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REVIEW

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Mitophagy in perioperative neurocognitive disorder: mechanisms and therapeutic strategies

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Abstract

Perioperative neurocognitive disorder (PND) is a common neurological complication after surgery/anesthesia in elderly patients that affect postoperative outcome and long-term quality of life, which increases the cost of family and social resources. The pathological mechanism of PND is complex and not fully understood, and the methods of prevention and treatment of PND are very limited, so it is particularly important to analyze the mechanism of PND. Research indicates that mitochondrial dysfunction is pivotal in the initiation and progression of PND, although the precise mechanisms remain elusive and could involve disrupted mitophagy. We reviewed recent studies on the link between mitophagy and PND, highlighting the role of key proteins in abnormal mitophagy and discussing therapeutic strategies aimed at mitophagy regulation. This provides insights into the mechanisms underlying PND and potential therapeutic targets.

Keywords Mitophagy, Perioperative neurocognitive disorder, NLRP3 inflammasome, Pyroptosis

Introduction

Perioperative neurocognitive disorder (PND) is a prevalent and severe neurological complication in elderly patients following surgery/anesthesia. It encompasses both objectively measured cognitive decline and subjectively reported cognitive deficits, as well as changes in daily living activities before and after surgery [1]. Affecting 5–55% of the elderly patients [2], PND significantly increases the rates of postoperative morbidity, mortality, and the incidence of long-term cognitive dysfunction [3, 4]. The pathogenesis of PND involves various factors, there are no effective drugs or interventions to prevent PND yet. Mitochondria, often referred to as the "powerhouse of the cell", play a crucial role in neuronal development and synaptic plasticity [5, 6]. Mitochondrial quality control is a key factor in the health and survival of brain neurons, and mitochondrial dysfunction is closely associated with a variety of neurodegenerative diseases [7–10]. Similarly, mitochondrial dysfunction is increasingly recognized as playing a critical role in the development and progression of PND [11–13], although the specific mechanisms remain poorly understood. Research in animal and cellular models of PND has led to the hypothesis that abnormal mitophagy, which lead to the accumulation of damaged mitochondria, may be a key factor [14–16]. This review examines the molecular mechanisms underlying mitophagy abnormalities associated with PND, as well as promising therapeutic strategies targeting mitophagy abnormalities in PND demonstrated in recent

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studies. The goal is to provide insights into the mechanisms behind the occurrence and progression of PND and to identify potential new therapeutic targets.

Mitophagy

Autophagy is the cellular process in which autophagosomes transport misfolded proteins, lipids, or damaged organelles within the cytoplasm to lysosomes for degradation and clearance, playing a significant role in hippocampal-dependent cognitive adaptation [17]. Mitophagy, a selective form of autophagy, preserves mitochondrial function and cellular homeostasis by specifically targeting damaged or redundant mitochondria for removal from the cytoplasm [18]. Mitophagy is crucial for maintaining intracellular mitochondrial quality and quantity equilibrium, thereby supporting normal mitochondrial function [19–21]. Under external stressors such as hypoxia, nutrient deprivation, and cellular senescence, damaged mitochondria produce substantial amounts of ROS, which triggers mitophagy to initiate self-clearance by removing damaged mitochondria, thereby reducing ROS accumulation and maintaining cellular stability [22]. Additionally, mitophagy can initiate caspase-family-induced apoptosis and support cell survival by eliminating damaged mitochondria and preventing the excessive release of cytochrome C associated with mitochondrial damage [23]. Neurons, as highly differentiated cells, demand substantial energy to sustain their intricate physiological functions, making mitophagy balance essential for neuronal health and survival [24]. Disruptions in neuronal mitophagy can lead to the accumulation of damaged mitochondria, increase ROS production, and compromise mitochondrial respiratory function, which in turn reduces energy supply. This energy deficit impairs neuronal function, diminishes physiological resilience, and ultimately trigger programmed cell death in neurons [25] (Fig. 1).

The PINK1/Parkin pathway is the most extensively studied mitophagy pathway in neurological diseases [26]. PINK1 is a mitochondrial serine/threonine kinase, with Parkin functions as an E3 ubiquitin ligase. Upon mitochondrial damage, PINK1 enters the inner mitochondrial membrane (IMM), accumulates on the outer mitochondrial membrane (OMM), and phosphorylates the serine 65 residue on ubiquitin molecules [27]. Concurrently, Parkin is recruited to the damaged mitochondria and phosphorylated by PINK1, then activates its E3 ligase activity and promotes the ubiquitination of multiple OMM proteins, leading to the formation of ubiquitin chains [28, 29]. Adaptor proteins, such as P62/SQSTM1, OPTN, NBR1, NDP52, and TAX1BP1, recognize phosphorylated ubiquitin chains on mitochondrial proteins. Through binding to microtubule-associated protein 1A/1B light chain 3 (LC3), these adaptor proteins label damaged mitochondria for phagocytosis and degradation by autophagosomes [30–32].

Mitophagy regulates the molecular mechanism of PND

With advancing insights into the regulatory network of mitophagy, its intricate role in the pathogenesis of PND has gradually become apparent. Furthermore, the involvement of Nod-like receptor protein 3 (NLRP3) inflammasome, Synaptosome Associated Protein 25 (SNAP25), pyroptosis, and neurotoxic proteins in the mitophagy process has been demonstrated in cellular and animal models of PND (Table 1), while the conclusions regarding the role of mitophagy in the onset and progression of PND are not yet consistent (Fig. 2).

