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REVIEW ARTICLE

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Effects of anesthetics on mitochondrial quality control: mechanisms and clinical implications

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Abstract

Focus on the implications of common perioperative drugs for mitochondrial quality control and their subsequent impact on the overall physiological condition has been increasing. This review discusses the effects of perioperative drugs, such as intravenous and inhaled anesthetics, analgesics, local anesthetics on mitochondrial quality and their underlying mechanisms. These drugs influence mitochondrial properties, including morphology, dynamics, energy metabolism, and protein expression, thereby affecting the clinical outcomes of patients undergoing surgery. Such effects can be either protective or detrimental and are contingent upon multiple variables such as the specific drug used, dosage, application timing, and the patient's overall health status. Recognizing the effects of these perioperative drugs on mitochondrial quality control is crucial to selecting safer anesthetic protocols, reducing postoperative complications, enhancing postoperative recovery, and gaining insights into the development of innovative treatment methodologies and optimization of perioperative care.

Keywords Anesthetics, Mitochondrial quality control, Organ function, Clinical outcome

1 Introduction

Anesthesia is a fundamental component of surgical procedures and a notable stressor, potentially affecting patients' metabolism and immune system. Evidence suggests that perioperative drugs, including anesthetics, analgesics, impact organ functions beyond the nervous system [1]. The mitochondria, the powerhouse of cellular functions, are pivotal in upholding cellular and organ functionality [2]. Recently, focus on the potential impact of perioperative drugs on mitochondrial quality and their consequent effects on overall physiological health has heightened.

Mitochondrial quality control is essential in mitochondrial homeostasis, including pivotal aspects such as mitochondrial morphology and dynamics, function and metabolism, and mitochondria-associated protein expression [3]. Perioperative drugs may interfere with these processes through diverse mechanisms, consequently altering mitochondrial quality, and subsequently affecting postoperative patient recovery and complications [4]. Although the influence of perioperative drugs on the mitochondria has been widely assessed, data on the precise mechanisms of these drugs and their clinical repercussions remain limited. Additionally, mitochondrial effects can be distinctly influenced by the specific drug used, dosage, application timing, and the subjects under study. The underlying causes of these disparities and their clinical ramifications remain to be thoroughly assessed.

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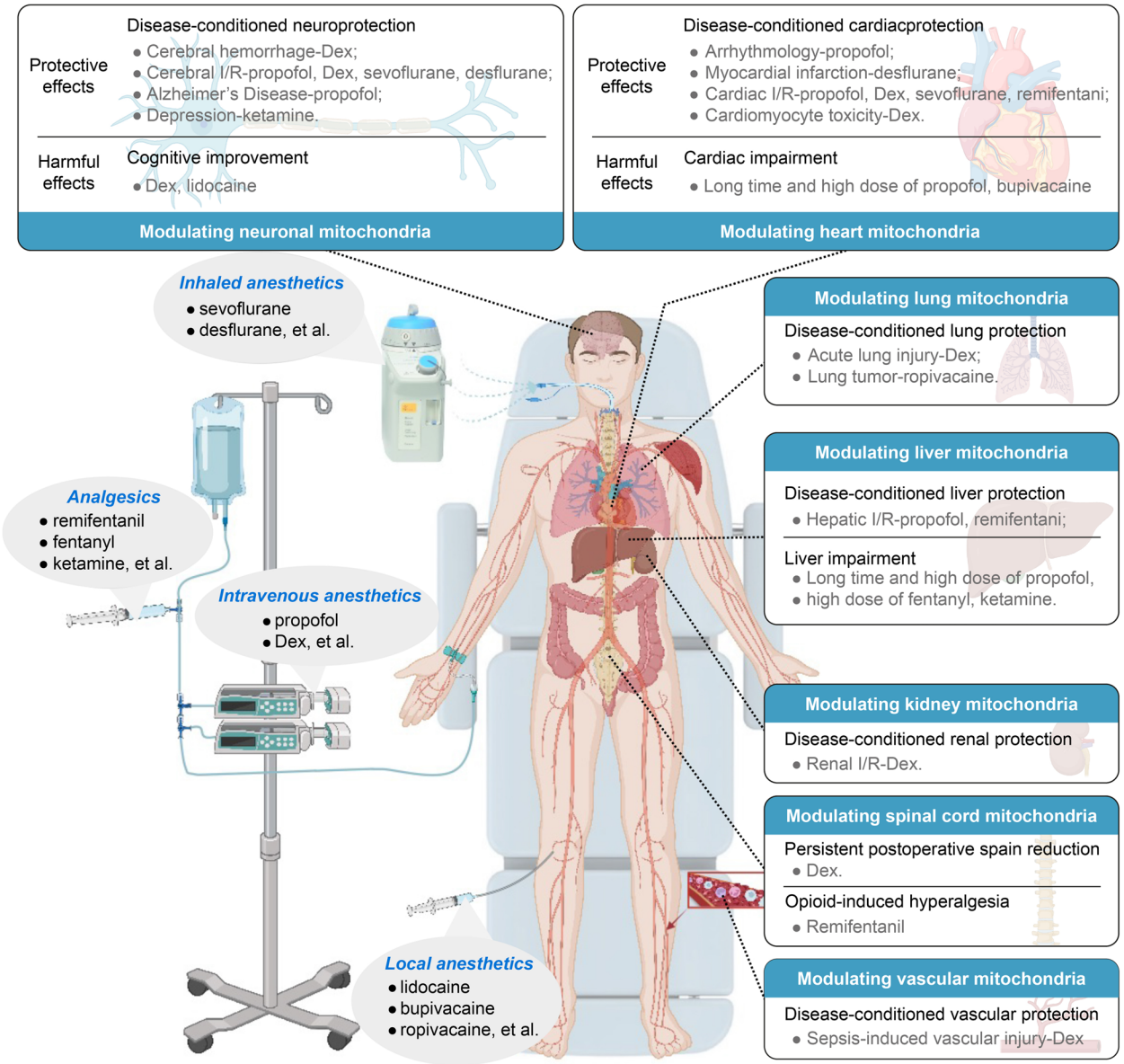

