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ROLE OF MITOCHONDRIAL DYSFUNCTION IN ANAESTHETIC-INDUCED NEUROTOXICITY: A SYSTEMATIC REVIEW

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ABSTRACT

General anaesthesia is broadly regarded as safe; however, increasing experimental and clinical evidence indicates possible long-term neurotoxic effects, especially in neonates, children, and the elderly. New research shows that mitochondria are the main players in neurotoxicity caused by anaesthetics. Mitochondrial function is essential for neurons because it makes ATP, buffers calcium, sends signals between neurons, and controls apoptosis. Sevoflurane, isoflurane, propofol, and ropivacaine are some examples of anaesthetics that can hurt mitochondrial respiration, lower membrane potential, raise the production of ROS, modulate calcium homeostasis, and change mitochondrial dynamics by causing too much fission through Drp1. These changes lead to synaptic dysfunction, problems with neurotransmitter release, and neuronal apoptosis, which all add to cognitive dysfunction after surgery and developmental neurotoxicity. Animal and cellular research has demonstrated age-dependent susceptibility, with developing brains being particularly prone due to elevated metabolic rates during synaptogenesis. Stress responses that engage NADPH oxidase and mitochondrial UPR may exacerbate oxidative damage. Consistent findings from clinical studies link repeated or prolonged exposures to neurodevelopmental risks. Mitochondrion-targeted interventions, encompassing antioxidants, mitophagy-inducing agents, and pharmacological modulators like dexmedetomidine, apocynin, and ciproxifan, have demonstrated potential in preclinical studies. Understanding the drug-specific actions of these agents in the realm of mitochondrial quality control is crucial for the development of safer anaesthetic protocols. This review is mostly about how problems with mitochondria can cause neurotoxicity from anaesthesia. It also stresses the need for more research into treatments that target mitochondria to improve neurological outcomes during the perioperative period.

KEYWORDS: neurotoxicity, sedatives, mitochondrial cytopathy, free radical toxicity, anaesthetic toxicity, cognitive defects,

1. INTRODUCTION

General anaesthesia is a highly significant element of medicine nowadays. It puts individuals in a state of reversible unconsciousness, pain alleviation, and muscle relaxation, which makes it possible to do challenging surgeries. People have believed for a long time that anaesthetics are safe and don't affect the nervous system in the long term. Still, more and more experimental and epidemiological research has raised concerns regarding the possible neurotoxic consequences of several anaesthetic drugs [1].

This case is particularly true for vulnerable groups like newborns, infants, and the elderly. Recent studies have demonstrated that exposing the brain to common anaesthetics during its early development might kill many neurons and produce cognitive issues that last a long time. Because of these results, it was necessary to do comprehensive research on the cellular mechanisms that make anaesthetics neurotoxic. More and more studies have shown that mitochondrial dysfunction is a major way that exposure to anaesthetics can damage neurons, leading to impaired energy production and increased oxidative stress, which contribute to neuronal death and long-term cognitive deficits [2].

Mitochondria are crucial for how neurons work. They control how much calcium there is in cells, produce and break down reactive oxygen species (ROS), and start signalling pathways that cause cells to die. Problems with mitochondria are especially detrimental for neurons because they need a lot of energy and employ oxidative metabolism.

Even little changes to the shape of mitochondria can stop synaptic transmission, make neurons less flexible, and cause programmed cell death [3]. Recent studies indicate that specific anaesthetics, including isoflurane, sevoflurane, propofol, and local anaesthetics such as ropivacaine, can directly impair mitochondrial integrity. These medications create too many ROS, change the potential of the mitochondrial membrane, alter the way mitochondria split and fuse, and start apoptotic signalling pathways that activate caspases [4, 5].

It is very important to understand how mitochondrial dysfunction contributes to anaesthetic-induced neurotoxicity to come up with ways to ease neurological problems caused by anaesthesia. Formulating strategies to alleviate neurological illness influenced by anaesthesia and consolidating the pioneer factors of mitochondrial dysfunction are indeed.