In 2018, Ye et al. were the first to propose a connection between PND and mitophagy [14]. They performed abdominal exploratory surgery on 4-month-old female C57BL/6J mice under sevoflurane anesthesia, and observed that surgery/anesthesia upregulated the expression of autophagy-related proteins, including LC3-II, Beclin-1, Parkin, and PINK1, damages mitochondria, and induces behavioral and cognitive impairments in mice. Pretreatment with Honokiol (HNK) was found to further enhance autophagy biomarker expression, reduce mitochondrial ROS levels, alleviate mitochondrial structural damage, and improve postoperative cognitive function in surgery/anesthesia-induced mice. In contrast, the use of the autophagy inhibitor 3-Methyladenine (3-MA) reversed the effects of HNK on mitophagy and cognition in these mice. In addition, Chen et al. demonstrated that mitophagy dysfunction is a primary cause of sevoflurane-induced mitochondrial damage in H4 cells and PND in aged rats [15]. Sevoflurane treatment induces mitochondrial dysfunction and mitophagy deficiencies in H4 cells and aged rat hippocampal neurons, which include increased ROS levels, decreased membrane potential, impaired respiratory function, accumulation of the mitochondrial marker protein Tomm20, and reduced levels of the lysosomal marker protein LAMP1. Ac-YVAD-cmk can inhibit sevoflurane-induced intracellular lysosomal dysfunction of H4 cell, promote mitophagy, and alleviate intracellular ROS levels and mtROS accumulation [33]. Administration of rapamycin, an autophagy activator, reduced sevoflurane-induced ROS production, restored mitochondrial phagocytosis levels, alleviated mitochondrial damage and improved cognitive function in aged rats. Conversely, it is worth noting that Wang and colleagues performed laparotomy on 18-month-old male C57BL/6J mice under sevoflurane anesthesia and found promoted mitophagy and reduced mitochondrial area in hippocampal neurons, accompanied by

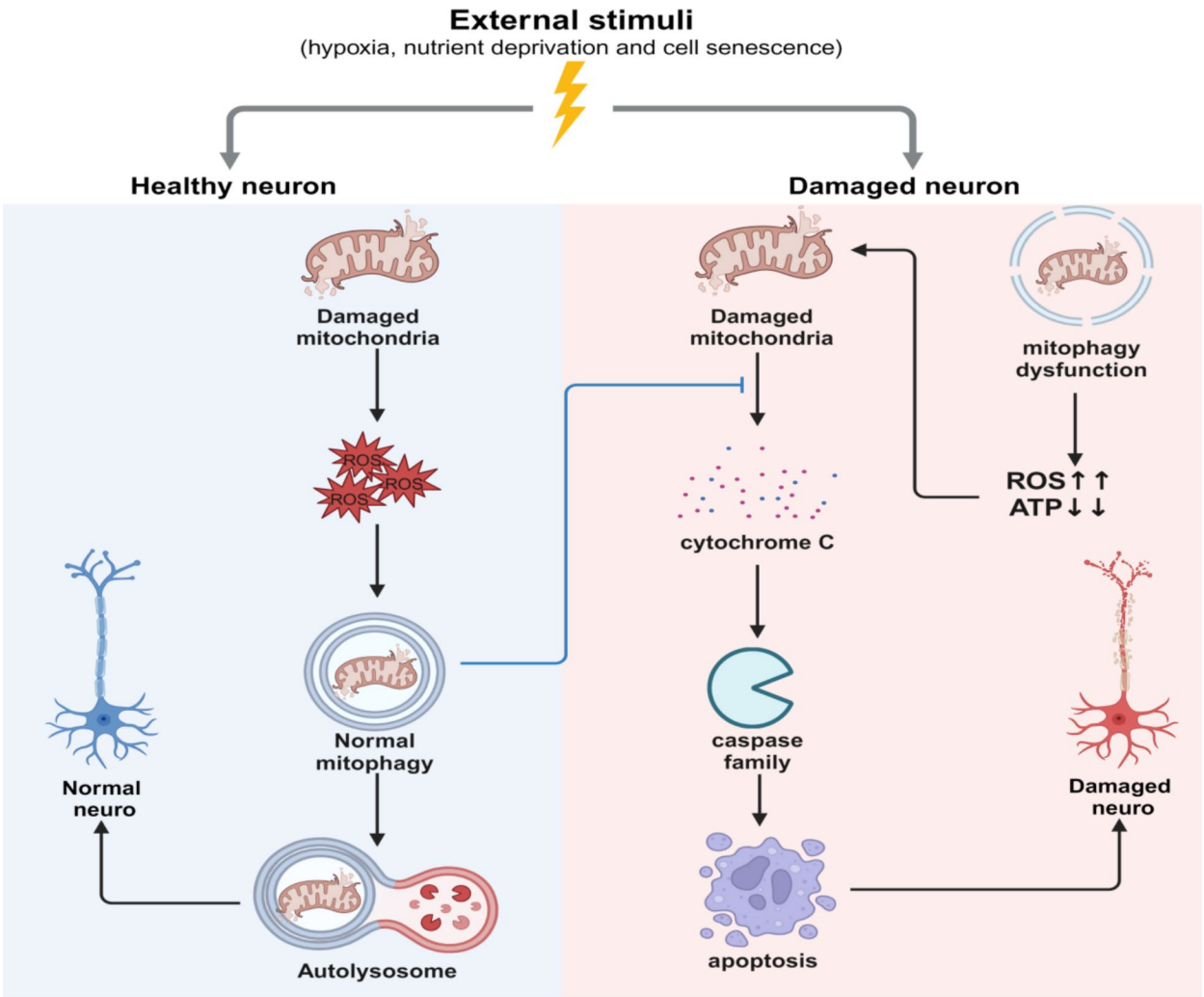

Fig. 1 Physiological function of mitophagy in neurons. Under conditions such as hypoxia, nutrient deprivation, and cellular senescence, damaged mitochondria generate high levels of ROS, triggering mitophagy to clear these damaged mitochondria. Concurrently, mitophagy initiates caspase-family-induced apoptosis by removing damaged mitochondria, thus preventing excessive cytochrome C release due to mitochondrial injury. When mitophagy is impaired, the resulting ROS accumulation reduces ATP production and initiates programmed neuronal death. (This image was generated and provided under the BioRender license using BioRender. All rights and ownership of BioRender content belong to BioRender.)

