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Anesthetic Agents and Mitochondrial Function A Comprehensive Review of Cellular Bioenergetics and Clinical Implications

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Abstract — General anesthetic agents have traditionally been understood to function by modulating synaptic receptors. However, emerging evidence highlights mitochondria as a critical, non-canonical target. A comprehensive synthesis of these interactions and their clinical implications is essential for advancing perioperative safety. This narrative review aims to provide a comprehensive analysis of the molecular interactions between common anesthetic agents and mitochondrial function, bridging the mechanisms of cellular bioenergetics with relevant clinical outcomes. A literature search was conducted across major databases, including PubMed, Scopus, and Web of Science, to synthesize and interpret findings from *in vitro*, *in vivo*, and clinical studies published between January 2000 and August 2025. Our synthesis reveals that anesthetics directly modulate the electron transport chain, leading to a dual-edged production of reactive oxygen species (ROS) that can be either protective (preconditioning) or damaging (oxidative stress). We find that agents exhibit distinct mitochondrial profiles: sevoflurane often confers protection, propofol shows dose-dependent toxicity linked to bioenergetic failure, and dexmedetomidine acts as a mito-protective adjunct. These interactions disrupt mitochondrial dynamics and can culminate in a "bioenergetic crisis" at the synapse, where energy demand is increased while mitochondrial ATP supply is compromised. Viewing anesthetics as potent mitochondrial modulators is crucial for the evolution of anesthesiology. This perspective shifts the paradigm towards personalized anesthetic strategies based on a patient's underlying mitochondrial vulnerability. We conclude that future research should focus on developing non-invasive biomarkers of mitochondrial health and creating "mito-sparing" anesthetic protocols to improve patient safety and long-term outcomes.

Keywords — *anesthetic agents; mitochondrial function; cellular bioenergetics; oxidative stress*.

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INTRODUCTION

General anesthesia represents a fundamental pharmacological intervention that has revolutionized modern medicine, enabling complex and invasive surgical procedures by reversibly eliminating patient consciousness and pain sensation [1]. Since its inception, the evolution of anesthetic agents has focused on enhancing safety, efficacy, and predictable pharmacokinetic profiles [2]. The primary mechanism of action has traditionally been attributed to interactions with specific molecular targets on neuronal membranes; for instance, electrophysiological data consistently demonstrate that volatile anesthetics like isoflurane can prolong the duration of GABA-A receptor-mediated inhibitory postsynaptic currents (IPSCs) by two- to threefold, thereby potently suppressing neuronal excitability [3]. However, this perspective is incomplete, as a growing body of evidence indicates that the pleiotropic effects of anesthetics extend to the subcellular level, where fundamental metabolic functions are governed [4]. A more holistic understanding of how these agents affect cellular physiology beyond the synapse is now a critical area of active scientific investigation, a shift driven by clinical observations not fully explained by synaptic mechanisms alone [5].

At the heart of cellular metabolism are mitochondria, dynamic organelles essential for eukaryotic life, often termed the cell's "powerhouses" [6]. Their unique structure, featuring a folded inner membrane that forms cristae, hosts the vital process of oxidative phosphorylation (OXPHOS), which generates over 90% of cellular ATP [7]. This process is executed by the electron transport chain (ETC), a series of protein complexes that sequentially transfer electrons and pump protons to create an electrochemical gradient; studies by Mitchell revealed that this gradient can establish a membrane potential of up to -180 mV,

which serves as the primary driving force for ATP synthase [8]. Beyond energy production, studies employing fluorescent calcium imaging have demonstrated that mitochondria can sequester large cytosolic calcium loads, acting as crucial buffers that prevent calcium toxicity during high-intensity cellular signaling [9]. Consequently, mitochondrial functional integrity, evidenced by a high respiratory control ratio (typically >10 in healthy mitochondria), is an absolute prerequisite for cell survival and function, particularly in tissues with high energy demands [10].