Fig. 1 Impact of perioperative drugs on mitochondrial quality and clinical outcomes. *I/R* ischemia–reperfusion, *Dex* dexmedetomidine, *VEC* vascular endothelial cell

This review systematically examines and analyzes the impacts of perioperative drugs, including intravenous anesthetics, inhaled anesthetics, analgesics, local anesthetics, on mitochondrial quality and the underlying mechanisms (Fig. 1). The findings presented in this review will expand anesthesiologists' knowledge of the cellular-level changes in perioperative patients and enhance perioperative management. Optimizing perioperative strategies with drugs known for mitochondrial protection or integrating interventions, such as preconditioning and nutritional therapies, can safeguard mitochondrial quality and alleviate perioperative stress. Furthermore, specific drugs that enhance mitochondrial quality may have therapeutic potential, laying the groundwork for advanced organ protection and tailored anesthesia protocols.

2 Effects and mechanisms of intravenous anesthetics on mitochondria

Intravenous anesthetics, such as propofol and dexmedetomidine (Dex), are commonly used in general anesthesia due to their rapid onset and short duration, making

them ideal for sedation and sleep induction. Propofol not only offers anesthetic depth and pain relief during surgery but also protects organs, inhibits platelet aggregation, and decreases postoperative nausea and vomiting [5]. Conversely, Dex is effective for sedation, stress reduction, pain management, and patient satisfaction augmentation and can induce deep sedation while retaining spontaneous respiration; it is invaluable for surgeries such as deep brain electrode implantation, where patient consciousness is crucial for neurofunctional tests [6].

Mechanistically, propofol enhances γ-aminobutyric acid (GABA) receptor activity, maintaining neurons in their resting state, while Dex, a selective α_2-adrenergic receptor agonist, primarily affects the locus coeruleus, resulting in effects resembling natural sleep. However, the potential risks of intravenous anesthetics should be considered. Propofol may induce allergies, hypotension [7], propofol infusion syndrome [8], and postoperative cognitive issues [9], while Dex may lead to heart rate and blood pressure decline [10]. Therefore, ensuring accurate dosage and monitoring the cardiovascular status of patients during drug administration are imperative.

2.1 Effects of propofol on mitochondria

The protective properties of propofol on mitochondrial quality have been extensively studied. In cerebral ischemia–reperfusion injury, propofol treatment at a concentration of 200 mM inhibited mitochondrial permeability transition pore (mPTP) channels, and reduced calcium-induced mitochondrial swelling and the production of associated reactive oxygen species (ROS); these collectively led to protection against brain damage [11]. Additionally, propofol was found to activate mitochondrial ATP sensitive potassium channels (mKATP), regulate calcium ion dynamics, and ensure calcium homeostasis in astrocytes [12]. Pretreatment with propofol (intravenous administration [1.0 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$] 1 h before ischemia) prevented neuronal mitochondrial DNA (mtDNA) release and decreased the mitochondrial membrane potential induced by cerebral ischemia–reperfusion [13]. Zhong et al. reported that propofol (60 $mg{\cdot}kg^{-1}$) can shield against DNA damage-induced cell death in cerebral ischemia–reperfusion mouse models by modulating calcium transfer between the endoplasmic reticulum and mitochondria [14]. Tao et al. revealed that propofol (1.0 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$) can inhibit mPTP channel opening and decrease neuronal apoptosis in cerebral ischemia–reperfusion rat models by reducing the transfer of apoptosis-inducing factor from the mitochondria to the cell nuclei [15]. In hippocampal neurons exposed to the oxygen–glucose deprivation and reoxygenation (OGD/R) model, propofol (0.1–50 μM) restricted excessive mitochondrial fission by inhibiting dynamin-related protein 1 (Drp1) and fission protein 1 (Fis1) binding; however, higher doses (100–200 μM) undermined neuronal survival [16]. In myocardial ischemia–reperfusion injury, propofol can dose-dependently enhance mitochondrial antioxidative capability, alleviate cardiac damage, and protect the heart in perioperative high-risk patients, such as those with diabetes [17]. But currently, there are no clinical studies indicating that the perioperative use of propofol has any significant advantages for patients with cerebral ischemia reperfusion compared to other sedatives. Further, propofol has been reported to upregulate the expression of the mitochondria-related protein LRP-PRC (Leucine-rich pentatricopeptide repeat-containing) and protect cardiomyocytes from oxidative stress [18]. Liu et al. found that propofol pretreatment (10 mg/kg) inhibited the occurrence of ventricular arrhythmias in rats by promoting the opening of mKATP channels [19]. OGD/R cardiomyocytes treatment with propofol (1–200 μM) can mitigate cardiomyocyte apoptosis by inhibiting extracellular signal-regulated kinase (ERK) activity to downregulate Drp1 phosphorylation, thereby reducing excessive mitochondrial fission [20]. Clinical research has also confirmed the cardioprotective effects of propofol. Xia et al. demonstrated that administering a high dosage of propofol (120 μg per kilogram per minute) during cardiopulmonary bypass (CPB) can reduce postoperative myocardial cell damage and shorten the duration of stay in the intensive care unit [21]. In liver ischemia–reperfusion injury, propofol (1 $mg{\cdot}kg^{-1}$) effectively inhibited mitochondrial oxidative stress, reducing liver damage by mitigating hypoxia-inducible factor 1 alpha (HIF-1α)-driven mitochondrial dysfunctions and cell apoptosis [22]. Additionally, in Alzheimer's disease, propofol (50 $mg{\cdot}kg^{-1}$, i.p.) weakened amyloid beta (Aβ)-induced mitochondrial mPTP channel disruptions, consequently enhancing cognitive functions [23].