ROS accumulation, neuronal apoptosis, and tau protein misfolding [16]. Preoperative administration of varenicline improved cognitive function in mice by reducing mitophagy levels, restoring mitochondrial function, lowering oxidative stress, and inhibiting tau phosphorylation. In all, these findings suggest that PND may be linked to the relative capacity of mitophagy and the accumulation of damaged mitochondria.

NLRP3 inflammasome

Neuroinflammation plays a central role in the pathogenesis of PND [34]. Surgery/anesthesia can trigger a systemic inflammatory response that activates inflammation in the central nervous system through various pathways, such as impairing neuronal function, hindering neuronal regeneration, and inducing apoptosis, which collectively lead to cognitive decline [35]. NLRP3 inflammasome is well expressed in neuronal tissues and plays a crucial role in the progression of chronic neurodegenerative diseases [36]. The NLRP3 inflammasome is a complex composed of sensors (NOD-like receptor protein 3, NLRP3), adaptors (apoptosis-associated speck-like protein with a caspase recruitment domain, ASC), and effectors (caspase-1) that are vital for inflammatory regulation [37]. Upon detecting exogenous pathogens or endogenous cell damage signals, NLRP3 recruits ASC proteins, triggering

Table 1 Molecular mechanisms of mitophagy and interventions in PND

References	Models	Molecular mechanisms	Interventions and mechanisms	
[14]	4-Month-old female mice received laparotomy under sevoflurane anesthesia	↑LC3 II/I, Beclin-1, Parkin, PINK1 ↑NLRPS, ASC, Caspase-1, IL-1, IL-8	HNK	↑↑LC3-II/I, Beclin-1, Parkin, PINK1 ↓NLRPS, ASC, Caspase-1, IL-1, IL-8
[15]	18-Month-old rats under sevoflurane anesthesia Primary hippocampal neurons and H4 human neuroglioma cells exposure to sevoflurane	↑LC3B II/I, P62, Tomm20 and COX4I1 ↓Parkin in mitochondria, OPA1, Mfn2, LAMP1	Rapamycin	↑↑LC3B II/I ↑Parkin in mitochondria, LAMP1 ↓P62, Tomm20 and COX4I1
[16]	18-Month-old male mice received laparotomy under sevoflurane anesthesia	↑AT8, LC3B II/1, P62, PINK1, Parkin, Beclin-1 ↓Caspase 3, BDNF	Varenicline	↓AT8, LC3B II/1, P62, PINK1, Parkin, Beclin-1 ↑ Caspase 3, BDNF
[43]	16- to 18-Month-old male mice received partial hepatectomy under isoflurane anesthesia	↓LAMP1, PINK1, Parkin, PSD-95, BDNF ↑LC3B II/I, P62, Tomm20, NLRP3, Caspase-1, ASC, IL-1β	TREM2	↑↑LC3B II/I, ↑LAMP1, PINK1, Parkin, PSD-95, BDNF ↓P62, Tomm20, NLRP3, Caspase-1, ASC, IL-1β
[33]	18-Month-old mice under sevoflurane anesthesia Primary hippocampal neurons and H4 human neuroglioma cells exposure to sevoflurane	↓LAMP2 ↑LC3B II/I, P62, Tomm20, NLRP3, cleaved caspase-1, IL-1β, IL-18, Hsp60	Ac-YVAD-cmk	↑ LAMP2 ↓LC3B II/I, P62, Tomm20, NLRP3, cleaved caspase-1, IL-1β, IL-18, Hsp60
[68]	12-Months-old male rats received laparotomy under isoflurane anesthesia SH-SY5Y cells exposure to LPS	↓LC3 II/I, PINK1 ↑P62, N-GSDME/GSDME, IL-1β, cleaved caspase-3,	AAV9-shPink1	↓ ↓ LC3 II/I, PINK1, ↑↑P62,Clevedcaspase-3, N-GSDME/GSDME, IL-1β
			AAV9-Pink1 OE	↑LC3 II/I, PINK1 ↓P62, N-GSDME/GSDME, IL-1β, cleaved caspase-3
[88]	20-Month-old male rats received laparotomy under sevoflurane anesthesia HT22 cells exposure to LPS	↓LC3 II/I ↑Drp1, P62, VDAC, SOD2, COXIV	Mdivi-1	↑LC3 II/I ↓P62, VDAC, SOD2, COXIV
[56]	12-Month-old rats received laparotomy under isoflurane anesthesia SH-SY5Y cells exposure to LPS	↓LC3 II/I, PINK1,Parkin, SNAP25 ↑P62, N-GSDME/GSDME, cleaved caspase-3	SNAP25	↑LC3II/I, PINK1, Parkin, SNAP25 ↓P62, N-GSDME/GSDME, cleaved caspase-3,
[44]	18- to 20-month-old male mice received myocardial ischemia–reperfusion surgery under isoflurane anesthesia	↓P62 ↑LC3B I/II, PINK1, Parkin, NLRP3, Caspase-1, IL-1β	Liraglutide	↑↑LC3B I/II, PINK1, Parkin ↓↓P62, ↓ NLRP3, Caspase-1, IL-1β
[57]	12-Month-old male mice received laparotomy under isoflurane anesthesia SH-SY5Y and HT22 cells exposure to isoflurane and LPS	↓LC3 II/I, PINK1, Parkin ↑P62, cleaved caspase-3, N-GSDME, IL-1β, IL-18	AAV9-hSyn-shTNFAIP1	↑LC3 II/I, PINK1, Parkin ↓P62, cleaved caspase-3, N-GSDME, IL-1β, IL-18
[45]	16-Month-old male mice received tibial fracture fixation under isoflurane anesthesia BV2 cells exposure to LPS	↓LC3 II/I, Beclin1 ↑NLRP3, ASC, IL-1β, Caspase-1	Olaparib	↑LC3 II/I, Beclin1 ↓NLRP3, ASC, IL-1β, Caspase-1
[108]	18-Month-old male mice received tibial fracture fixation under isoflurane anesthesia BV2 cells exposure to LPS	↑Tomm20, LC3 II/I, PHB2, PINK1, Parkin, IL-1β, IL-18, TNF-α ↓P62	Elamipretide (SS-31)	↑↑Tomm20, LC3 II/I, PHB2, PINK1, Parkin, IL-1β, IL-18, TNF-α ↓↓P62
[66]	18-Month-old male rats received laparotomy under isoflurane anesthesia H19-7 cells exposure to isoflurane and LPS	↓LC3 II/I, PINK1 ↑Tomm20, P62, IL-1β, IL-18, cleaved Caspase-1/Caspase-1, cleaved Caspase-11/Caspase-11, N-GSDME/GSDMD	Dexmedetomidine	↑LC3 II/I, PINK1, ↓Tomm20, P62, IL-1β, IL-18, cleaved Caspase-1/Caspase-1, cleaved Caspase-11/Caspase-11, N-GSDME/GSDMD