The nexus between anesthetic agents and mitochondrial function becomes particularly relevant when considering the primary target of anesthesia: the brain [11]. Data from positron emission tomography (PET) imaging studies consistently show that while comprising only 2% of body mass, the brain accounts for approximately 20% of the body's total resting oxygen and glucose consumption, highlighting its exceptionally high basal metabolic rate [12]. This ATP-dependent energy is vital for neurons, with quantitative data estimating that the Na+/K+-ATPase pump alone consumes 40-60% of all ATP produced in the brain simply to maintain the ion gradients required for action potentials and synaptic transmission [13]. It logically follows that pharmacological agents designed to profoundly suppress neuronal activity would also interact, directly or indirectly, with the bioenergetic machinery that fuels this activity; a hypothesis substantiated by findings that cerebral oxygen consumption decreases significantly (by up to 50%) during general anesthesia [14]. This premise forms the foundation of a rapidly expanding research field exploring mitochondria as significant non-synaptic targets of anesthetic agents [15].

[4] The direct interaction between anesthetics and the mitochondrial apparatus has been extensively documented through both *in vitro* and *in vivo* research data [16]. For example, research by Schaefer et al. (2008) using mitochondria isolated from rat brains demonstrated that isoflurane at clinically relevant concentrations (1-2 MAC) inhibits Complex I activity by 25-30%, significantly impairing NADH-linked respiration [17]. Meanwhile, studies on HepG2 cell cultures revealed that a 24-hour exposure to 50 μM propofol led to a 40% decrease in mitochondrial membrane potential and a 60% depletion of cellular ATP [18]. In addition to direct inhibition, some agents can act as mild uncouplers; research by Branca et al. (1991) on liver mitochondria found that halothane increased the rate of oxygen consumption without a corresponding synthesis of ATP, a classic hallmark of uncoupling [19]. An unavoidable consequence of such ETC disruption is an increase in superoxide production, with studies using mitochondria-specific probes like MitoSOX indicating a 2- to 4-fold increase in ROS generation in cells exposed to volatile anesthetics compared to controls [20].

The impact of anesthetic agents on mitochondria extends beyond bioenergetics to other equally critical functional aspects [21]. Mitochondrial dynamics, a continuous cycle of fusion and fission, are essential for maintaining a healthy mitochondrial population [22]. Microscopy data from primary hippocampal neurons exposed to sevoflurane have shown a significant upregulation of the pro-fission protein Drp1 and downregulation of the pro-fusion protein Mfn2, which morphologically resulted in a 50% reduction in average mitochondrial length and an increased number of fragmented mitochondria [23]. Furthermore, anesthetics can modulate the sensitivity of the mitochondrial permeability transition pore (mPTP); laboratory studies indicate that some volatile anesthetics can lower the calcium threshold required to trigger mPTP opening by 30-40%, particularly under conditions of oxidative stress, thereby increasing cellular vulnerability to necrotic death [24]. This mPTP opening was verified through mitochondrial swelling assays and calcein release, which directly measure the permeabilization of the inner mitochondrial membrane [25].

The clinical implications of this anesthetic-induced mitochondrial dysfunction are extensive and are supported by a wealth of observational and translational data [26]. Systemically, bioenergetic impairment may contribute to ischemia-reperfusion injury; animal models have shown that administering volatile anesthetics prior to ischemia can reduce myocardial infarct size by up to 50% a protective phenomenon known as anesthetic preconditioning mediated by mitochondrial modulation. However, prolonged exposure can abolish this effect and become toxic [27]. Clinical data from large cohort studies, such as the

ISPOCD1 study, revealed an incidence of postoperative cognitive dysfunction (POCD) of 25.8% in patients over 60 one week after major surgery, and subsequent translational research by Xie et al. linked this to increased β-amyloid deposition in the brains of anesthetized animal models, a process known to be exacerbated by mitochondrial oxidative stress [28]. Moreover, studies in aged animals demonstrate that a single anesthetic exposure can cause prolonged neuroinflammation and memory deficits not seen in younger counterparts, a phenomenon linked to an age-related decline in mitochondrial respiratory capacity [29]. Given this complexity, a comprehensive review is urgently needed to synthesize current knowledge, identify research gaps, and provide evidence-based guidance for safer clinical practice [30].