However, the influence of propofol on mitochondrial quality is multifaceted and hence not uniformly beneficial. Indeed, propofol can be neurotoxic to the developing brain. Liang et al. treated neural stem cells (NSCs) isolated from the hippocampus of E15.5 mouse embryos with propofol (5–50 μM) and revealed that propofol inhibits NSC proliferation and accelerates NSC apoptosis through PTEN-induced kinase 1(PINK1)-mediated mitophagy [24]. Furthermore, Kajimoto et al. reported that propofol hindered mitochondrial complex II activity, which in turn impedes the entry of acetyl-CoA into the tricarboxylic acid cycle via pyruvate dehydrogenase, leading to lactic acid accumulation that culminates in neuronal death in the developing brain [25]. A clinical study also confirmed that while anesthesia with propofol does not affect long-term memory in children, it

does impair short-term memory [26]. Therefore, the use of propofol should be minimized in pediatric patients. Moreover, prolonged exposure to high doses of propofol can be detrimental to mitochondrial quality. Administering rats with a high dose of propofol for prolonged duration (20 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$) disrupted the inner mitochondrial membrane, affecting electron flow in the mitochondrial respiratory chain at the coenzyme Q site and suppressing the activity of mitochondrial complexes II and III in liver and skeletal muscle tissues [27]. Meanwhile, propofol administration at varying concentrations (50, 100, and 200 mM) to isolated adult guinea pig hearts dose-dependently reduced oxygen utilization by myocardial cells, impeding the mitochondrial respiratory chain and diminishing the ventricular wall function of perfused hearts [28]. Propofol (1–10 $\mu g{\cdot}mL^{-1}$) considerably limited fatty acid oxidation in human skeletal muscle cells, impacting energy metabolism by depleting mitochondrial respiratory spare capacity [29]. Clinical observations of patients have indicated that long-term exposure to high doses of propofol (surpassing 4–5 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ and lasting over 48 h) can induce propofol infusion syndrome (PRIS) by damaging mitochondrial complexes II and IV in the muscles [30]. However, the role of coenzyme Q supplementation as a potential preventive or therapeutic strategy against PRIS requires further investigation.

The influence of propofol on mitochondrial quality is organ-specific. Herminghaus et al. reported that propofol attenuated the coupling between the liver mitochondrial electron transport chain (ETC) and oxidative phosphorylation (OXPHOS), causing the degradation of liver mitochondrial quality. This decline is associated with liver dysfunction in PRIS. Conversely, within colon mitochondria, propofol enhances the coupling between the ETC and OXPHOS, leading to the amelioration of colon mitochondrial quality [31].

Propofol garners preference among anesthesiologists due to its advantages, including rapid onset and swift metabolism. Nonetheless, its potential mitochondrial protective effects within organ tissues are a subject of ongoing debate. Diverse studies have indicated that propofol's efficacy can significantly differ, even when examining identical disease models, producing divergent outcomes. Presently, a substantial body of clinical trial data substantiating propofol's superior organ protective benefits over alternative anesthetics is absent. Consequently, our investigative efforts are pivoting towards exploring other anesthetic options for the perioperative care and organ preservation in critically ill patients, with a particular interest in emerging anesthetics like remimazolam and cyclopropofol. However, the exploration of these novel anesthetics' organ-protective properties is in its infancy, marking a critical direction for future research endeavors.

2.2 Effects of dexmedetomidine on mitochondria

Dex provides perioperative organ protection and exerts anti-inflammatory and antioxidant effects by preserving mitochondrial quality. It has been shown to protect essential organs by maintaining mitochondrial dynamics [32]. The protective role of Dex in maintaining mitochondrial quality has been corroborated across multiple perioperative outcomes, notably in ischemia/reperfusion, pain, and postoperative cognitive function.