inflammasome assembly and activating caspase-1. Activated caspase-1 then promotes the maturation and secretion of inflammatory cytokines IL-1β and TNF-α, intensifying inflammation and initiating pyroptosis [38]. Mitochondrial dysfunction prompts the overproduction of mitochondrial ROS (mtROS) and the release

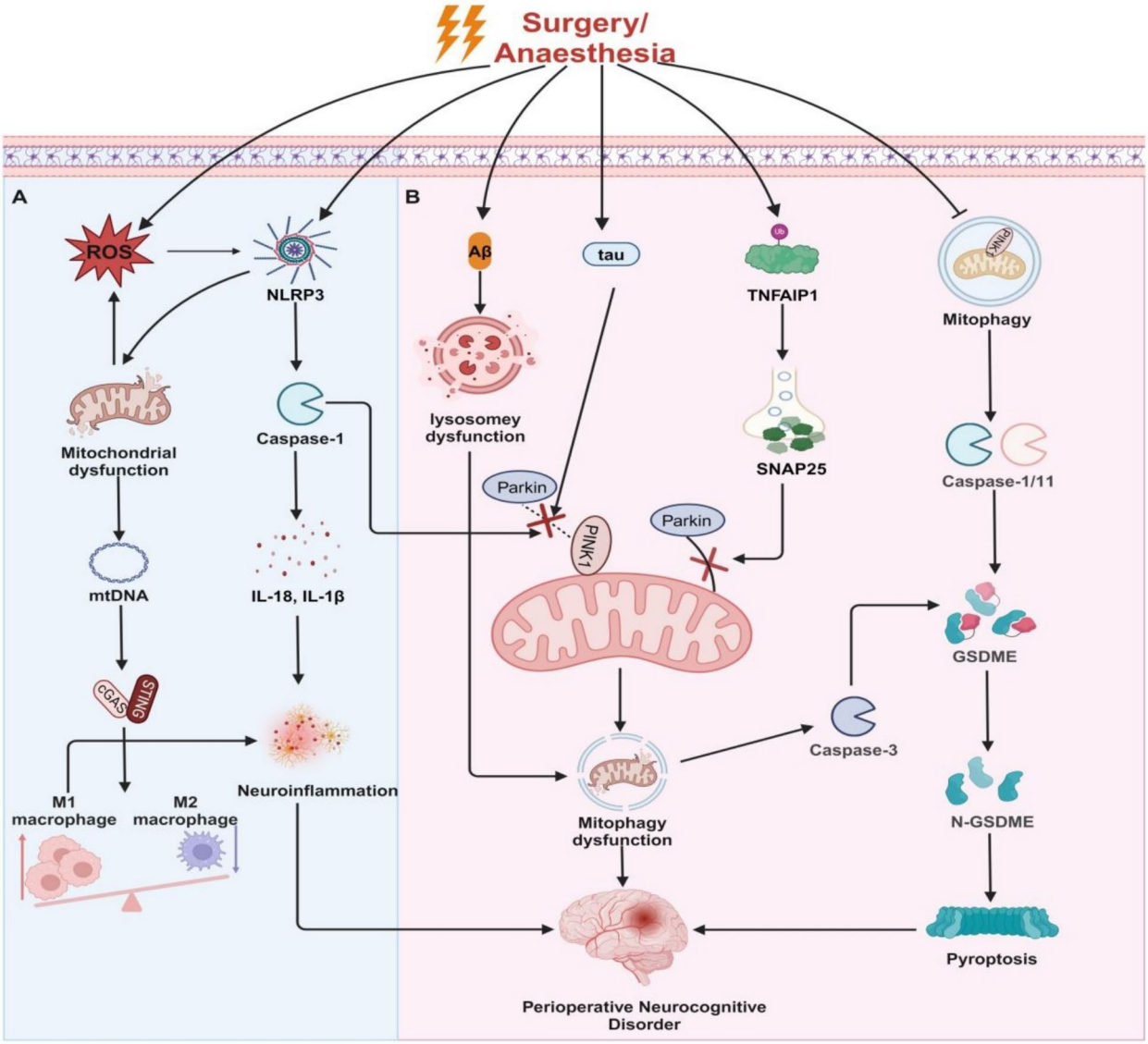

Fig. 2 Molecular mechanism by which mitophagy regulates PND. **A** Surgery/anesthesia elevates ROS levels in the hippocampus, activates NLRP3 inflammasomes, stimulates the release of pro-inflammatory cytokines, intensifies neuroinflammatory responses, and contributes to the development of PND. Activation of the NLRP3 inflammasome induces mitochondrial damage, mtDNA buildup, and mtROS production, while inhibiting mitophagy by promoting caspase-1-dependent Parkin cleavage. **B** Surgery/anesthesia can inhibit mitophagy and promote the production of PND by promoting the production of proteins such as Aβ, tau and TNFAIP1. (This image was generated and provided under the BioRender license using BioRender. All rights and ownership of BioRender content belong to BioRender.)