This scoping review looks into how anaesthetic drugs affect the structure and function of mitochondria, what it means for neurological health, and potential treatments that target mitochondrial pathways. It does this by combining the most recent findings from both clinical and experimental trials.

2. METHODOLOGICAL APPROACH

This review was conducted using a structured literature search of PubMed, Scopus, and Web of Science databases up to 2025. Keywords included "anaesthetic neurotoxicity," "mitochondrial dysfunction," "oxidative stress," and "neuronal apoptosis."

Both experimental (in vitro, in vivo) and clinical studies were included. Studies were screened based on relevance to mitochondrial mechanisms underlying anaesthetic exposure. Duplicate and non-English articles were excluded. Data were synthesised qualitatively, focusing on oxidative stress, mitochondrial dynamics, and apoptosis pathways. Study quality was appraised using standard risk-of-bias principles. Findings were integrated to provide a mechanistic overview.

2.1 Assessment of Bias Risk

Standard risk-of-bias criteria suitable to research design were used to assess the quality of included studies. Clinical trials were evaluated using Cochrane risk-of-bias domains, such as randomization, allocation concealment, blinding, and outcome reporting; animal studies were evaluated using SYRCLE standards.

Due to insufficient reporting of randomization and blinding protocols, the majority of preclinical research showed a moderate risk of bias.

Despite constraints including limited sample numbers and short follow-up periods, clinical investigations demonstrated comparatively lower risk. Overall, the robustness and generalizability of the findings may be impacted by methodological constraints and study design heterogeneity.

2.2 Mitochondrial Function in Neurons

Mitochondrial metabolism is particularly crucial for neurons because they demand a lot of energy and can't break down glucose very well. Oxidative phosphorylation is how mitochondria create ATP. This ATP supplies energy to the cycling of synaptic vesicles, the release of neurotransmitters, and the ion pumps that keep membrane potentials steady.

Fig. 1 demonstrates the key roles of mitochondrial functional features in Neurons. Mitochondria not only create energy, but they also control neurons to perform multitudinous crucial functions, such as maintaining calcium homeostasis (the regulation of calcium ion concentrations), monitoring ROS, signalling for apoptosis (programmed cell death), facilitating synaptic plasticity (the ability of synapses to strengthen or weaken over time), and pruning (the

process of eliminating unnecessary synapses).

Along with key mechanisms of neurotransmitter metabolism, mitochondria act as key sites for neurotransmitters' (NTs) synthesis, specifically for glutamate, which is an excitatory neurotransmitter, and GABA, which is an inhibitory neurotransmitter, that mediate local protein translation and RNA transport to ensure sufficient proteins are synthesised at branch points and synaptic locations [6].

Maintaining the ionic gradients between the synaptic clefts by fuelling the essential ionic pumps like Na+/K+ ATPase for providing energy to the brain maintains resting membrane potential and preserves neuronal excitability. Handling neurodevelopmental procedures drives required cytoskeletal changes (LTP and LTD) simultaneously, which are crucial for proper neuronal development and function and ultimately influence synaptic plasticity and overall brain health. Mitochondrial quality control processes like fission, fusion, and mitophagy keep mitochondria healthy by getting rid of damaged organelles and changing mitochondrial networks to fit the needs of the cell. When these processes go wrong, it can cause energy failure, oxidative damage, and neuron death [7]. This feature makes mitochondria a main target for cellular damage caused by anaesthetics.