In mice with acute lung injury, Dex modulates the PKC-α (protein kinase C alpha)/HIF-1α/HO-1 (heme-oxygenase 1) signaling pathway, thereby upregulating mitochondrial fusion proteins mitofusin-1 (MFN1), mitofusin-2 (MFN2), and optic atrophy factor 1 (OPA1), while simultaneously downregulating the mitochondrial fission proteins Drp1 and Fis1, which together benefit the mitochondria and reduce injury [33]. A clinical study has also confirmed that perioperative use of dexmedetomidine in patients undergoing thoracoscopic surgery can enhance arterial oxygenation in adult thoracic surgery patients and reduce postoperative pulmonary complications [34]. In septic rats induced by cecal ligation and puncture (CLP), Dex administration (10 $\mu g{\cdot}kg^{-1}$ both 30 min before and 12 h after CLP) inhibited Drp1 activity in vascular endothelial cells, moderating mitochondrial fission and fortifying the vascular barrier under septic conditions [35]. In a clinical randomized trial, Cioccari et al. found that early administration of dexmedetomidine for sedation in septic patients on mechanical ventilation led to a decreased requirement for vasopressor agents, compared with conventional care [36]. Additionally, a multicenter randomized clinical trial demonstrated that sedation with dexmedetomidine could alleviate the inflammatory response in septic patients requiring mechanical ventilation [37]. Contrastingly, Hughes et al., in a multicenter, double-blind trial, observed no significant difference in clinical outcomes between septic patients on mechanical ventilation sedated with dexmedetomidine and those sedated with propofol. Consequently, it is evident that while the primary treatment of the underlying disease is paramount for critically ill patients, the choice of sedative may offer symptomatic relief but does not alter the final clinical outcomes [38].

In addition, Dex can activate the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)-mediated mitochondrial biogenesis pathway to enhance organ function. Huang et al. observed improved neural functionality in a cerebral hemorrhage mouse model treated with Dex (50 $mg{\cdot}kg^{-1}$, i.p.), attributed to the PGC-1α pathway [39]. Similarly, Yu et al. found that

Dex (50 μg·kg^{-1}) mitigated doxorubicin-induced cardiotoxicity in mice through the same pathway [40]. Dex exerts protective effects on organs by limiting mitochondrial autophagy and apoptosis. In OGD/R-treated neural cells, Dex (1 μM) inhibits the mitochondrial calcium uniporter (MCU) channel and reduces mitophagy, providing neuroprotection [41]. Deng et al. observed that Dex (50 μg·kg^{-1}) decreased mitochondrial apoptosis in myocardial ischemia–reperfusion rats via the JAK2/STAT3 (janus kinase 2/signal transducer and activator of transcription 3) signaling pathway [42].

Previous research has underscored the influence of Dex on mitochondrial membrane channels. In rats with cerebral ischemia–reperfusion, administration of Dex (50 μg·kg^{-1}, i.p.) both before and after reperfusion activated mKATP channels, thereby reducing cerebral injury [43]. The neuroprotective effects of dexmedetomidine have also been validated clinically. A meta-analysis by Jiang et al. suggests that the perioperative administration of an appropriate dose of dexmedetomidine can reduce the release of inflammatory mediators and neuroendocrine hormones, maintain cerebral homeostasis, and alleviate ischemic brain injury, thereby exerting a protective effect on the brain [44]. In rats with myocardial ischemia–reperfusion, Dex treatment exerted cardiac protective effects across different reperfusion phases, primarily attributed to the modulation of mitochondrial K^+ channels with Dex activating mKATP and large-conductance calcium and voltage-activated potassium channels (BK_{Ca}) during early reperfusion and exclusively the BK_{Ca} channel during late reperfusion [45].

Yu et al. indicated that Dex enhanced mitochondrial function, reduced ROS production, and protected against myocardial damage by upregulating SLC7A11 (cystine transporter solute carrier family 7 member 11) and GPX4 (glutathione peroxidase 4), thereby inhibiting ferroptosis [46]. Zhou et al. found that administering dexmedetomidine perioperatively to patients undergoing heart valve replacement surgery could significantly reduce cTnI (cardiac troponin I) levels 24 h after CPB and lessen the inflammatory response [47]. Furthermore, Ji et al. demonstrated that the use of dexmedetomidine during the perioperative period can decrease the mortality rate, the occurrence of postoperative complications, and the rate of delirium in patients undergoing cardiac operations [48]. Thus, employing dexmedetomidine in the perioperative management of cardiac surgery patients is deemed essential. In rats with intestinal ischemia–reperfusion, Dex activated the Sirtuin 3 (SIRT3)-mediated PINK1/HDAC3 (histone deacetylase 3)/p53 (Tumor protein P53) pathway, preventing enteric glial cells' mitochondrial apoptosis and subsequently attenuating intestinal injury [49]. Similarly, Dex (1.2 μM) prevented intestinal apoptosis through p38-MAPK (p38 mitogen-activated protein kinases) activation, subsequently preventing ischemia–reperfusion-induced mitochondrial apoptosis and inflammatory responses [50]. In a renal ischemia–reperfusion model, Dex (25 μg·kg^{-1}, i.p.) amplified SIRT3 activity, curtailed the release of cytochrome c (Cyt C), and reduced CypD (Cyclophilin D) acetylation and mitochondrial apoptosis, providing renoprotection [51]. Cho et al. discovered that administering dexmedetomidine perioperatively to patients undergoing heart valve surgery significantly lowers the occurrence and intensity of acute kidney injury, thereby enhancing the outcomes for those who have undergone cardiac valve procedures [47]. For a rat model mimicking persistent postoperative pain, local Dex delivery (1 μg) inhibited dorsal root ganglion glial cell activation, attenuated mitochondrial swelling, and curbed lysosomal abundance, alleviating mirror pain symptoms [52]. Interestingly, the study of Abd-Elshafy et al. utilizing a randomized, prospective, double-blind design, demonstrated that incorporating dexmedetomidine into neuraxial blockade agents for patients undergoing thoracoscopic surgeries significantly decreases the rate of postoperative chronic pain [53]. The application of dexmedetomidine in neuraxial blockade for improving postoperative pain management is progressively becoming a focal point of interest. Dex has shown potential in augmenting cognitive function post-surgical anesthesia, likely by bolstering the expression of cyclooxygenase (COX), which not only protects the mitochondrial respiratory chain but also regulates mitochondrial energy metabolism [54]. Lin et al. found that Dex can induce oxidative stress and associated mitochondrial functional impairment linked to diabetic peripheral neuropathy by downregulating miR-34a and impeding the SIRT2 (Sirtuin 2)/S1PR1 (sphingosine-1-phosphate receptor 1) pathway [55].

