPLC with electrochemical detector (ECD-300, EICOM)	In young rats, isoflurane significantly enhances methamphetamine (MAPT)-induced DA	Kimura-Kuroiwa <i>et al.</i> [56]
Dopamine receptors	Adult rats	Morphine	3 mg/kg	<i>In vivo</i> electrophysiological recording techniques	Systemic injection of morphine can induce DA D1 receptor-mediated synaptic potentiation in hippocampal neurons	Hu <i>et al.</i> [57]

On the clinical side, the use of DA drugs can reduce PND and patients with dopaminergic system disorders, such as Parkinson's disease, have also received a lot of attention. Currently, the number of middle-aged and elderly patients is gradually increasing, as is the proportion of elderly patients with Parkinson's disease. Tinkhauser *et al.* [65] have found that during surgery, DA drugs can inhibit the excessive activity of basal ganglia β in patients with Parkinson's disease and reduce the probability of post-operative cognitive dysfunction. More importantly, Zech *et al.* [66] have found that withdrawal of DA drugs or use of DA antagonists during anesthesia could lead to malignant neuroleptic syndrome in patients with Parkinson's disease. Simultaneously, anesthetics also damage the hippocampal DA nervous system. Currently, it is known that a combination of multiple drugs during anesthesia reduces the adverse damage of a single drug. For example, it has been shown that the use of dexmedetomidine combined with sevoflurane reduces the inflammatory response produced by sevoflurane [67]. Similarly, propofol and dexamethasone have also been experimentally verified to reduce the inflammation produced by a single narcotic [68,69]. Therefore, it requires anesthesiologists to comprehensively consider how to choose anesthetic drugs during anesthesia and explore which DA drugs to choose during anesthesia and surgery. And after anesthesia, a more comprehensive cognitive function assessment method should be used to monitor a patient's learning, memory and attention functions. According to the assessment results, targeted cognitive function interventions should be developed to help patients recover normal cognitive function.

6. Conclusions

This review examines the relationship between the hippocampal DA system and perioperative neurocognitive function, with the aim of understanding how the two interact and elucidating possible mechanisms that contribute to PND. Here, it is believed that the hippocampus plays an important role in cognitive functions such as learning, memory and spatial navigation and many types of neurotransmitters in the hippocampus are associated with PND. By summarizing the previous literature, it is concluded that DA neurotransmitters are closely related to emotion, reward and learning. Therefore, special attention should be paid to the hippocampal DA system. Physiological and metabolic effects of anesthesia on the hippocampus and DA system are discussed, along with their potential impact on synaptic plasticity and neurotransmitter regulation. The mechanisms through which anesthesia induces an inflammatory response are summarized. The review demonstrates how anesthesia can influence the hippocampus, highlighting the potential effects of anesthesia drugs on cognitive function by affecting the hippocampus and DA system. Finally, a direction for future research is highlighted, including an in-depth study of molecular mechanisms, application of neu-

roimaging techniques and improvement of animal models; it is suggested that the selection and administration of anesthetic drugs should be optimized, cognitive function assessed and interventions developed to reduce the cognitive risk of patients after anesthesia in clinical practice.

In summary, this review provides a more comprehensive understanding of the complex relationship between the hippocampal DA system and perioperative neurocognitive function by exploring the foregoing aspects in depth. This not only has important implications for improving clinical practice and surgical management, but also provides useful guidance for future research on drugs to treat PND or anesthesia methods to assist prevention of PND. It is hoped that further research reveals more detail of the link between the multi-systems and provides a more complete strategy for the prevention and treatment of PND, ultimately improving the quality of life of patients.

Author Contributions

FNJ and ARC found references and drafted the manuscript. FNJ drew figures. CCY and HHL designed literature retrieval strategy, reviewed the manuscript and obtained fundings. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Bedford PD. Adverse cerebral effects of anaesthesia on old people. *Lancet*. 1955; 269: 259–263.
- [2] Silva AR, Regueira P, Albuquerque E, Baldeiras I, Cardoso AL, Santana I, *et al.* Estimates of Geriatric Delirium Frequency in Noncardiac Surgeries and Its Evaluation Across the Years: A Systematic Review and Meta-analysis. *Journal of the American Medical Directors Association*. 2021; 22: 613–620.e9.
- [3] Safavynia SA, Goldstein PA, Evered LA. Mitigation of perioperative neurocognitive disorders: A holistic approach. *Frontiers in Aging Neuroscience*. 2022; 14: 949148.