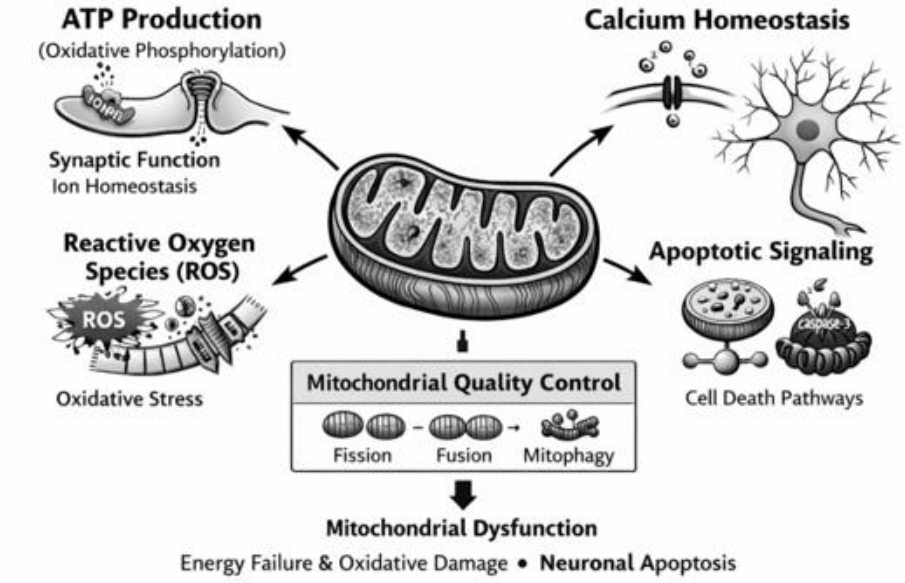

Figure 1: Mitochondrial functional features in Neurons

3. MECHANISMS OF ANAESTHETIC-INDUCED MITOCHONDRIAL DYSFUNCTION

3.1 Oxidative Stress and ROS Production

One of the first and most consistent effects of anaesthesia is that the body creates more reactive oxygen species. When there is too much ROS, it oxidises mitochondrial DNA, proteins, and lipids, which makes it harder for mitochondria to breathe. Research examining exposure to isoflurane indicates that brain cells produce significant amounts of ROS. Researchers have found that hydrogen-rich saline can lower oxidative stress. This suggests that ROS represent a big part of the harm that anaesthetics do to mitochondria [8]. Hydrogen therapy worked as a special antioxidant by reducing damage from oxidation, keeping the mitochondrial membrane stable, and stopping the activation of caspase-3 in brain cells. Likewise, ROS produced by NADPH oxidase in the hippocampus has been linked to cognitive deficits following surgery. When this enzyme system is turned on, it increases oxidative stress further and helps microglial cells become active. This makes neurons even more damaged [9].

3.2 Mitochondrial Membrane Potential and ATP Depletion

The mitochondrial membrane potential plays a crucial role in the production of ATP through oxidative phosphorylation. Some anaesthetic agents have been reported to interfere with the mitochondrial membrane potential, leading to a decrease in the production of ATP. Isoflurane exposure has been reported to cause a decrease in mitochondrial membrane potential and intracellular ATP levels in neuronal cells. A reduction in cellular ATP levels undermines synaptic function and neuronal viability. The decrease in ATP production also causes the opening of mitochondrial permeability transition pores (mPTP), leading to a compromise in mitochondrial integrity and apoptosis [10].

3.3 *Mitochondrial Dynamics: Fission and Fusion*

Cell organelles, especially neurons, are constantly changing shape through processes called fission and fusion. These processes are responsible for the size, number, and function of mitochondria. However, if these processes are disrupted, mitochondria can be fragmented, and cells can fail to function properly. Recent research has shown that dynamin-related protein 1 (Drp1) plays a crucial role in causing excessive fission in mitochondria after being subjected to anaesthesia. In old mice, surgery and anaesthesia cause disruptions in how mitochondria divide and fuse. These disruptions are responsible for cognitive problems after surgery [11]. Exposure to propofol in neurons derived from human stem cells causes fragmentation of mitochondria through Drp1-dependent mechanisms. Pharmacological inhibition of mitochondrial division through Mdivi-1 showed its ability to protect neurons from anaesthetic-induced cytotoxicity, thus confirming its role in neurotoxicity [12].

3.4 Apoptotic Signalling Pathways

Mitochondrial failure typically initiates intrinsic apoptotic pathways. Anaesthetics cause cytochrome c to leave the mitochondria, which may start the process of activating caspase-3, an important enzyme that kills cells during apoptosis. The lab tests reveal that when isoflurane is put on neural cells, it makes caspase-3 much more active. This is linked to problems with mitochondria, oxidative stress, and lower amounts of ATP. Developing mice exposed to sevoflurane also experience neuronal death and cognitive impairments, indicating that anaesthetics activate mitochondrial pathways [13, 14, 15].