In summary, Dex preserves mitochondrial quality by modulating various processes, including mitochondrial fission, fusion, biogenesis, autophagy, apoptosis, and opening of mitochondrial membrane channels, thereby safeguarding organ function during the perioperative period, mitigating pain, and enhancing postoperative cognitive function. However, it's important to note that for critically ill patients, the choice of sedative drugs during the perioperative period does not seem to alter the ultimate clinical outcomes. Furthermore, while a significant body of animal research suggests dexmedetomidine has promising organ-protective effects, extensive clinical trials are still required to validate these findings.

3 Effects and mechanisms of inhaled anesthetics on mitochondria

Inhaled anesthetics, such as sevoflurane, isoflurane, and desflurane primarily used for the induction and maintenance of general anesthesia, reduce presynaptic glutamate release and suppress its postsynaptic ion receptor activity, while augmenting GABA and glycine ion channel function in postsynaptic areas and increasing presynaptic GABA release. Inhaled anesthetics allow for enhanced muscle relaxation when paired with neuromuscular blockers; however, certain side effects such as postoperative cognitive dysfunction and nausea occur. The use of such anesthetics also causes environmental concerns as it can lead to pollution and pose occupational exposure risks.

3.1 Effects of sevoflurane on mitochondria

The effect of sevoflurane on mitochondrial quality is age-dependent. Brief exposure to sevoflurane induces age-related alterations in mitochondrial quality in the developing brain. This mechanism is pivotal for enhancing synaptic transmission. Sevoflurane exerts neurotoxic effects in neonates, while in adults, it exerts protective effects on mitochondria.

Exposure to 3% sevoflurane in neonatal mice for 2 h per day over three consecutive days induced neurotoxicity linked to GSK3β (glycogen synthase kinase-3 beta)/Drp1-mediated mitochondrial fission and heightened apoptosis [56]. One-day-old SD rats exposed to 4% sevoflurane showed an increase in intracellular calcium ions, which led to mitochondrial damage and subsequent hippocampal neuronal apoptosis [57]. In a similar study, 7-day-old SD rats exposed to 3% sevoflurane showed alternations in Drp1 and MFN2 expression, activating caspase-3 and triggering Cyt C release [58]. Moreover, Hogarth et al. found that early exposure to sevoflurane had detrimental effects on the maturing brain. Upon raising 7-day-old SD rats previously exposed to sevoflurane to adulthood, a 37% decrease in the average mitochondrial area was observed in the brain tissue, coupled with significant swelling of the internal crest structures [59]. These data suggest that sevoflurane-induced anesthesia during early development can trigger a lasting state of mitochondrial energy deficiency, leading to prolonged cellular functional impairment. This results in continued neuroinflammation and alterations in protein homeostasis, a pathological progression akin to chronic neurodegenerative changes [60]. Despite extensive clinical studies, there's no conclusive evidence that perioperative use of sevoflurane in neonates or children results in neurodevelopmental impairment. An international, multicenter, randomized, controlled trial conducted by McCann et al. demonstrated that, compared to awake-regional anesthesia, infants subjected to less than an hour of general anesthesia with sevoflurane do not exhibit altered neurodevelopmental outcomes at 5 years of age [61]. This absence of adverse effects may be due to the greater complexity and plasticity of the human brain. Nevertheless, the effects of sevoflurane on mitochondrial quality in adults are distinct from those in neonates. Adult mice exposed to 2.5% sevoflurane for 6 h exhibited increased expression of mitochondrial stress response proteins (UPRmt) such as ATF5 (activating transcription factor 5), HSP60 (heat shock protein family D), and HSP70 (70-kDa heat shock proteins), safeguarding protein-folding stability and augmenting mitochondrial function [62], a response not observed in neonates. Similarly, adult guinea pigs subjected to sevoflurane showed reduced mitochondrial calcium overload during ischemia, mitigating ischemia–reperfusion injury [63].

Unfortunately, despite the extensive use of sevoflurane over the years, there remains a notable gap in research regarding its effects on the prognosis and clinical outcomes in patients with ischemic injuries within clinical settings. With the ever-expanding array of anesthetic options, the objective extends beyond merely achieving effective anesthesia. There is a growing aspiration to tailor anesthetic choice to the patient's specific condition, with an ultimate aim of providing organ protection.

3.2 Effects of desflurane on mitochondria

The effects of desflurane on mitochondrial quality and learning and memory function markedly differ from those of isoflurane. The detrimental effects of desflurane on mitochondrial quality or learning and memory functions remain to be fully investigated [64].