MATERIALS AND METHOD

Study Approach

This study was conducted as a narrative review, aiming to provide an integrative overview of the interactions between anesthetic agents and mitochondrial function. The approach focuses on bridging the findings from fundamental cellular bioenergetics with their broader clinical implications [31]. The methodology combines literature synthesis, secondary data analysis, and mechanistic interpretation of existing experimental (both *in vitro* and *in vivo*) and relevant clinical studies to construct a comprehensive understanding of the topic.

Data Collection

Scientific articles, original research papers, and reputable reviews published between January 2000 and August 2025 were retrieved from major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. This systematic search strategy is essential for ensuring comprehensive coverage of the available literature [32]. Keywords used for the search, both individually and in combination, included: “anesthetic agents”, “mitochondrial function”, “sevoflurane”, “isoflurane”, “propofol”, “cellular bioenergetics”, “oxidative phosphorylation”, “electron transport chain”, “mitochondrial dynamics”, “mitochondrial permeability transition pore”, “reactive oxygen species”, “anesthetic preconditioning”, and “perioperative organ injury”. Additionally, clinical trial registries such as ClinicalTrials.gov were reviewed to identify clinical studies assessing organ protection or dysfunction related to anesthetic choice.

Selection Criteria

Studies were selected based on their relevance to a set of predefined inclusion and exclusion criteria to ensure the focus and quality of the review [33]. Inclusion criteria were: (1) identification of direct molecular interactions between anesthetic agents and mitochondrial components; (2) investigation of anesthetic effects on key mitochondrial functions; (3) exploration of impacts on mitochondrial dynamics and quality control; and (4) studies linking these mitochondrial mechanisms to clinical phenomena. Studies focusing exclusively on local anesthetics, those where mitochondrial effects were only speculated without direct measurement, or articles such as case reports and editorials without primary data were excluded from this review.

Data Analysis

The collected data were analyzed qualitatively using a thematic synthesis approach, allowing for the identification and categorization of key concepts across multiple studies [34]. Findings were thematically categorized based on key mechanistic domains: (1) direct effects on the Electron Transport Chain and oxidative phosphorylation; (2) modulation of mitochondrial dynamics and quality control pathways; (3) impact on reactive oxygen species (ROS) production and cellular redox state; and

(4) translation to clinical outcomes, including both organ protection and toxicity. Results from *in vitro*, *in vivo*, and human studies were comparatively analyzed to identify consistent patterns, dose-dependent effects, and existing knowledge gaps.

Limitations

This study acknowledges the limitations inherent to a narrative review format. Unlike systematic reviews, narrative reviews can be susceptible to selection bias and do not involve a quantitative meta-analysis, which may limit the generalizability of the conclusions [35]. The heterogeneity of experimental models, anesthetic concentrations, and exposure durations across studies also presents a challenge for direct comparison. Nevertheless, a rigorous effort was made to include recent and high-impact studies to ensure a comprehensive and balanced coverage of the topic.

RESULTS AND DISCUSSION

The findings from this comprehensive review collectively compel a paradigm shift in our understanding of anesthesiology, moving from a purely synaptocentric model to an integrated, neuro-bioenergetic framework. The literature analysis confirms that anesthetic agents are not merely central nervous system depressants but are potent modulators of mitochondrial function, affecting these organelles with a specificity and potency comparable to their classic synaptic targets [36]. This synthesis reveals that mitochondrial effects are not incidental side effects but rather a fundamental component of the anesthetic mechanism of action, with profound implications for patient safety and perioperative outcomes. This new perspective positions the mitochondrion as a central arena where the balance between the protective and toxic effects of anesthesia is determined.