4. AGE-DEPENDENT VULNERABILITY

One of the most significant findings in anaesthetic neurotoxicity research is the age-dependent susceptibility of the brain.

4.1 *Stage of brain development:*

The brain is especially sensitive to mitochondrial dysfunction while it is still growing because synaptogenesis and neuronal maturation require a lot of energy. Experiments on newborn rodents show that exposure to common anaesthetics can cause widespread neurodegeneration during important times in brain development. These changes could cause long-term problems with learning and memory, which suggests that damage to mitochondria during development can have long-lasting effects [16].

4.2 *Stage of aged brain:*

Older adults also show a higher risk of mitochondrial dysfunction caused by anaesthesia. As people grow older, their mitochondrial quality control systems get worse. This process makes it harder for the brain to cope with oxidative stress and metabolic problems. Studies on animals show that anaesthesia in older mice changes the way mitochondria work and makes them more likely to have cognitive problems after surgery [17].

5. MITOCHONDRIAL STRESS PATHWAYS

5.1 *NADPH oxidase activation and mitochondrial unfolded protein response*

In the central nervous system, NADPH oxidase is a big source of ROS. This enzyme complex's activation has been shown to help microglial activation and inflammatory responses after anaesthesia. Researchers have linked increased ROS production in older mice to issues with hippocampal interneurons and cognitive impairment [18]. The mitochondrial unfolded protein response (UPRmt) is a cellular defence system that kicks in when mitochondria are under stress and starts repair pathways. But if this response is turned on too often after being exposed to anaesthesia, it could cause long-lasting changes in how mitochondria work and how neurons use energy [19].

6. NEUROPROTECTIVE STRATEGIES TARGETING MITOCHONDRIA

Given the central role of mitochondria in anaesthetic neurotoxicity, several therapeutic approaches targeting mitochondrial pathways have been explored. Fig. 2 depicts the Anaesthetic-induced mitochondrial dysfunction and neurotoxicity with mitochondrial targets and protective treatments. Antioxidants are one of the best ways to reduce oxidative stress caused by anaesthesia. Hydrogen-rich saline has been shown to be able to protect neurons from damage caused by isoflurane by lowering the levels of reactive oxygen species (ROS) and keeping mitochondria working properly. Melatonin has also been shown to help older mice think better after they are given sevoflurane. This neuroprotective effect seems to involve turning on the Nrf2 signalling pathway, which boosts antioxidant defences and lowers ferroptosis [20].

Mitochondrial-targeted antioxidants (mtAOx) such as MitoQ (a coenzyme Q10 derivative of ubiquinone), SkQ1 (10-(6'-plastoquinonyl) decyltriphenylphosphonium), and SkQR1 (similar to SkQ1 but conjugated with rhodamine 17) are involved in mechanisms to combat ROS. They act as

antioxidants to stop apoptosis that depends on mitochondria, which makes brain injury and swelling less severe. Mitochondrial-Targeted Peptides for Cardiolipin Stabilisation includes Elamipretide (SS-31) to prevent the release of pro-apoptotic factors like cytochrome C. This molecule binds to the cardiolipin and integrates the mitochondria structurally and functionally. Steps include mitochondrial membrane stabilisation, inhibiting the opening of the mitochondrial permeability transition pore, and increasing ATP synthesis. Another notable mechanism is that it prevents the ROS-induced peroxidation of cardiolipin [21, 22, 23]. DrP1 inhibitors like Mdivi-1 and mitophagy inducers like rapamycin execute the protective mechanisms, such as reducing excessive fission and maintaining the structural integrity of mitochondria, apoptosis inhibition, and the pruning of damaged mitochondria, which protect and promote neural health [24].