In a cerebral ischemia–reperfusion model, desflurane maintained mitochondrial function, enhanced the activities of mitochondrial complexes I, III, and IV, limited mitochondrial swelling, and strengthened the mitochondrial membrane potential [65]. Similarly, cardiomyocytes showed the protective effects of desflurane exposure on mitochondrial quality. In a canine myocardial infarction model, desflurane diminished infarct size and offered cardiac protection by activating mKATP channels on the mitochondrial membrane, suggesting its potential benefits in perioperative care for patients with myocardial infarction [66]. Clinically, this has been substantiated by the findings of Landoni et al., who observed that among patients undergoing mitral valve surgery, the deployment of volatile anesthetics like desflurane did not lead to a significant reduction in myocardial injury measured by cardiac troponin release compared to those administered total intravenous anesthesia, such as propofol.

The myocardial troponin release levels between the two groups did not exhibit a significant difference. However, within the subgroup of patients with coexisting coronary artery disease, a notable decrease in the peak levels of cardiac troponin I was seen in patients anesthetized with desflurane as opposed to those given total intravenous anesthesia [67]. Thus, the selection of anesthetic agents for patients undergoing mitral valve surgery should be tailored, considering individual patient characteristics, such as the presence of coronary artery disease, to ensure the most effective myocardial protection for the specific patient demographics.

4 Effects and mechanisms of analgesics on mitochondria

Remifentanil, fentanyl, and ketamine are pivotal in perioperative pain management and anesthesia. Remifentanil and fentanyl act on the opioid receptors of the nervous system, mimicking endogenous opioids to achieve pain relief, sedation, and hypnotic effects [68]. Remifentanil is characterized by its quick onset and recovery. Conversely, ketamine, a non-opioid, blocks N-methyl-D-aspartate (NMDA) receptors, offering unique advantages in the management of certain types of pain that are unmanaged by opioids, such as neuropathic or cancer-related pain [69].

However, these drugs have some negative side effects. For instance, opioids are linked to respiratory depression, nausea, and vomiting [70], whereas ketamine can cause tachycardia, elevated blood pressure, and psycho-neurological effects such as hallucinations and disorientation [71]. Therefore, it is important to balance the benefits and risks of these drugs and closely monitor patients during treatment.

4.1 Effects of remifentanil and fentanyl on mitochondria

Remifentanil and fentanyl, two synthetic opioids commonly used in clinical settings, affect mitochondrial quality; however, this effect depends on the concentration and context of the application. At typical clinical concentrations, neither of these drugs impedes the function of brain mitochondria [72]. However, at above typical clinical concentrations (e.g., remifentanil > 10 μg/mL and fentanyl > 4 μg/mL), they can disrupt the mitochondrial respiratory chain, with fentanyl having a more pronounced effect on bioenergy than remifentanil. Delogu et al. demonstrated that prolonged fentanyl exposure altered mitochondrial membrane potential in blood lymphocytes, triggering apoptosis [73]. However, Yeager et al. discovered that intravenous administration of fentanyl at clinical doses does not lead to a reduction in lymphocytes; instead, it significantly increases the cytotoxicity of natural killer cells as well as the percentage of $CD16^+$ and $CD8^+$ cells in peripheral blood [74]. Therefore, for patients with compromised immune systems, the use of fentanyl should not be restricted due to concerns of immunosuppression. While Zamparelli et al. revealed that high-dose fentanyl impaired the mitochondrial respiratory chain in rat liver cells, thus affecting cellular energy metabolism [75].

Furthermore, Lu et al. found that remifentanil (1.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, iv) administered to rat models of opioid-induced hyperalgesia activated MCU channels on the mitochondrial membrane, elevating intracellular Ca^{2+} levels, which is linked to postoperative mechanical pain. This treatment has also been reported to elevate the levels of NMDA receptors and phosphorylated ERK, mitigated by the MCU antagonist Ru360 [76]. This demonstrates the therapeutic potential of targeting mitochondrial MCU to counter opioid-induced pain sensitization.

Additionally, remifentanil can exert protective effects, especially in organ function, during perioperative care. In rats with hepatic ischemia–reperfusion, Zhao et al. found that pretreatment with remifentanil (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, iv) prevented mitochondrial swelling, maintained membrane potential, and reduced inflammatory markers and oxidative stress, ultimately lowering liver cell apoptosis [77]. In a retrospective analysis conducted by Uchida et al., involving 4,502 patients who underwent craniotomies for intracranial aneurysm clipping, it was determined that remifentanil administration was associated with a reduction in in-hospital mortality rates [78]. Consequently, remifentanil is considered to significantly mitigate severe complications post-cerebral ischemia–reperfusion and enhance patient outcomes. Similarly, in rats with cardiac ischemia–reperfusion, Sheng et al. observed that remifentanil restored zinc ion concentrations in the heart, reduced mitochondrial ROS production, and enhanced cardiac function [79]. Hou et al. further emphasized remifentanil's role in cardiac protection, demonstrating its efficacy in preserving mitochondrial morphology and structure post-ischemia [80]. However, actual clinical studies have found that anesthesia with isoflurane combined with propofol and remifentanil in patients undergoing off-pump coronary artery bypass graft surgery did not show a statistically significant difference in postoperative adverse outcomes [81]. The discrepancy between clinical studies and basic research could be attributed to the fact that certain drugs used during surgery and anesthesia, as well as the surgical procedures themselves, may also impact cardiac function.

