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Molecular Mechanisms of Anesthetic-Induced Neurotoxicity and Neuroprotection Bridging Experimental Models with Clinical Practice: Systematic Review

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Abstract — General anesthesia is a cornerstone of modern surgical practice, yet growing evidence indicates that commonly used volatile anesthetics such as sevoflurane and isoflurane are not neurobiologically inert. Instead, they can induce mitochondrial dysfunction, oxidative stress, endoplasmic reticulum (ER) stress, neuroinflammation, and synaptic dysregulation, thereby contributing to postoperative delirium and postoperative cognitive dysfunction (POCD), particularly in vulnerable populations. This narrative review aims to provide an integrative overview of the molecular mechanisms underlying anesthetic-induced neurotoxicity, evaluate emerging neuroprotective strategies, and discuss translational challenges in bridging preclinical findings with clinical outcomes. Literature published between 2000 and 2025 was systematically retrieved from PubMed, Scopus, Web of Science, and Embase. Eligible studies included experimental and clinical research on anesthetic neurotoxicity, molecular pathways, neuroprotection, and translational perspectives. Data were qualitatively analyzed and categorized into pathophysiological mechanisms, neuroprotective interventions, and translational barriers. Key mechanisms of anesthetic-induced neuronal injury include inhibition of mitochondrial complex I, reactive oxygen species generation, prolonged ER stress with CHOP activation, microglial-mediated neuroinflammation, and Alzheimer's-like pathology characterized by tau hyperphosphorylation and amyloid-beta aggregation. Promising neuroprotective agents such as dexmedetomidine, xenon, antioxidants, and preconditioning strategies demonstrate multi-pathway protective effects but face translational limitations. Emerging biomarkers, particularly neurofilament light chain (NfL) and tau protein, show potential for objective detection of neuronal injury and perioperative risk stratification. General anesthesia poses significant risks of neurotoxicity, underscoring the need for a paradigm shift from passive harm avoidance toward proactive, biomarker-guided neuroprotection. Future directions include the integration of molecular insights, precision monitoring, and multi-modal interventions to establish brain-protective perioperative care and ensure long-term cognitive safety.

Keywords *— Neurotoxicity; Postoperative Cognitive Dysfunction (POCD); Mitochondrial Dysfunction; Neuroinflammation*

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INTRODUCTION

General anesthesia is an indispensable medical intervention and serves as the fundamental cornerstone of modern surgical practice [1]. Each year, millions of patients, including highly vulnerable populations such as infants and the elderly, are exposed to general anesthetic agents for various procedures [2]. A growing body of evidence unequivocally indicates that these agents are not inert compounds, but rather bioactive molecules that can trigger significant and lasting changes in the central nervous system [3]. Specifically, commonly used volatile anesthetics such as sevoflurane and isoflurane have been demonstrated in numerous preclinical models to cause neuronal cell death and synaptic disruption [4]. These preclinical findings are congruent with alarming clinical observations, such as the high incidence of postoperative delirium and postoperative cognitive dysfunction (POCD), which can persist for weeks to months following surgery [5,6]. Therefore, a profound understanding of the molecular mechanisms underlying these phenomena has become an urgent priority for enhancing perioperative patient safety [7].

The molecular basis of anesthetic-induced neurotoxicity is highly complex and involves the interplay of multiple cellular pathways [8]. One of the most consistently reported primary mechanisms is mitochondrial dysfunction, wherein volatile

anesthetics directly inhibit complex I of the electron transport chain [9]. This inhibition not only impairs ATP synthesis but also triggers a burst of reactive oxygen species (ROS) production, leading to oxidative stress and macromolecular damage [10]. In parallel, anesthetic agents can disrupt protein homeostasis within the endoplasmic reticulum (ER), triggering the unfolded protein response (UPR) [11]. If ER stress becomes prolonged, the UPR can switch from an adaptive to a pro-apoptotic function, primarily through the activation of the transcription factor CHOP (CCAAT-enhancer-binding protein homologous protein) [12]. Furthermore, neuroinflammation plays a central role, whereby anesthetics can directly activate microglia, the resident immune cells of the brain [13]. These activated microglia release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), which amplify neuronal injury and synaptic dysfunction [14]. Moreover, several studies have linked anesthetic exposure to Alzheimer's disease-like pathology, including the increased phosphorylation of tau protein and the aggregation of amyloid-beta peptide [15,16].