Pharmacological agents that mediate the restoring functions of mitochondria are acetyl-L-carnitine, methylene blue and dexmedetomidine (DEX). To facilitate the entry of fatty acids into the mitochondria, it aids energy production by rerouting the electrons directly from NADH to cytochrome C, promoting mitochondrial action and ROS reduction specifically during ischaemic conditions. DEX, a selective alpha subunit 2 adrenergic agonist, inhibits anaesthetic-induced apoptosis via facilitating the AO effect on mitochondria and upregulating mitochondrial fusion proteins like MFN1/2 and OPA1 [25, 26]. Histamine H3 receptor antagonists such as ciproxifan have also demonstrated protective effects against anaesthetic-induced cognitive impairment in animal models [27]. The emerging therapeutic strategies in today's scenarios are mitochondrial transplantation, iron chelators, and anaesthetic reconditioning (low-dose exposure to isoflurane and xenon).

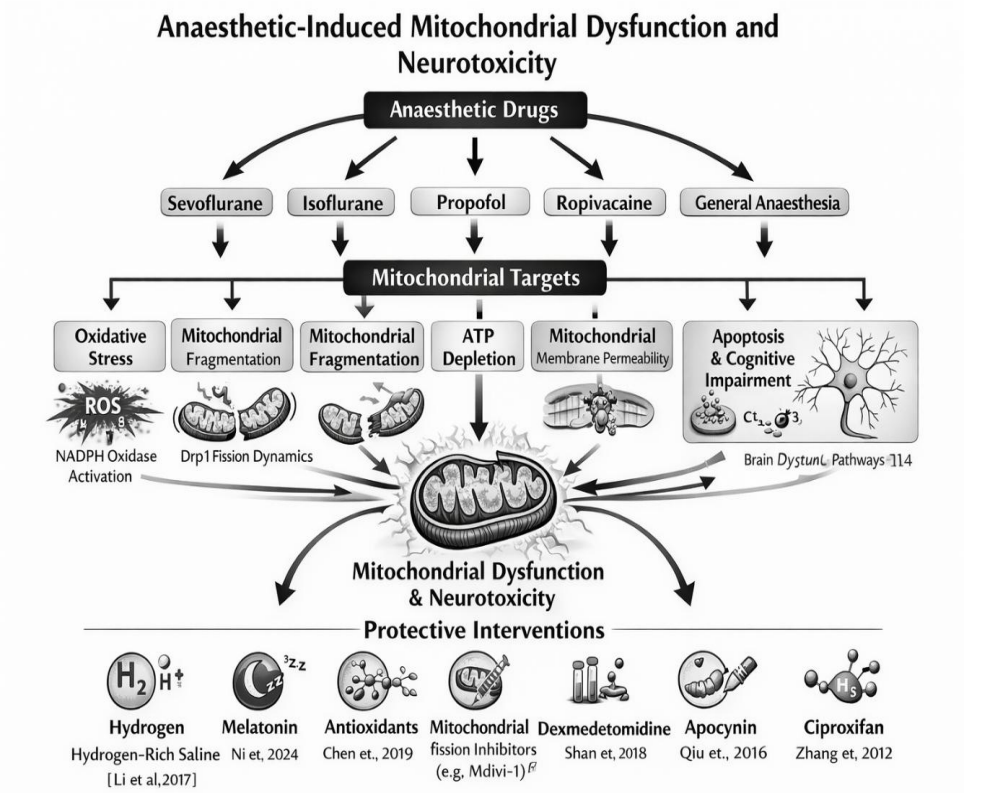

Figure 2: Anaesthetic-induced mitochondrial dysfunction and Neurotoxicity

7. CLINICAL EVIDENCE

While experimental evidence robustly endorses mitochondrial mechanisms of anaesthetic neurotoxicity, clinical findings are inconclusive. Extensive observational studies have indicated correlations between early exposure to anaesthesia and subsequent cognitive or behavioural deficits. Nevertheless, randomised clinical trials have yielded less definitive outcomes. The GAS trial, which compared general anaesthesia with awake regional anaesthesia in infants undergoing surgery, found no significant difference in neurodevelopmental outcomes at two years of age. These results suggest that being exposed to anaesthesia once or for a short time may be fairly safe, but being exposed to it more than once or for a long time may be more dangerous. More long-term studies are needed to figure out what mitochondrial dysfunction means for neurological outcomes related to anaesthesia.