of mitochondrial DNA (mtDNA), which activates the NLRP3 inflammasome and induces an inflammatory response [39]. The activation of the NLRP3 inflammasome, in turn, damages mitochondria, reduces mitochondrial membrane potential, accumulates mtDNA, elevates mtROS production, and blocks mitophagy by activating caspase-1-dependent cleavage of Parkin. Caspase-1, a key cysteine protease activated by the NLRP3 inflammasome, cleaves Parkin into N-terminal (Parkin-N) and C-terminal (Parkin-C) fragments [40]. This cleavage disrupts Parkin's structure, leading to the loss of its E3 ubiquitin ligase activity. Consequently, mitochondrial outer membrane proteins cannot be ubiquitinated effectively, blocking the initiation of mitophagy. This impairment further exacerbates mitochondrial dysfunction, elevating intracellular ROS levels and intensifying the inflammatory response, which inhibits mitophagy, intensifies the mitochondrial inflammatory response, and further exacerbates mitochondrial dysfunction [41, 42]. In aged mice, surgery/anesthesia was shown to increase hippocampal

mtROS levels, activate NLRP3 inflammasomes, stimulate the release of pro-inflammatory cytokines, amplify neuroinflammatory responses, and impair spatial cognition [43]. Enhancing mitophagy can mitigate mitochondrial structural damage, lower mtROS and MDA production [14], inhibit NLRP3 inflammasome activation, reduce neuroinflammatory responses, and improve cognitive function [44]. Zheng et al. demonstrated that sevoflurane raised the expression of NLRP3, cleaved caspase-1, IL-1β, and IL-18 in the hippocampus of aged mice. The caspase-1 inhibitor Ac-YVAD-cmk was able to alleviate mitochondrial dysfunction and restore mitophagic balance by inhibiting NLRP3 inflammasome activation, thereby improving sevoflurane-induced cognitive impairment [33]. After lipopolysaccharide (LPS) treatment, the expression levels of NLRP3, caspase-1 and IL-1β in BV2 microglia cell were significantly higher than those in normal BV2 microglia cell, and the mitochondrial membrane potential was lower than that in normal BV2 microglia cell. Rapamycin could significantly reduce the activation of NLRP3 inflammasome [45]. Additionally, a retrospective clinical study demonstrated that elevated levels of serum NLRP3 protein, IL-18, and IL-1β after cardiac surgery were associated with an increased risk of cognitive impairment 7 days after surgery. After adjusting for confounding variables, high serum NLRP3 protein levels immediately after surgery were identified as an independent risk factor for the development of PND [46]. This evidence supports the involvement of NLRP3 in PND in human studies. Altogether, NLRP3 inflammasome activation can inhibit mitophagy, promote mitochondrial damage, and then impair cognitive function. The enhancement of mitophagy can alleviate mitochondrial damage and inhibit the activation of NLRP3 inflammasome, thereby improving cognitive impairment.

SNAP25

As a presynaptic protein, SNAP25 is a critical component of the SNARE complex, playing a significant role in regulating neurotransmitter release, synaptic plasticity, neuronal repair, and long-term memory formation [47–49]. SNAP25 is the only protein known to localize to mitochondrial OMMs and has been shown to influence autophagy in neuronal cells [50, 51]. Reduced expression of SNAP25 is also associated with the inactivation of the PINK1/Parkin pathway [52]. Studies have shown that the reduction of SNAP25 leads to defects in presynaptic short-term plasticity, abnormal dendritic spine morphology, and a significant decrease in the long time potentiation amplitude of postsynaptic terminals, which in turn affects learning and memory functions [53]. At the same time, the downregulation of SNAP25 expression was detected in the brain tissues of AD patients and PND model mice induced by anesthesia [54, 55]. Wang et al. found that surgery/anesthesia inhibited the expression of PINK1 and LC3 while promoting the cleavage of caspase-3 and GSDME. Overexpression of SNAP25 using AAV9 particles counteracted these effects, reducing PND severity. In SH-SY5Y cells treated with isoflurane and lipopolysaccharide (LPS), levels of PINK1, Parkin, and LC3-II decreased, while P62 accumulated. SNAP25 knockdown blocked the accumulation of PINK1 in the OMM and the transport of Parkin to the mitochondria, further worsening mitophagy defects induced by isoflurane and LPS. Conversely, SNAP25 overexpression helped inhibit cell death in SH-SY5Y neuronal cells by restoring PINK1-dependent mitophagy [56]. The expression of TNFAIP1 was significantly upregulated in the hippocampus of mice after surgery/anesthesia. TNFAIP1 is a ubiquitin ligase whose N-terminal region contains a BTB domain capable of binding to SNAP25. Through the K48-linked polyubiquitination pathway, TNFAIP1 can be targeted for degradation of SNAP25. Targeted knockdown of TNFAIP1 expression could ameliorate surgery/anesthesia induced memory deficits and PINK1/Parkin-dependent mitophagy defects by stabilizing SNAP25 [57]. Therefore, stabilizing or upregulating the expression of SNAP25, which can restore PINK1/Parkin-dependent mitophagy, contributes to the improvement of cognitive dysfunction induced by surgical anesthesia.