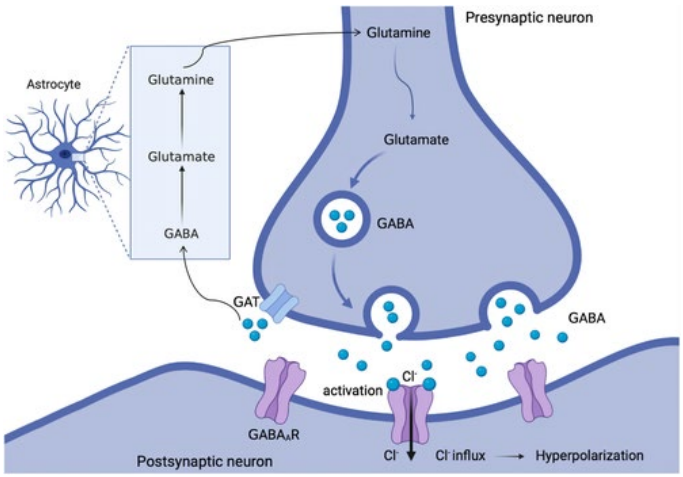

Fig. 1. A Paradigm Shift in Anesthetic Mechanisms, a schematic figure comparing two models. The left side depicts the traditional view: an anesthetic molecule targeting a synaptic receptor (e.g., GABA-A) on a neuron [51].

This fig. 1 provides a detailed illustration of an inhibitory GABAergic synapse, which represents the canonical molecular target for a majority of general anesthetic agents and serves as a critical foundation for understanding their deeper bioenergetic implications [51]. The diagram depicts the complete lifecycle of the neurotransmitter GABA: its synthesis from glutamine within the presynaptic terminal, packaging into vesicles, and subsequent release into the synaptic cleft. Upon binding to postsynaptic GABA-A receptors ($GABA_aR$), it triggers an influx of chloride ions (Cl^-), resulting in hyperpolarization and neuronal inhibition. The cycle is completed by the crucial role of adjacent astrocytes, which clear GABA from the synapse and recycle it back to glutamine for presynaptic reuse, a process known as the glutamate-glutamine cycle [52]. Critically, general

anesthetics such as propofol and volatile agents act as positive allosteric modulators of the $GABA_aR$, potentiating this chloride current to induce the profound CNS depression characteristic of anesthesia [53]. However, this synaptic-centric view is incomplete without considering the profound bioenergetic demands of these processes, which directly connects this image to the central thesis of this review. Every step depicted—from neurotransmitter synthesis and vesicular packaging to the astrocytic recycling and the vital restoration of postsynaptic ion gradients by Na^+/K^+-ATPase—is an energy-intensive process critically dependent on a continuous supply of ATP [54]. This juxtaposition reveals a potential "bioenergetic crisis" induced by anesthetics: they simultaneously enhance GABAergic activity, thus *increasing* the metabolic demand for ATP at the synapse, while concurrently *impairing* the mitochondrial function responsible for ATP *supply*, primarily through the inhibition of the electron transport chain [55]. Consequently, this anesthetic-induced mismatch between heightened energetic demand and compromised supply at the synapse offers a powerful mechanistic framework for understanding perioperative neurological complications, such as postoperative cognitive dysfunction, particularly in patients with diminished mitochondrial reserve [56].

An in-depth analysis of *in vitro* data reveals that the most direct and consistent interaction of anesthetic agents is the inhibition of the Electron Transport Chain (ETC), particularly at Complex I [37]. Volatile anesthetics such as sevoflurane and isoflurane exhibit significant yet reversible inhibition at this key electron entry point, whereas intravenous agents like propofol display a broader inhibitory profile across multiple complexes [38]. When synthesized, these findings suggest that these distinct ETC inhibition profiles may underpin some of the observed clinical differences between agents, such as the more robust cardioprotective potential of volatile anesthetics. Rather than viewing it as non-specific toxicity, this ETC inhibition can be interpreted as a predictable biophysical modulation that inherently reduces the cellular metabolic rate, an effect that aligns with the primary pharmacological goal of suppressing energy-intensive neuronal activity [39].