Table 1: Mechanistic features of anaesthetic-induced mitochondrial abnormalities and neurotoxic events

S. no.	Study	Anaesthetic Intervention	Model	Mitochondrial Mechanism	Key Findings	References
1	Jevtovic-Todorovic et al. 2003	Isoflurane, Nitrous oxide, Midazolam	Neonatal rat brain	Mitochondrial apoptosis pathways	Early anaesthetic exposure caused widespread neuronal degeneration and long-term learning deficits.	28
2	Lu et al. 2020	Surgery + Anaesthesia	Aged mice	Mitochondrial fission/fusion imbalance	Anaesthesia disrupted mitochondrial dynamics in the brain and contributed to postoperative delirium.	29
3	Twaroski et al. 2015	Propofol	Human stem cell–derived neurons	Drp1-mediated mitochondrial fragmentation	Propofol induced mitochondrial fission and neuronal cell death via mitochondrial dysfunction.	12
4	Chen et al. 2019	Ropivacaine	Neuronal cells	Drp1 activation and mitochondrial dysfunction	Ropivacaine caused mitochondrial fragmentation and neurotoxicity mediated by Drp1 signalling.	30
5	Shan et al. 2018	Sevoflurane + Dexmedetomidine	Developing the rat brain	Autophagy and mitochondrial apoptosis signalling	Dexmedetomidine protected against sevoflurane-induced neurotoxicity by regulating mitochondrial pathways.	31
6	Li et al. 2017	Isoflurane + Hydrogen-rich saline	Human neuroglioma cells & mice	Oxidative stress, mitochondrial permeability transition, ATP depletion	Hydrogen-rich saline reduced ROS, preserved mitochondrial function, and improved cognitive outcomes.	8
7	Qiu et al. 2016	Anaesthesia/surgery	Aged mice	NADPH oxidase-derived ROS	Increased hippocampal ROS promoted microglial activation and cognitive dysfunction.	32
8	Lee et al. 2019	General anaesthesia	C. elegans & mouse brain	Mitochondrial unfolded protein response	Anaesthesia activated mitochondrial stress responses, leading to long-term mitochondrial changes.	33
9	Zhang et al. 2012	Isoflurane + Ciproxifan	Mouse model	Oxidative stress and synaptic dysfunction	Histamine H3 antagonist ciproxifan reduced anaesthetic-induced cognitive impairment.	34
10	Qiu et al. 2016	Anaesthesia	Aged mice	ROS-mediated interneuron dysfunction	NADPH oxidase-mediated oxidative stress caused hippocampal neuronal phenotype loss.	35
11	Xu et al. 2016	Isoflurane + Mdivi-1	Mammalian neurons	Inhibition of mitochondrial fission	Mdivi-1 protected neurons by preventing excessive mitochondrial fragmentation.	36
12	Davidson et al. 2016 (GAS Trial)	General anaesthesia vs regional	Human infants	Clinical outcomes study	No significant neurodevelopmental difference at 2 years after a single short anaesthesia exposure.	37
13	Flick et al. 2011	Multiple anaesthetic exposures	Human cohort	Developmental neurotoxicity risk	Repeated anaesthesia exposure is associated with increased cognitive and behavioural deficits.	38
14	Sun et al. 2016	Astragaloside IV + anaesthesia	Neonatal rat brain	Anti-apoptotic mitochondrial protection	Astragaloside IV reduced anaesthetic-induced neuronal apoptosis.	39
15	Zhang et al. 2013	Sevoflurane	Young mice	Caspase-mediated apoptosis	Sevoflurane induced neuronal apoptosis and cognitive impairment in developing brains.	40
16	Ni et al. 2024	Sevoflurane + Melatonin	Aged mice	Nrf2 signalling and ferroptosis regulation	Melatonin reduced oxidative stress and improved learning and memory via mitochondrial protection.	20

Table 1 and 2 Explains the in vitro, in vivo, and clinical trials of anaesthesia-induced toxicity on varied ranges. Every anaesthetic agent has its own futuristic mechanism to mediate mitochondrial dysfunction, which then leads to neurotoxic events. So, analysing the mode of action of anaesthetics is vital to tackle precise treatments for amelioration and protection of neural cells.