Pyroptosis

Pyroptosis, an inflammatory form of programmed cell death mediated by gasdermin (GSDM) family proteins, plays a critical role in the pathogenesis of PND [58, 59]. GSDMS is a gene family with conserved structural motifs, which plays an important role in cell differentiation and proliferation, cell death, mitochondrial homeostasis, anti-microbial, inflammation and tumorigenesis [60]. All members of the GSDM family (except DFNB59) contain a cytotoxic n-terminal domain (NT) and a c-terminal inhibitory domain (CT), which are connected by a flexible connecting region [61]. After being activated by pathogenic or damaging signals, the N-terminal domains of GSDM proteins A–E induce pyroptosis by binding to membrane lipids after cleavage by activated caspases, forming pores in the cell membrane. This leads to osmotic imbalance, cell swelling, and eventual rupture of the cell membrane [62]. The NLRP3/caspase-1/GSDMD pathway is a classic pyroptosis pathway, and its activation in microglia and astrocytes has been linked to postoperative cognitive deficits [63]. In neonatal rats, continuous exposure to 2% sevoflurane for 6 h significantly increased the expression of pro-apoptotic proteins such as Bax and pyroptosis-related proteins, including cleaved caspase-1, cleaved GSDMD, NLRP3, and ASC, leading

to both apoptosis and pyroptosis of hippocampal neurons [64]. In aged mice, surgery/anesthesia-induced hippocampal mitochondrial dysfunction activates NLRP3 inflammasome–caspase-1-dependent pyroptosis, which impairs learning and memory in behavioral tests [65]. Chen et al. recently demonstrated that dexmedetomidine promotes mitophagy by upregulating PINK1, reducing caspase-1/11–GSDMD-dependent hippocampal neuron death, and improving postoperative cognitive function in elderly rats [66]. Interestingly, GSDME is more highly expressed than GSDMD in the brain and in certain neuronal cell lines, such as SH-SY5Y neuroblastoma and HT-22 hippocampal neurons, suggesting a significant role for GSDME in nervous system pyroptosis [67]. Wang et al. highlighted in in vivo and in vitro studies that PINK1 downregulation promotes caspase-3/GSDME-dependent pyroptosis by reducing mitophagy, leading to PND-like behaviors in rats [68]. In animal experiments, surgery/anesthesia induced downregulation of PINK1 and LC3-II in the hippocampus of 12-month-old male rats, along with abnormal accumulation of P62. Further PINK1 knockdown inhibited mitophagy, promoted caspase-3/GSDME-dependent pyroptosis, and worsened cognitive dysfunction. Conversely, PINK1 overexpression alleviated cognitive impairment, restored mitophagy, and inhibited GSDME-dependent pyroptosis. In in vitro studies, LPS-treated SH-SY5Y cells displayed PINK1-mediated mitophagy deficiency and GSDME-dependent pyroptosis, with these effects worsening when PINK1 function was lost. Accordingly, pyroptosis through the NLRP3/caspase-1/GSDMD and caspase-3/GSDME pathways, regulates the expression of PINK1 and mitophagy, playing a key role in the pathogenesis of PND.

Neurotoxic proteins

Recent studies have revealed the increased levels of tau and Aβ proteins in the cerebrospinal fluid of patients undergoing anesthesia [69–73], which is associated with the incidence and severity of postoperative delirium [74, 75]. Tau protein, a member of the microtubule-binding protein family, is primarily enriched around neuronal axons and plays a crucial role in regulating and maintaining microtubule stability, which is essential for neuronal axon transport [76]. Abnormal phosphorylation and aggregation of tau protein disrupt neuronal structure and function, are linked to mitochondrial dysfunction, and contribute significantly to the pathogenesis of surgically induced cognitive dysfunction and neurodegenerative diseases such as AD [77–79]. Aberrant tau phosphorylation and aggregation can impact mitochondrial dynamics, bioenergetics, and mitophagy, either by inhibiting Parkin translocation to mitochondria [80] or by altering mitochondrial membrane potential [81]. Aβ protein, a neurotoxic peptide of 39–43 amino acids, is produced through the cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase [82]. Aβ protein can accumulate within mitochondria by interacting with mitochondrial proteins, which promotes excessive ROS production and leads to mitochondrial damage. Additionally, Aβ protein can impair the mitophagy–lysosomal pathway by causing lysosomal dysfunction, leading to abnormal aggregation of mitophagosomes and substrates [83]. Enhancing mitophagy has been shown to reduce Aβ protein accumulation and tau hyperphosphorylation, thereby reversing memory impairment in mice [84]. In conclusion, the abnormal accumulation of tau and Aβ proteins after anesthesia is closely related to PND. By regulating the abnormal accumulation of these proteins and enhancing mitophagy, it may provide new strategies for the prevention and treatment of PND and AD.

Mitophagy-related intervention strategies and potential clinical applications in PND research models

PND affects the prognosis and quality of life of patients after surgery, and increases the consumption of family and medical resources. It is urgent to adopt effective prevention and treatment strategies to reduce the occurrence and development of PND. In view of the role of mitophagy in PND, we summarized the existing pharmacological and non-pharmacological strategies targeting mitophagy in order to provide new ideas for the prevention and treatment of PND.

Pharmacological strategies

Rapamycin is an immunosuppressant that binds specifically to the mammalian target of rapamycin (mTOR) by forming a complex with a 12-kDa FK506 binding protein (FKBP12) [85]. Mammalian target of rapamycin (mTOR) is a highly conserved serine-threonine kinase, can regulate protein synthesis, energy metabolism, lipid metabolism, mitochondrial and lysosomal biogenesis [86]. Rapamycin has been shown to reverse sevoflurane-induced autophagic flux damage through the mTOR signaling, thereby improving cognitive deficits in aged rats [87]. In sevoflurane-treated hippocampal tissue, rapamycin counteracts the increased levels of mitochondrial markers Tomm20 and P62 and the decreased expression of the lysosomal marker LAMP1, promoting mitophagy and reducing the number of damaged mitochondria. At the same time, rapamycin improving mitochondrial quality in neuronal cells, which significantly alleviates sevoflurane-induced cognitive impairment in rats [15]. Additionally, rapamycin promotes mitophagy in LPS-treated HT22 cells, reducing mitochondrial hyperdivision and improving mitochondrial function [88].

Honokiol (HNK), a natural bisphenol compound derived from magnolia officinalis, exhibits multiple pharmacological activities, including anti-tumor, antioxidant, anti-inflammatory, and neuroprotective properties [89]. As a small polyphenolic molecule, HNK easily crosses the blood–brain barrier, inhibiting intracellular Ca^2+ influx, caspase-3 activity, and the abnormal aggregation of Aβ protein, thereby providing neuroprotection [90]. HNK has been shown to support microglial phagocytic function by improving mitochondrial function [91]. Furthermore, HNK alleviates neuroinflammation and reverses surgery- and anesthesia-induced learning and memory deficits in mice by promoting mitophagy, lowering mtROS levels, and inhibiting NLRP3 inflammasome activation [14].