- [4] Kim JL, Bulthuis NE, Cameron HA. The Effects of Anesthesia on Adult Hippocampal Neurogenesis. *Frontiers in Neuroscience*. 2020; 14: 588356.
- [5] Liu Y, Fu H, Wang T. Neuroinflammation in perioperative neurocognitive disorders: From bench to the bedside. *CNS Neuroscience & Therapeutics*. 2022; 28: 484–496.
- [6] Xiong C, Liu J, Lin D, Zhang J, Terrando N, Wu A. Complement activation contributes to perioperative neurocognitive disorders in mice. *Journal of Neuroinflammation*. 2018; 15: 254.
- [7] Shen Y, Chen L, Zhang Y, Du J, Hu J, Bao H, *et al.* Phosphatase and Tensin Homolog Deleted on Chromosome Ten Knockdown Attenuates Cognitive Deficits by Inhibiting Neuroinflammation in a Mouse Model of Perioperative Neurocognitive Disorder. *Neuroscience*. 2021; 468: 199–210.
- [8] Isaeva EV, Isaev DS. Anaesthetic and postanaesthetic effect of isoflurane on the multiple-unit activity of the immature rat hippocampus. *Fiziologichnyi Zhurnal*. 2011; 57: 17–20.
- [9] Ogawa SK, Tanaka E, Shin MC, Kotani N, Akaike N. Volatile anesthetic effects on isolated GABA synapses and extrasynaptic receptors. *Neuropharmacology*. 2011; 60: 701–710.
- [10] Joksimovic SM, Osuru HP, Oklopcic A, Beenhakker MP, Jevtovic-Todorovic V, Todorovic SM. Histone Deacetylase Inhibitor Entinostat (MS-275) Restores Anesthesia-induced Alteration of Inhibitory Synaptic Transmission in the Developing Rat Hippocampus. *Molecular Neurobiology*. 2018; 55: 222–228.
- [11] Ju X, Jang Y, Heo JY, Park J, Yun S, Park S, *et al.* Anesthesia affects excitatory/inhibitory synapses during the critical synaptogenic period in the hippocampus of young mice: Importance of sex as a biological variable. *Neurotoxicology*. 2019; 70: 146–153.
- [12] Edelmann E, Lessmann V. Dopaminergic innervation and modulation of hippocampal networks. *Cell and Tissue Research*. 2018; 373: 711–727.
- [13] Wise RA. Catecholamine theories of reward: a critical review. *Brain Research*. 1978; 152: 215–247.
- [14] Speranza L, di Porzio U, Viggiano D, de Donato A, Volpicelli F. Dopamine: The Neuromodulator of Long-Term Synaptic Plasticity, Reward and Movement Control. *Cells*. 2021; 10: 735.
- [15] Hasegawa K, Kamiya H, Morimoto Y. Sevoflurane inhibits presynaptic calcium influx without affecting presynaptic action potentials in hippocampal CA1 region. *Biomedical Research*. 2018; 39: 223–230.
- [16] Yang Y, Ju W, Zhang H, Sun L. Effect of Ketamine on LTP and NMDAR EPSC in Hippocampus of the Chronic Social Defeat Stress Mice Model of Depression. *Frontiers in Behavioral Neuroscience*. 2018; 12: 229.
- [17] Zhou J, Wang F, Zhang J, Li J, Ma L, Dong T, *et al.* The interplay of BDNF-TrkB with NMDA receptor in propofol-induced cognition dysfunction: Mechanism for the effects of propofol on cognitive function. *BMC Anesthesiology*. 2018; 18: 35.
- [18] Tian H, Xu Y, Liu F, Wang G, Hu S. Effect of acute fentanyl treatment on synaptic plasticity in the hippocampal CA1 region in rats. *Frontiers in Pharmacology*. 2015; 6: 251.
- [19] Makaryus R, Lee H, Yu M, Zhang S, Smith SD, Rebecchi M, *et al.* The metabolomic profile during isoflurane anesthesia differs from propofol anesthesia in the live rodent brain. *Journal of Cerebral Blood Flow and Metabolism*. 2011; 31: 1432–1442.
- [20] Huang L, Liu Y, Jin W, Ji X, Dong Z. Ketamine potentiates hippocampal neurodegeneration and persistent learning and memory impairment through the PKC γ -ERK signaling pathway in the developing brain. *Brain Research*. 2012; 1476: 164–171.
- [21] Qu X, Xu C, Wang H, Xu J, Liu W, Wang Y, *et al.* Hippocampal glutamate level and glutamate aspartate transporter (GLAST) are up-regulated in senior rat associated with isoflurane-induced spatial learning/memory impairment. *Neurochemical Research*. 2013; 38: 59–73.