The inescapable biochemical consequence of ETC inhibition is an increased "leak" of electrons and the production of mitochondrial Reactive Oxygen Species (ROS), a phenomenon identified as a double-edged sword [40]. At low to moderate levels, this controlled ROS surge serves as a powerful intracellular signal, activating pro-survival pathways like the PI3K/Akt pathway and inducing the protective response known as anesthetic preconditioning [41]. However, this review finds that when ROS production overwhelms the cellular antioxidant buffering capacity—due to high anesthetic doses, prolonged exposure, or a patient's compromised baseline mitochondrial status—the outcome inverts to pathological and damaging oxidative stress [42]. This dichotomy suggests the existence of an anesthetic-modulated "ROS signaling rheostat," where the final outcome (protection vs. injury) is highly context-dependent rather than being an absolute drug effect.

Beyond bioenergetics, this synthesis of the literature highlights an often-overlooked impact of anesthetics on mitochondrial dynamics and morphology. A significant body of evidence from microscopy studies indicates that many anesthetic agents shift the dynamic equilibrium towards excessive fission (fragmentation) by modulating key proteins like Drp1 [43]. These fragmented mitochondria are not only less efficient at ATP production but are also more prone to dysfunction and are less effectively cleared via mitophagy [44]. This finding provides a potential novel mechanistic link between acute anesthetic exposure and long-term neurological outcomes like postoperative cognitive dysfunction (POCD). It is plausible that disruption of the mitochondrial network architecture at the synapse could impair synaptic plasticity and local energy homeostasis, persisting long after the anesthetic agent has been cleared from the body.

The Mitochondrial Permeability Transition Pore (mPTP) emerges from this analysis as a critical convergence point for various anesthetic-induced stress signals, including cytosolic calcium overload and oxidative stress [45]. The literature suggests that some anesthetics can lower the calcium threshold required to trigger mPTP opening, effectively sensitizing the cell to necrotic or apoptotic cell death under stressful conditions like ischemia-reperfusion [46]. The mPTP can therefore be conceptualized as a molecular "switch" where the effect of an anesthetic can transition from reversible, physiological modulation

to irreversible, pathological damage. This modulation of the mPTP offers a compelling explanation for the context-dependent protective and detrimental effects of the same agents.

Bridging these mechanistic findings with clinical practice reveals a complex yet illuminating picture. The phenomenon of anesthetic preconditioning, where brief exposure to a volatile anesthetic protects the heart from a subsequent ischemia-reperfusion injury, can be elegantly explained by the activation of protective pathways mediated by mitochondrial ROS [47]. Conversely, the incidence of POCD in elderly patients can be attributed to an age-related decline in mitochondrial reserve, which renders their neurons unable to withstand the same anesthetic-induced bioenergetic stress and mitochondrial fragmentation [48]. This synthesis leads to the proposed concept of a patient's "mitochondrial vulnerability" as a crucial yet currently unmeasured predictor of postoperative outcomes that extends beyond traditional risk factors.

Table 1. Comparative mitochondrial effects of three commonly studied anesthetic agents (Sevoflurane, Propofol, and Dexmedetomidine).

Agent	Primary ETC Target	ROS Production	Effect on Dynamics (Fission/Fusion)	mPTP Modulation	Proposed Key Clinical Implication	Citation
Sevoflurane	Mild Complex I inhibition; activates mitoK_ATP (signaling)	Transient mild ↑ (preconditioning trigger)	Shifts toward fusion; attenuates excessive Drp1-mediated fission	Delays mPTP opening; limits Ca^{2+} overload	Cardioprotective / organ preconditioning	[57]
Propofol	Complex I inhibition; impairs FA entry (CPT-1) at high dose	Biphasic: ↓ at low (antioxidant), ↑ at high / toxic	Promotes fission/fragmentation at higher doses; loss of network integrity	Facilitates mPTP opening in stress/PRIS-like states	Potential neuro-/myo-toxicity with prolonged high dose (PRIS risk)	[58]
Dexmedetomidine	No direct complex inhibition; supports ETC via PGC-1α/SIRT pathways	↓ (enhances antioxidant defenses)	Favors fusion and biogenesis; stabilizes network	Reduces propensity for mPTP opening	Mito-protective; cardio- & neuroprotective adjunct	[59]