In response to these risks, intensive research has focused on developing neuroprotective strategies to counteract the adverse effects of anesthesia [17]. Dexmedetomidine, a highly selective α2-adrenergic agonist, has emerged as a particularly promising agent in various experimental models [18]. Its protective effects are mediated through several mechanisms, including the attenuation of catecholamine release, suppression of inflammatory responses, and activation of cell survival pathways such as PI3K/Akt [19]. The noble gas xenon has also demonstrated potent neuroprotective properties, primarily due to its ability to non-competitively inhibit the N-methyl-D-aspartate (NMDA) receptor, which is implicated in excitotoxicity [20]. This NMDA receptor antagonism prevents excessive calcium influx into neurons, a key trigger of cell death cascades [21]. Other potential strategies under active investigation include the use of antioxidants like melatonin, anti-inflammatory agents, and the application of pharmacological or ischemic preconditioning techniques to enhance neuronal resilience to perioperative stressors [9,22].

The greatest obstacle in translating these promising discoveries into effective clinical practice is the significant translational gap between laboratory findings and human outcomes [23]. The vast majority of our mechanistic data is derived from rodent models, which possess substantial neuroanatomical, metabolic, and genetic differences compared to humans [24]. The complexity of human surgical procedures, which involves surgical trauma, systemic stress responses, hemodynamic fluctuations, and polypharmacy, cannot be accurately replicated in a highly controlled laboratory environment [25]. Furthermore, the doses and durations of anesthetic exposure used in animal studies to induce measurable neurotoxicity often exceed those typically employed in routine clinical practice [26]. These fundamental discrepancies collectively contribute to the failure of many neuroprotective agents that were successful in animal testing when evaluated in human randomized controlled trials [27].

To bridge this gap, future research directions must adopt a more integrated and clinically relevant approach [28]. This includes the use of more sophisticated animal models, such as aged animals or those with pre-existing comorbidities (e.g., diabetes or mild cognitive impairment), to better mimic at-risk patient populations [29]. There is an urgent need to develop and validate sensitive and specific biomarkers of neuronal injury, such as plasma neurofilament light chain (NfL) and tau protein, which can non-invasively detect and quantify neurotoxicity [30]. The identification of such biomarkers would permit patient risk stratification, real-time monitoring, and the objective assessment of the efficacy of neuroprotective interventions [5]. Ultimately, integrating molecular data from preclinical studies with cognitive phenotype and biomarker data from well-designed clinical studies will be key to translating our understanding into safer, more personalized anesthetic practices for all patients [31].

MATERIALS AND METHOD

Study Approach

This study was conducted as a narrative review, aiming to provide an integrative overview of the molecular mechanisms of anesthetic-induced neurotoxicity and neuroprotection [32]. The approach focuses on bridging the findings from experimental

models with clinical practice. The methodology combines literature synthesis, secondary data analysis, and mechanistic interpretation of existing experimental (*in vitro* and *in vivo*) and clinical studies.

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 Embase [33]. Keywords used for the search included: *"anesthetic neurotoxicity"*, *"postoperative cognitive dysfunction"*, *"sevoflurane"*, *"isoflurane"*, *"molecular mechanisms"*, *"neuroinflammation"*, *"apoptosis"*, *"mitochondrial dysfunction"*, *"neuroprotection"*, *"dexmedetomidine"*, and *"translational research"*. Additionally, clinical trial registries such as ClinicalTrials.gov were reviewed to identify relevant clinical studies.

Selection Criteria

Studies were selected based on their relevance to the following criteria: identification of molecular pathways involved in anesthetic-induced neurotoxicity (e.g., apoptotic cascades, oxidative stress, neuroinflammation); investigation of the mechanisms of action and efficacy of neuroprotective agents; and exploration of the links between preclinical findings and clinical phenomena such as postoperative delirium and cognitive dysfunction. Studies focusing exclusively on local anesthetics, those not discussing central nervous system mechanisms, or articles such as case reports and editorials without primary data were excluded from this review, following a systematic selection process [34].