- [22] Xu Z, Qian B. Sevoflurane anesthesia-mediated oxidative stress and cognitive impairment in hippocampal neurons of old rats can be ameliorated by expression of brain derived neurotrophic factor. *Neuroscience Letters*. 2020; 721: 134785.
- [23] Peng S, Zhang Y, Li GJ, Zhang DX, Sun DP, Fang Q. The effect of sevoflurane on the expression of M1 acetylcholine receptor in the hippocampus and cognitive function of aged rats. *Molecular and Cellular Biochemistry*. 2012; 361: 229–233.
- [24] Lamsa K, Lau P. Long-term plasticity of hippocampal interneurons during in vivo memory processes. *Current Opinion in Neurobiology*. 2019; 54: 20–27.
- [25] Zhang JQ, Xu WY, Xu CQ. Neonatal Propofol and Etomidate Exposure Enhance Inhibitory Synaptic Transmission in Hippocampal Cornu Ammonis 1 Pyramidal Neurons. *Chinese Medical Journal*. 2016; 129: 2714–2724.
- [26] Khodaei S, Wang DS, Orser BA. Reduced excitatory neurotransmission in the hippocampus after inflammation and sevoflurane anaesthesia. *BJA Open*. 2023; 6: 100143.
- [27] Zhang J, Cheng Z, Tian Y, Weng L, Zhang Y, Yang X, *et al.* Cerebral Tissue Oxygen Saturation Correlates with Emergence from Propofol-Remifentanyl Anesthesia: An Observational Cohort Study. *Journal of Clinical Medicine*. 2022; 11: 4878.
- [28] Useinovic N, Maksimovic S, Liechty C, Cabrera OH, Quillinan N, Jevtovic-Todorovic V. Systemic inflammation exacerbates developmental neurotoxicity induced by sevoflurane in neonatal rats. *British Journal of Anaesthesia*. 2022; 129: 555–566.
- [29] Lin L, Chen D, Yu X, Zhong W, Liu Y, Feng Y, *et al.* The role and mechanism of TLR4-siRNA in the impairment of learning and memory in young mice induced by isoflurane. *Advances in Clinical and Experimental Medicine*. 2022; 31: 769–780.
- [30] Zhao W, Song S, Chu W, Li Y, Chen S, Ji Y, *et al.* Disruption of hippocampal P2RX2/CaMKII/NF- κ B signaling contributes to learning and memory impairment in C57BL/6 mice induced by surgery plus anesthesia in neonatal period. *Biomedicine & Pharmacotherapy*. 2022; 149: 112897.
- [31] Xu F, Han L, Wang Y, Deng D, Ding Y, Zhao S, *et al.* Prolonged anesthesia induces neuroinflammation and complement-mediated microglial synaptic elimination involved in neurocognitive dysfunction and anxiety-like behaviors. *BMC Medicine*. 2023; 21: 7.
- [32] Li ZQ, Rong XY, Liu YJ, Ni C, Tian XS, Mo N, *et al.* Activation of the canonical nuclear factor- κ B pathway is involved in isoflurane-induced hippocampal interleukin-1 β elevation and the resultant cognitive deficits in aged rats. *Biochemical and Biophysical Research Communications*. 2013; 438: 628–634.
- [33] Wei P, Zheng Q, Liu H, Wan T, Zhou J, Li D, *et al.* Nicotine-Induced Neuroprotection against Cognitive Dysfunction after Partial Hepatectomy Involves Activation of BDNF/TrkB Signaling Pathway and Inhibition of NF- κ B Signaling Pathway in Aged Rats. *Nicotine & Tobacco Research*. 2018; 20: 515–522.
- [34] Liu Q, Sun YM, Huang H, Chen C, Wan J, Ma LH, *et al.* Sirtuin 3 protects against anesthesia/surgery-induced cognitive decline in aged mice by suppressing hippocampal neuroinflammation. *Journal of Neuroinflammation*. 2021; 18: 41.
- [35] Lu J, Tao X, Dai H, Gao S, Zhou H. Peripheral and cerebral inflammation induced by repeated anesthesia and surgery do not cause impairment of learning and memory in middle aged mice. *Acta Neurobiologiae Experimentalis*. 2023; 83: 45–56.
- [36] Tan W, Cao X, Wang J, Lv H, Wu B, Ma H. Tau hyperphosphorylation is associated with memory impairment after exposure to 1.5
- [37] Liu W, Tan X, Xiong X, Yang J, Xiao X. Effects of hypothermia during propofol anesthesia on learning and memory ability and hippocampal apoptosis in neonatal rats. *Journal of Anesthesia*. 2019; 33: 9–16.
- [38] Lin D, Zuo Z. Isoflurane induces hippocampal cell injury and