Table 2 : Vote-counting synthesis of mitochondrial mechanisms in anaesthetic-induced neurotoxicity

Mechanism	No. of Studies Supporting	Study Types (In vitro / In vivo / Clinical)	Overall Direction of Effect
Oxidative stress (ROS ↑)	10–12	In vitro, In vivo, Limited clinical	Consistent increase
ATP depletion / mPTP opening	6–8	In vitro, In vivo	Decrease in ATP
Mitochondrial fission (Drp1 ↑)	5–7	In vitro, In vivo	Increased fragmentation
Apoptosis (caspase activation)	8–10	In vitro, In vivo	Increased neuronal death
NADPH oxidase activation	3–5	In vivo	Increased ROS production
UPRmt activation	2–3	In vivo	Stress response activation
Clinical cognitive impairment	4–6	Clinical	Mixed / inconclusive

8. FUTURE RESEARCH DIRECTIONS

Despite significant progress, certain questions remain unanswered. To begin with, more research needs to be done to find out exactly what the anaesthetics do to the mitochondria that makes them stop working. This will help make anaesthesia safer. Second, biomarkers that can find the first signs of mitochondrial problems in people who are under anaesthesia will be useful for finding people who are likely to develop neurological disorders. Thirdly, further research is required to ascertain whether therapies that have proven effective in experimental models will translate to efficacy in real-world applications. Antioxidants and genes are two new treatments that will help protect neurons from the effects of anaesthesia.

9. CONCLUSION

There is increasing evidence that mitochondrial dysfunction is a significant contributor to neurotoxicity induced by anaesthesia. Anaesthetic drugs can disrupt mitochondrial respiration, elevate oxidative stress, disturb mitochondrial dynamics, and activate apoptotic pathways. All of these things can damage neurons and make thinking less clear. Experimental research indicates that these mitochondrial dysfunctions impact developing and ageing brains more significantly than other brain types. Clinical evidence remains inconclusive; however, repeated or prolonged exposure to anaesthesia may increase the risk of neurological impairment. Drugs that target mitochondria, such as antioxidants, drugs that alter mitochondrial movement, and neuroprotective drugs, have shown promise in studies not yet conducted in humans, indicating potential therapeutic avenues for improving outcomes in patients undergoing anaesthesia and those with neurological problems. We need to learn more about mitochondrial biology in the context of anaesthesia to make anaesthesia safer and help patients with neurological problems.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Both the authors have significantly contributed

AI USE STATEMENT

The author used the tools named Grammarly and QuillBot for a specific purpose, e.g., grammar checking and improving sentence clarity. The author reviewed and edited the output and takes full responsibility for the final content.

ABBREVIATIONS

ROS - Reactive Oxygen Species
NADPH – Nicotinamide adenine dinucleotide phosphate
ATP – Adenosine triphosphate
NTs – Neurotransmitter
GABA – Gamma-aminobutyric acid
LTP – Long-Term Potentiation
LTD – Long-Term Depression
mPTP - mitochondrial permeability transition pores
Drp1 – dynamic-related protein 1
Midivi-1 – mitochondrial division inhibitor 1
UPRmt - mitochondrial unfolded protein
Nrf2 – nuclear factor erythroid-related factor 2
mtAOx - Mitochondrial-targeted antioxidants
MitoQ - Coenzyme Q
SkQ1 - (10-(6'-plastoquinonyl) decyltriphenylphosphonium)
SkQR1 – 10-(6'-Plastoquinyl)decylrhodamine 1

DEX – Dexmedetomidine
MFN1/2 – Mitofusin 1 and 2
OPA1 – Optic Atrophy 1
GAS-Trial – General Anaesthesia compared to Spinal Anaesthesia

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