Data Analysis

The collected data were analyzed qualitatively. Findings were thematically categorized based on pathophysiological pathways (e.g., mitochondrial, inflammatory pathways), neuroprotective mechanisms (e.g., receptor modulation, activation of pro-survival pathways), and challenges in clinical translation [35]. Results from *in vitro*, *in vivo*, and human studies were comparatively analyzed to identify consistent patterns and knowledge gaps. Key molecular pathways modulated by anesthetic and neuroprotective agents (e.g., NF-κB signaling, caspase cascades, the PI3K/Akt pathway) were discussed in depth to elucidate their underlying mechanisms of action.

Limitations

This study acknowledges the limitations inherent to a narrative review format, including potential selection bias and the absence of quantitative meta-analysis [36]. Nevertheless, an effort was made to include recent and high-impact studies to ensure a comprehensive and balanced coverage of the topic.

RESULTS AND DISCUSSION

General anesthesia is a primary pillar of modern medicine, an intervention that enables complex surgical procedures to be performed safely and painlessly [37]. For several decades, anesthetic agents were considered to be entirely reversible and benign compounds to the central nervous system [38]. We are now confronted with a paradox: the very intervention designed to protect patients from surgical stress can trigger a series of damaging molecular cascades, particularly in the most vulnerable populations—the rapidly developing brains of children and the aging brains of the elderly with diminished cognitive reserve [39]. The clinical manifestations of this damage, such as postoperative cognitive dysfunction (POCD) and postoperative delirium,

are no longer considered minor complications but rather as serious challenges that affect long-term recovery outcomes, quality of life, and even patient mortality [40].

The clinical implementation of this molecular understanding is critically dependent on our ability to objectively detect neuronal injury in individual patients [72]. Historically, the diagnosis of POCD and delirium has relied on neurocognitive testing, which is often difficult to perform reliably in elderly or acutely ill patients in the postoperative period [73]. The emergence of blood-based fluid biomarkers, particularly neurofilament light chain (NfL) and Tau protein, offers a revolution in the monitoring of perioperative brain health [74]. NfL is released into the circulation in response to axonal damage, while elevated Tau levels are often associated with neuronal cell body injury, providing a specific profile of the type and extent of neuronal damage [75]. The validation and integration of these biomarkers into the clinical workflow—for preoperative risk stratification, early postoperative diagnosis, and as objective endpoints in trials of neuroprotective strategies represent the critical next step toward realizing a precision, neurocentric anesthesiology [76].

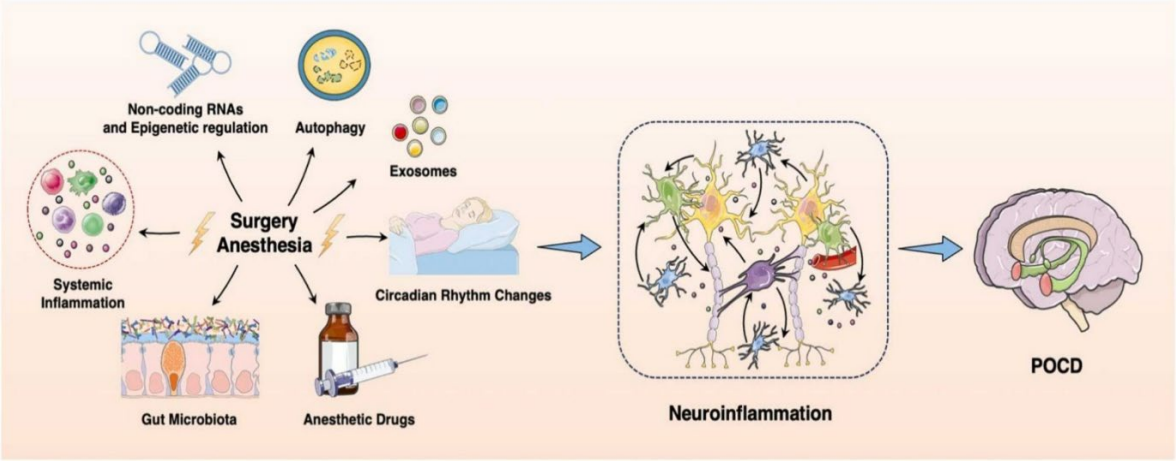


Figure 1. Postoperative Cognitive Dysfunction (PCD).