- cognitive impairments in adult rats. *Neuropharmacology*. 2011; 61: 1354–1359.
- [39] Doi H, Matsuda T, Sakai A, Matsubara S, Hoka S, Yamaura K, *et al.* Early-life midazolam exposure persistently changes chromatin accessibility to impair adult hippocampal neurogenesis and cognition. *Proceedings of the National Academy of Sciences of the United States of America*. 2021; 118: e2107596118.
- [40] Karaman T, Karaman S, Doğru S, Tapar H, Şahin A, Süren M. Short-Term and Long-Term Effects of Dexamethasone on Cognitive Dysfunction Induced by Sevoflurane in Adult Rats. *Turkish Journal of Anaesthesiology and Reanimation*. 2017; 45: 158–163.
- [41] Tzimas P, Andritsos E, Arnaoutoglou E, Papathanakos G, Papadopoulos G. Short-term postoperative cognitive function of elderly patients undergoing first versus repeated exposure to general anesthesia. *Middle East Journal of Anaesthesiology*. 2016; 23: 535–542.
- [42] Linassi F, De Laurenzis A, Maran E, Gadaldi A, Spano' L, Gerosa G, *et al.* Influence of Previous General Anesthesia on Cognitive Impairment: An Observational Study Among 151 Patients. *Frontiers in Human Neuroscience*. 2022; 16: 810046.
- [43] Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*. 1993; 361: 31–39.
- [44] Bailey CH, Giustetto M, Huang YY, Hawkins RD, Kandel ER. Is heterosynaptic modulation essential for stabilizing Hebbian plasticity and memory? *Nature Reviews. Neuroscience*. 2000; 1: 11–20.
- [45] Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. *Nature Reviews. Neuroscience*. 2004; 5: 97–107.
- [46] Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature*. 1998; 391: 892–896.
- [47] Madadi Asl M, Vahabie AH, Valizadeh A. Dopaminergic Modulation of Synaptic Plasticity, Its Role in Neuropsychiatric Disorders, and Its Computational Modeling. *Basic and Clinical Neuroscience*. 2018; 10: 1–12.
- [48] Navakkode S, Chew KCM, Tay SJN, Lin Q, Behnisch T, Soong TW. Bidirectional modulation of hippocampal synaptic plasticity by Dopaminergic D4-receptors in the CA1 area of hippocampus. *Scientific Reports*. 2017; 7: 15571.
- [49] Zhou ZW, Shu Y, Li M, Guo X, Pac-Soo C, Maze M, *et al.* The glutaminergic, GABAergic, dopaminergic but not cholinergic neurons are susceptible to anaesthesia-induced cell death in the rat developing brain. *Neuroscience*. 2011; 174: 64–70.
- [50] Bao WW, Xu W, Pan GJ, Wang TX, Han Y, Qu WM, *et al.* Nucleus accumbens neurons expressing dopamine D1 receptors modulate states of consciousness in sevoflurane anesthesia. *Current Biology*. 2021; 31: 1893–1902.e5.
- [51] Koulchitsky S, De Backer B, Quertemont E, Charlier C, Seutin V. Differential effects of cocaine on dopamine neuron firing in awake and anesthetized rats. *Neuropsychopharmacology*. 2012; 37: 1559–1571.
- [52] He E, Xu S, Dai Y, Wang Y, Xiao G, Xie J, *et al.* SWCNTs/PEDOT:PSS-Modified Microelectrode Arrays for Dual-Mode Detection of Electrophysiological Signals and Dopamine Concentration in the Striatum under Isoflurane Anesthesia. *ACS Sensors*. 2021; 6: 3377–3386.
- [53] Belov D, Fesenko Z, Efimov A, Lakstygal A, Efimova E. Differential sensitivity to anesthesia according to ECoG data in dopamine transporter knockout and heterozygous rats. *Neuroscience Letters*. 2022; 788: 136839.