Varenicline, a non-nicotine smoking cessation drug approved by the U.S. Food and Drug Administration, acts as a selective partial agonist of the α4β2-nicotinic acetylcholine receptor (nAChR) [92]. The α4β2-nAChR, a ligand-gated ion channel widely distributed in the nervous system, regulates neurotransmitters such as acetylcholine, γ-aminobutyric acid, and norepinephrine, playing a central role in learning, memory, cognition, attention, inflammation, and pain [93]. This nAChR subunit in the central nervous system has been proposed as a potential target for treating age-related cognitive decline and various neurodegenerative and psychiatric disorders [94, 95]. Studies have shown that varenicline reduces neuroinflammation, tau misfolding, DNA damage, and apoptosis, thereby mitigating PND-like behaviors in aged mice [96]. Varenicline also alleviates surgery and anesthesia-induced hippocampal oxidative stress, mitochondrial dysfunction, and aberrant mitophagy, reducing tau phosphorylation and improving cognitive function in mice through the PKR/STAT3 pathway [16].

Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is primarily used to treat type 2 diabetes and obesity [97]. Recent research has expanded our understanding of liraglutide's pharmacological effects, showing potential efficacy in managing neurological diseases. Liraglutide improves neural encoding in the ventromedial prefrontal cortex and ventral striatum, correcting adaptation mispredictions in patients with impaired insulin sensitivity and normalizing sensory-related learning deficits in obese patients [98]. In AD mouse models, liraglutide improves learning and memory by reducing Aβ protein deposition and tau hyperphosphorylation, promoting synaptic plasticity, and reducing neuronal degeneration [99, 100]. In alcohol-dependent mice, liraglutide significantly increased dendritic spine density and synaptic protein levels, alleviating anxiety and memory deficits linked to alcohol withdrawal [101]. Additionally, liraglutide mitigates neuroinflammation, reduces synaptic loss and impaired plasticity, and alleviates anxiety-like behaviors and cognitive deficits in aged mice post-cardiac surgery by increasing mitophagy and inhibiting NLRP3 inflammasome and microglial activation [44]. Recently, results from a Phase 2b clinical trial presented at the Alzheimer's Association International Conference (AAIC) demonstrated that liraglutide can slow the atrophy of key brain regions in AD patients and reduce the rate of cognitive decline [102]. However, it has not yet been reported in clinical trials of PND, and further research is still needed.

Elamipretide (SS-31), a novel mitochondria-targeted antioxidant, primarily localizes to the inner mitochondrial membrane, where it directly scavenges ROS and stabilizes the electron transport chain. SS-31 has demonstrated neuroprotective effects across various neurological disorders [103–106]. It has been shown to reverse isoflurane-induced mitochondrial dysfunction in the hippocampus of aged mice, promote brain-derived neurotrophic factor (BDNF) signaling and synaptic plasticity, reduce neuronal damage, and improve cognitive function [107]. In mouse models with LPS-induced neuroinflammation, SS-31 significantly increased energy production and mitochondrial membrane potential in the hippocampus, indicating its potential to restore function in damaged neurons [105]. SS-31 inhibits activation of the NLRP3 inflammasome–caspase-1 pathway in the hippocampus following surgery or anesthesia, thereby reducing lesion-related cell death and neuroinflammation, rescuing neuronal damage and synaptic dysfunction, and alleviating cognitive impairment [65]. Furthermore, SS-31 promotes PHB2-mediated mitophagy activation, inhibiting mtDNA release, M1 microglial polarization, and inflammation via the cGAS–STING pathway, ultimately restoring neurocognitive function in elderly mice after surgery [108].

Dexmedetomidine (Dex), is a highly selective α2 adrenergic receptor agonist with sedative, anxiolytic, hypnotic, and analgesic properties that is commonly used in the induction and maintenance of general anesthesia [109]. In recent years, studies have found that Dex has a positive effect on cognitive impairment, especially PND, which is expected to become an ideal drug for the treatment of PND. Clinical studies have found that the prophylactic use of low-dose Dex significantly reduces postoperative delirium in older patients after cardiac and noncardiac surgery [110]. In animal experiments, Chen et al. found that Dex improved motor symptoms in Parkinson mice by enhancing PINK1/Parkin-induced mitophagy, improving mitochondrial function, and protecting dopaminergic neurons [111]. Suo and Wang found that Dex alleviated sevoflurane-induced neurotoxic effects by activating mitophagy in the hippocampus of rats and improved learning and memory ability in rats

[112], it provides a potential strategy for the treatment of PND.

Propofol is a general anesthetic widely used in the induction and maintenance of general anesthesia and sedation of regional anesthesia. Propofol produces sedation, hypnosis, and amnesia effects by activating the inhibitory transmitter γ-aminobutyric acid (GABA) in the central nervous system [113]. Dai et al. found that propofol could reduce the damage of mitochondria by inhibiting the PINK1/Parkin mitophagy pathway, and alleviate the impairment of learning and memory in sleep-deprived rats [114]. However, Liang et al. found that propofol time-dependently decreased the expression levels of PINK1 mRNA and protein, inducing apoptosis in hippocampal neurons [115]. As early as 2015, Han et al. suggested that repeated use of low-dose propofol had no apparent effect on cognitive function. However, repeated administration of propofol at recommended or higher doses caused a significant increase in the expression of apoptotic factors and pro-inflammatory cytokine in the hippocampus of neonatal rats, impairing cognitive function [116]. Therefore, more research is needed to explore the dose and timing of propofol administration to mitigate side effects and improve its role in the prevention and treatment of PND.