4.2 Effects of ketamine on mitochondria

The impact of ketamine on mitochondrial quality is multifarious, primarily manifested in its ability to lower mitochondrial membrane potential. Chang et al. reported that ketamine disrupts intracellular calcium mobilization and adenosine triphosphate (ATP) synthesis by attenuating the activity of mitochondrial complex I and destabilizing the cytoskeleton comprised of F-actin (filamentous actin) and microtubules, thereby leading to altered cellular stability and function [82]. Complementing these findings, Bai et al. found that ketamine-induced reductions in mitochondrial membrane potential correlate with increased Cyt C release, augmented mitochondrial fission, and enhanced ROS generation, with consequential effects ranging from neural stem cell proliferation in the short term to neuronal apoptosis with prolonged exposure [83]. These shifts in mitochondrial dynamics underscore the delicate balance ketamine imposes on cellular energy homeostasis. Further supporting this notion, Venâncio et al. observed that long-term low-dose ketamine administration in adult rats led to inhibited activity of mitochondrial complex I in liver cells, concomitant with a reduction in hepatic glycogen content, underscoring a systemic effect on energy reserves [84]. In a developmental context, Robinson et al. demonstrated that ketamine exposure (2 mM) in zebrafish embryos resulted in the downregulation of the mitochondrial ATP synthase subunit atp5α1 and an upregulation of atp5β and total ATP synthase protein levels, suggesting a compensatory mechanism in response to disrupted mitochondrial energy metabolism [85].

Ketamine's role extends beyond energy metabolism to the induction of oxidative stress and neurotoxicity. Dose-dependent study has linked ketamine exposure with increased ROS production and the differential expression of oxidative stress-related genes in human embryonic stem cells [86], while high-dose ketamine exposure (500 μM) has been shown to exacerbate ROS production leading to neuronal apoptosis [87]. Paule et al. conducted a study where ketamine anesthesia was administered intrauterinely to rhesus monkeys during the sensitive period of brain development on gestational 120–123 days. The findings revealed that exposure to ketamine anesthesia at this critical stage resulted in persistent impairments in cerebral function among primate subjects [88]. Despite these findings, the question of whether ketamine similarly affects brain development in human neonates and children continues to be a contentious issue in clinical settings. Nonetheless, under certain conditions, ketamine might exert antioxidative properties and potential antidepressant effects through the modulation of oxidative stress [89]. Rezin et al. demonstrated that ketamine (15 mg/kg) can improve activities of mitochondrial respiratory chain complexes compromised by chronic mild stress in an animal model of depression, revealing a nuanced role for ketamine in modulating oxidative stress responses [90].

The pro-apoptotic effects of ketamine are further elucidated by studies focusing on mitochondrial apoptosis pathways. Lee et al. reported ketamine's activation of the mitochondria-associated Caspase pathway, leading to cellular apoptosis [91], a finding echoed by Ye et al. who found a close association between mitochondrial p53 protein levels and ketamine-induced apoptosis [92].

In summary, the current body of research indicates that ketamine has a diverse impact on mitochondrial function, affecting cellular energy metabolism, inducing oxidative stress, and triggering apoptosis. These findings suggest a potential dual role for ketamine, where it could be neuroprotective or neurotoxic depending on the context, dose, and duration of exposure. The therapeutic implications of these effects, particularly in the context of neuropsychiatric disorders such as depression, are promising yet demand a thorough understanding of ketamine's multifaceted impact on mitochondrial dynamics.

5 Impact and mechanism of local anesthetics on mitochondria

Local anesthetics such as lidocaine, bupivacaine, and ropivacaine block sodium ion channels on nerve fibers, inhibiting pain signal transmission, reduce general anesthesia requirements during surgery, and assist in postoperative pain management. However, when misused or overdosed, local anesthetics can cause systemic toxicity, nerve damage, and local reactions [93].

5.1 Effects of lidocaine on mitochondria

Lidocaine induces mitochondrial apoptosis and increases intracellular Ca^{2+} concentrations, leading to mitochondrial dysfunction and amplifying apoptosis during hyperthermia through the mitochondria-dependent cysteine-aspartic acid protease pathway [94]. The pro-apoptotic effect of lidocaine is associated with reduced mitochondrial membrane potential and caspase-3 activation [95].

Lidocaine can alleviate cognitive deficits attributed to isoflurane anesthesia by counterbalancing the reduced activity of the mitochondrial respiratory chain complex caused by isoflurane [96]. Regrettably, current clinical research indicates that perioperative intravenous administration of lidocaine does not reduce postoperative cognitive decline [97]. Moreover, for diabetic patients, the use of high doses of lidocaine can lead to a decrease in cognitive function [98]. Additionally, lidocaine has been reported to enhance breast cancer treatment outcomes

by reducing the mitochondrial membrane potential in tumor cells, promoting Cyt C release, and inhibiting protein synthesis linked to mitochondria [96]. This finding has been applied in clinical research, with Badwe et al. discovering that peri-tumoral injection of lidocaine before breast cancer surgery significantly increases disease-free survival and overall survival and can prevent tumor metastasis [99].

As our understanding of lidocaine's mechanisms has evolved, its applications have extended well beyond its traditional use as a local anesthetic. Today, lidocaine is also utilized in treating ventricular arrhythmias, providing intravenous pain relief, and offering anti-tumor benefits as previously mentioned. The exploration of lidocaine in these non-traditional domains is crucial, not just for expanding the scope of current treatments but also for encouraging interdisciplinary collaboration and advancing the discovery of new therapeutic options.