- [54] Kashiwagi Y, Rokugawa T, Yamada T, Obata A, Watabe H, Yoshioka Y, *et al.* Pharmacological MRI response to a selective dopamine transporter inhibitor, GBR12909, in awake and anesthetized rats. *Synapse*. 2015; 69: 203–212.
- [55] Brodnik ZD, España RA. Dopamine uptake dynamics are preserved under isoflurane anesthesia. *Neuroscience Letters*. 2015; 606: 129–134.
- [56] Kimura-Kuroiwa K, Adachi YU, Mimuro S, Obata Y, Kawamata M, Sato S, *et al.* The effect of aging on dopamine release and metabolism during sevoflurane anesthesia in rat striatum: an in vivo microdialysis study. *Brain Research Bulletin*. 2012; 89: 223–230.
- [57] Hu L, Jing XH, Cui CL, Xing GG, Zhu B. NMDA receptors in the midbrain play a critical role in dopamine-mediated hippocampal synaptic potentiation caused by morphine. *Addiction Biology*. 2014; 19: 380–391.
- [58] Wei X, Ma T, Cheng Y, Huang CCY, Wang X, Lu J, *et al.* Dopamine D1 or D2 receptor-expressing neurons in the central nervous system. *Addiction Biology*. 2018; 23: 569–584.
- [59] Bagot RC, Parise EM, Peña CJ, Zhang HX, Maze I, Chaudhury D, *et al.* Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. *Nature Communications*. 2015; 6: 7062.
- [60] Gunaydin LA, Kreitzer AC. Cortico-Basal Ganglia Circuit Function in Psychiatric Disease. *Annual Review of Physiology*. 2016; 78: 327–350.
- [61] Lisman J, Grace AA, Duzel E. A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends in Neurosciences*. 2011; 34: 536–547.
- [62] Xu X, Zheng C, An L, Wang R, Zhang T. Effects of Dopamine and Serotonin Systems on Modulating Neural Oscillations in Hippocampus-Prefrontal Cortex Pathway in Rats. *Brain Topography*. 2016; 29: 539–551.
- [63] Kanthan M, Cumming P, Hooker JM, Vasdev N. Classics in Neuroimaging: Imaging the Dopaminergic Pathway with PET. *ACS Chemical Neuroscience*. 2017; 8: 1817–1819.
- [64] Tian L, Xia Y, Flores HP, Campbell MC, Moerlein SM, Perlmuter JS. Neuroimaging Analysis of the Dopamine Basis for Apathetic Behaviors in an MPTP-Lesioned Primate Model. *PLoS ONE*. 2015; 10: e0132064.
- [65] Tinkhauser G, Pogosyan A, Tan H, Herz DM, Kühn AA, Brown P. Beta burst dynamics in Parkinson's disease OFF and ON dopaminergic medication. *Brain*. 2017; 140: 2968–2981.
- [66] Zech N, Sinner B. Anaesthesia and Perioperative Management for Patients with Parkinson's Disease. *Anesthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie*. 2022; 57: 578–586.
- [67] Wang N, Wang M. Dexmedetomidine suppresses sevoflurane anesthesia-induced neuroinflammation through activation of the PI3K/Akt/mTOR pathway. *BMC Anesthesiology*. 2019; 19: 134.
- [68] Lian F, Cao C, Deng F, Liu C, Zhou Z. Propofol alleviates post-operative cognitive dysfunction by inhibiting inflammation via up-regulating miR-223-3p in aged rats. *Cytokine*. 2022; 150: 155783.
- [69] Vizuete AFK, Hansen F, Negri E, Leite MC, de Oliveira DL, Gonçalves CA. Effects of dexamethasone on the Li-pilocarpine model of epilepsy: protection against hippocampal inflammation and astrogliosis. *Journal of Neuroinflammation*. 2018; 15: 68.