In conclusion, various drugs have shown significant potential therapeutic effects in animal models by improving PND through modulation of mitophagy. For example, sirolimus improves cognitive function by restoring mitophagy and reducing the accumulation of damaged mitochondria, and HNK reduces neuroinflammation by enhancing mitophagy and reducing oxidative stress. By reducing Aβ protein deposition and tau protein hyperphosphorylation, liraglutide enhances mitophagy and improves cognitive function. However, these strategies still face challenges in clinical application. Future studies need to further optimize drug dosage and administration time to improve treatment efficacy and reduce side effects. For example, the effects of the dose and timing of administration of propofol on cognitive function vary and require further investigation. In addition, long-term follow-up studies are needed to evaluate the durable effects of the drug and to consider the accessibility and safety of the drug, especially for older patients. Meanwhile, exploring the synergy between drugs, such as the combined use of rapamycin and Dex, may improve PND more effectively by enhancing mitophagy and inhibiting neuroinflammation.

Non-pharmacological treatment strategies

Electroacupuncture (EA) is an innovative therapy that combines physical nerve stimulation with Traditional Chinese Medicine (TCM) acupuncture and is widely applied to treat various cognitive dysfunctions [117]. Preoperative EA therapy has been shown to reduce the incidence of PND and decrease levels of inflammatory markers in elderly patients [118]. Studies suggest that the mechanisms by which EA alleviates PND may involve neuroinflammation, oxidative stress, autophagy, and the microbiota–gut–brain axis [119]. In PND rat models, EA has been found to improve spatial memory by reducing mitochondrial damage from oxidative stress and increasing mitophagy to prevent the buildup of damaged mitochondria [120]. Additionally, inhibiting ROS production and IL-1β expression has been shown to further improve spatial memory in these models [121].

Cognitive training (CT) is to improve cognitive function through the guidance of different cognitive domains such as memory, attention, execution and language [122]. Common CT methods include computerized CT (CCT), multimedia education, paper-and-pencil cognitive training, memory training, and communication with patients [123]. CT can increase the density of dopamine D1 receptors in the cortex and improve the capacity of working memory [124]. At the same time, CT can also improve the cognitive reserve of patients [125] and reduce the incidence of PND [126]. In AD mice, repeated CT reduced glycogen synthase kinase-3β (gsk3β) activity, reduced phosphorylated tau deposition, and improved spatial memory [127]. However, more research is needed to determine whether CT can affect mitophagy to improve cognitive function.

Physical activity (PA) is widely regarded as beneficial for physical and mental health, and can significantly improve cognitive function [128]. Studies have shown that regular exercise before surgery and early postoperative exercise can significantly reduce the incidence of PND [129, 130]. PA can increase BDNF levels, increase hippocampal volume, and improve memory function [131]. PA can also affect the activation of microglia and astrocytes, reduce neuroinflammation, and enhance cognitive function in AD patients [132]. Continuous aerobic exercise for 12 weeks can promote the level of mitophagy in the hippocampus of APP/PS1 transgenic AD mice, clear damaged or abnormal mitochondria, maintain mitochondrial protein homeostasis, and improve the learning and spatial memory levels of mice [133]. Zhao et al. also found that PA can enhance PINK1/Parkin-mediated mitophagy activity by upregulating the SIRT1–FOXO1/3 axis, reduce Aβ protein deposition, and improve the learning and memory ability of AD mice [134]. These findings suggest that PA-activated mitophagy may be a promising strategy for the prevention of PND.

In summary, non-pharmacological strategies such as EA, CT, and PA show potential positive effects in the prevention and treatment of PND. For example, EA

modulates neuroinflammation and oxidative stress by physical nerve stimulation, increases mitophagy, and improves cognitive function; CT reduces the incidence of PND by enhancing cognitive reserve; PA improves cognitive function by increasing BDNF levels and enhancing mitophagy. However, further optimization and long-term efficacy evaluation of these strategies need to be further investigated. The effects of different types and durations of CT and PA on PND need to be explored in the future and their long-term effects evaluated. At the same time, accessibility and safety of non-pharmacological strategies need to be considered. In addition, explore the synergy of non-pharmacological strategies with pharmacological treatments to more effectively improve PND.

Conclusion

PND is a common complication in elderly patients following surgery or anesthesia, with its underlying pathophysiological mechanisms primarily involving neuroinflammation, oxidative stress, insufficient energy supply, and neuronal apoptosis. Recent studies suggest that mitochondrial dysfunction plays a crucial role in the development of PND. Mitophagy, a key mechanism to maintain mitochondrial homeostasis, alleviates oxidative stress by clearing damaged mitochondria and protecting neuronal function. This review explores the relationship between PND and abnormal mitophagy, detailing the molecular mechanisms involved and potential intervention strategies. Studies have indicated that the occurrence of PND is closely related to the balance of mitophagy and the accumulation of damaged mitochondria. In the PND model, NLRP3 inflammasome activation inhibits mitophagy, exacerbating mitochondrial damage, while enhancing mitophagy alleviates inflammation and improves cognitive function. Furthermore, proteins such as SNAP25, pyroptosis mediators, and neurotoxic proteins play pivotal roles in PND pathogenesis and are linked to mitophagy regulation. Although some pharmacological and non-pharmacological interventions have demonstrated potential in improving PND by regulating mitophagy in animal models, their clinical efficacy and safety remain to be fully validated. Future research should focus on identifying the specific regulatory pathways of mitophagy in PND and exploring the temporal interplay of various pathological processes during its pathogenesis. Additionally, more clinical trials are necessary to evaluate the safety and efficacy of current intervention strategies and to develop more effective prevention and treatment approaches for PND.

Author contributions

First author Zhen Feng wrote the main text of the manuscript, and co-first author Yan Hou made substantial contributions to its conception. The second author Chang Yu and the third author Ting Li acquired, analysed, and interpreted the data. Fourth author Haoyang Fu prepared Table 1. Corresponding author Feng Lv critically revised the manuscript for important intellectual content, and corresponding author Ping Ling approved the publication of the version. All authors revised the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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