5.2 Effects of bupivacaine on mitochondria

Bupivacaine inhibits lipid-based respiration in cardiac mitochondria, mainly by blocking acylcarnitine exchange, which reduces mitochondrial respiratory function. This highlights the clinical implication of local anesthetics' inhibitory effects on carnitine palmitoyltransferase [100]. Bupivacaine also elevates mitochondrial ROS production, which in turn stimulates the JNK (C-Jun N-terminal kinase) signaling pathway during bupivacaine-induced oxidative stress, enhancing superoxide dismutase (SOD2) transcription. The increased antioxidant function of SOD2 may be vital in counteracting bupivacaine-induced neurotoxic damage [101]. In various cell lines, bupivacaine has been reported to hinder the functions of mitochondrial respiratory chain complexes I and III [102], potentially inducing excessive activation of mitochondrial mPTP channels [103], which can lead to mitochondrial depolarization and cell apoptosis [104].

5.3 Effects of ropivacaine on mitochondria

The effects of ropivacaine on mitochondrial dynamics and functions have been well documented. In SH-5Y5Y neurons, ropivacaine disrupts mitochondrial dynamics, thereby reducing mitochondrial membrane potential and ATP production, a process reliant on the expression of Drp1 [105]. Yang et al. investigated the effects of ropivacaine on endothelial cells associated with human lung tumors and showed that ropivacaine inhibited mitochondrial respiratory chain complex II, suppressing both mitochondrial function and tumor angiogenesis, offering a novel theoretical perspective on the potential antitumor applications of ropivacaine [106]. Due to the local anesthetic toxicity of ropivacaine, various nanomaterials combined with ropivacaine have been developed to achieve the objectives of inhibiting tumor recurrence or providing long-term analgesia [107]. Niu et al. revealed that ropivacaine adversely affected mitochondrial biogenesis, manifested as deteriorated mitochondrial quality, a diminished ratio of mtDNA to nuclear DNA, decreased COX activity, and reduced expression of COX I within the mitochondria. These alterations imply that ropivacaine considerably influences cellular energy metabolism [108]. Moreover, ropivacaine has been shown to activate proteins related to mitochondrial apoptosis, such as caspase-3, affect the expression of mitochondrial proteins, notably Bcl-2 and apoptotic protease activating factor 1 (APAF-1) [109], and impede the functionality of mitochondrial STAT3 [110].

6 Conclusion and prospects

During the perioperative period, surgery and anesthesia induce significant stress, impacting patients' metabolic and immune states. Central to regulating metabolic responses and cellular functions such as apoptosis and signal transduction, mitochondria are vital for understanding the complex changes in perioperative patients. A better understanding of mitochondrial functions can help devise strategies to address challenges such as hypoxia and pain, enhancing cellular response during critical anesthetic events like myocardial infarction and shock.

Anesthetic can alter mitochondrial attributes, affecting energy metabolism and protein expression. Such modifications influence the clinical outcomes of perioperative patients (Fig. 1). However, these effects depend on various factors such as drug type, dosage, and patient health; therefore, comprehending how these drugs impact mitochondrial quality is crucial to improving perioperative care and clinical outcomes.

Nevertheless, numerous unresolved questions remain regarding the influence of anesthetic on mitochondrial quality and how these effects ultimately affect clinical outcomes. First, most studies have predominantly focused on in vitro cell models; hence, clinical evidence remains lacking. Second, the dose-response relationships of various anesthetics concerning mitochondrial quality have not been clearly defined. Previous studies have provided descriptive findings without fully investigating the underlying mechanisms, resulting in a plethora of contradictory conclusions that await further substantiation. Furthermore, current research is focused on short-term effects, and long-term clinical studies remain warranted to ascertain the sustained effects and clinical relevance of anesthetic drugs on mitochondrial quality. In addition, a cross-disciplinary

approach that combines techniques from molecular biology, cell biology, pharmacology, and clinical anesthesiology will provide a holistic and nuanced understanding of this field. Through these endeavors, we aim to attain a robust scientific foundation for optimizing perioperative management to enhance patient outcomes.

Abbreviations

ATP	Adenosine triphosphate
BK_{ca}	Large-conductance calcium and voltage-activated potassium channels
CLP	Cecal ligation and puncture
COX	Cyclooxygenase
CPB	Cardiopulmonary bypass
Cyt C	Cytochrome c
Dex	Dexmedetomidine
Drp1	Dynamin-related protein 1
ERK	Extracellular signal-regulated kinase
ETC	Electron transport chain
Fis1	Fission protein 1
GABA	γ-aminobutyric acid
HIF-1α	Hypoxia-inducible factor 1-alpha
MCU	Mitochondrial calcium uniporter
MFN2	Mitofusin-2
mKATP	Mitochondrial ATP sensitive potassium channels
mPTP	Mitochondrial permeability transition pore
mtDNA	Mitochondrial DNA
NMDA	N-methyl-D-aspartate
NSCs	Neural stem cells
OGD/R	Oxygen-glucose deprivation and reoxygenation
OXPHOS	Oxidative phosphorylation
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PINK1	PTEN-induced kinase 1
PRIS	Propofol infusion syndrome
ROS	Reactive oxygen species
SOD2	Superoxide dismutase

Authors' contributions

D.C.Y. wrote the manuscript and provided funding support. T.X.X. and L.R.X. conducted literature search, sorted relevant literature, and summarized the findings. H.H. and D.L. conducted manuscript revision and editing. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable

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Competing interests

The authors declare no competing interests.

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