This table provides a comparative analysis summarizing the distinctly different mitochondrial impacts of three commonly used anesthetic agents: sevoflurane, propofol, and dexmedetomidine. Sevoflurane exhibits a largely protective profile; it acts as a mild inhibitor of ETC Complex I and activates mitoK-ATP channels, which initiates a transient, low-level ROS signal. This signaling event is crucial for inducing organ preconditioning mechanisms, an effect reinforced by its ability to promote mitochondrial fusion and delay mPTP opening, collectively conferring cardioprotection [57]. In contrast, propofol displays a dose-dependent, biphasic effect. At low concentrations, it can function as an antioxidant, yet at high doses or with prolonged infusion, it becomes a significant mitochondrial inhibitor by impairing Complex I and disrupting fatty acid metabolism. This leads to excessive ROS production, promotes fragmentation of the mitochondrial network, and facilitates mPTP opening—a toxic profile that underlies the risk of pathological conditions such as Propofol Infusion Syndrome (PRIS) [58]. Fundamentally distinct from the other two, dexmedetomidine does not directly inhibit the ETC. Instead, it confers a mito-protective effect by activating transcriptional signaling pathways such as PGC-1α/SIRT, which enhances endogenous antioxidant defenses and supports mitochondrial biogenesis. This action, combined with its ability to stabilize the mitochondrial network and reduce the propensity for mPTP opening, positions it as a valuable adjunct for neuroprotection and cardioprotection during the perioperative period [59].

Despite significant progress, this review identifies several critical knowledge gaps that warrant future investigation. First, the vast majority of data is derived from animal or cell models, and studies on human mitochondria in the perioperative context are scarce. Second, how different cell types within the same organ (e.g., neurons vs. astrocytes in the brain) exhibit differential mitochondrial vulnerability to anesthetics remains poorly understood [49]. Third, the development of non-invasive biomarkers to assess a patient's mitochondrial health preoperatively presents a formidable yet crucial challenge for actualizing precision anesthesiology. Addressing these questions will be key to translating these mechanistic insights into safer clinical practice.

The evidence reviewed convincingly repositions mitochondria as central, not peripheral, players in anesthetic pharmacology. The interaction of anesthetic agents with mitochondria is not an epiphenomenon but a predictable series of molecular events that significantly contributes to the therapeutic and toxic profiles of these agents. The future perspective for the field should shift towards the development of "mito-sparing" anesthetic strategies. This could involve selecting anesthetic agents based on a patient's mitochondrial profile or co-administering novel "mito-protective" agents designed to support mitochondrial function during the perioperative stress period [50]. Ultimately, understanding and respecting the role of the mitochondrion will be the cornerstone for the next generation of safer, personalized anesthetic care.

CONCLUSION

This comprehensive review firmly positions mitochondria not as incidental, secondary targets, but as a central and active pharmacological arena for anesthetic agents. The synthesized evidence demonstrates that interactions with the mitochondrial apparatus ranging from Electron Transport Chain inhibition and the dual-edged modulation of ROS production to the disruption of fusion and fission dynamics are an integral component of the anesthetic mechanism of action, not merely a side effect. The comparative analysis between different agents, such as the protective profile of sevoflurane, the dose-dependent toxicity of propofol, and the mito-protective nature of dexmedetomidine, highlights the heterogeneity of these impacts. The concept of a "bioenergetic crisis" at the synapse, where anesthetics simultaneously increase energy demand while suppressing its supply, emerges as a powerful unifying framework to explain diverse clinical phenomena, from organ preconditioning to postoperative cognitive dysfunction. The implications of this paradigm shift are profound, driving an evolution from a "one-size-fits-all" anesthetic practice towards a more personalized, mechanism-based approach that considers a patient's "mitochondrial vulnerability." Future research directions should center on three key areas: **(1)** the development and validation of non-invasive biomarkers to assess preoperative mitochondrial health; **(2)** the design of clinical trials that specifically test tailored anesthetic strategies in high-risk populations; and **(3)** the discovery of "mito-protective" adjunct agents that can preserve mitochondrial function during the perioperative stress period. Ultimately, the integration of cellular bioenergetics into clinical practice promises a new era in anesthesiology one that is safer, more precise, and individually tailored.

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