At the core of many anesthetic neurotoxicity mechanisms lies the most vital cellular organelle: the mitochondrion [41]. In-depth research indicates that volatile anesthetics, particularly sevoflurane and isoflurane, have an affinity for inhibiting Complex I (NADH dehydrogenase) of the electron transport chain [9]. This inhibition effectively clogs the cell's energy production machinery, resulting in a drastic decrease in ATP synthesis [42]. This energy deficit cripples essential neuronal functions, such as the action of ion pumps (e.g., Na+/K+-ATPase) that are critical for maintaining membrane gradients [43]. Consequently, ionic imbalance, membrane depolarization, and cellular swelling (cytotoxic edema) occur [44]. Furthermore, "congestion" in the electron transport chain causes electron leakage, which reacts with oxygen to produce a burst of reactive oxygen species (ROS) [10]. These ROS, such as superoxide and hydroxyl radicals, are highly destructive molecules that trigger lipid peroxidation in cell membranes, damage functional proteins, and cause mitochondrial DNA damage, creating a self-perpetuating cycle of damage [45].

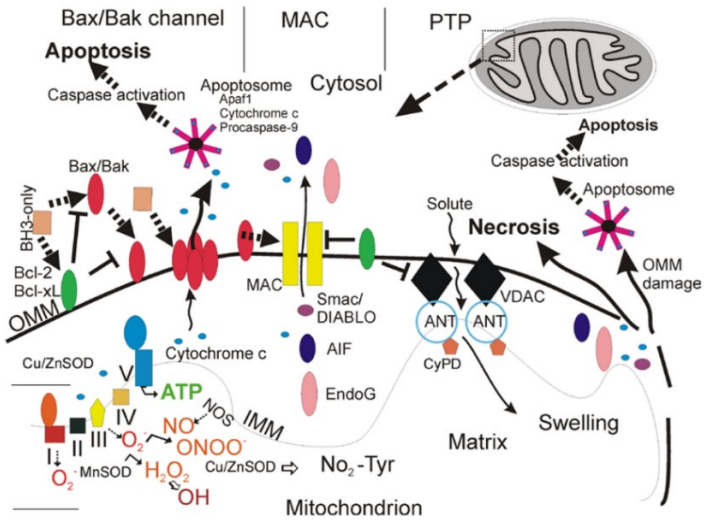


Figure 2. Mitochondrial and Cell Death Mechanisms in Neurodegenerative Diseases.

This fig 2. provides a detailed illustration of the "ground zero" of cellular damage we have discussed, the mitochondrion, and visually explains how anesthetic exposure can trigger neuronal death [87]. In the lower-left portion, the electron transport chain (complexes I-V) is depicted, where volatile anesthetics are known to inhibit Complex I [88]. This inhibition, as shown, triggers the production of superoxide radicals (O_2^-) which are subsequently converted into other highly damaging reactive oxygen species (ROS) such as hydroxyl radicals (·OH) and peroxynitrite ($ONOO^-$), the core of oxidative stress [89]. Furthermore, the figure illustrates two primary cell death pathways initiated by mitochondrial damage [90]. The first pathway is apoptosis (upper left), where cellular stress activates the pro-apoptotic proteins Bax/Bak to form pores in the outer mitochondrial membrane (OMM), a process known as MOMP (*Mitochondrial Outer Membrane Permeabilization*) [91]. These pores permit the release of cytochrome c into the cytosol, which then forms the apoptosome and activates the caspase cascade that executes the cell [92]. The second pathway is necrosis (right), which is triggered by the opening of the permeability transition pore (PTP) in the inner mitochondrial membrane [93]. The opening of this large pore causes the mitochondrion to swell dramatically, rupture, and uncontrollably release its contents, resulting in a more chaotic form of cell death [94]. Thus, this diagram perfectly encapsulates how a single trigger the disruption of mitochondrial function by anesthetics can bifurcate into either the programmed pathway of apoptosis or the catastrophic pathway of necrosis.

The modern understanding of the pathophysiology of POCD has now moved beyond classic neuronal damage pathways toward an integrated, multi-system disease model, as depicted in the diagram [77]. A growing body of evidence highlights the crucial role of the gut-brain axis, wherein the disruption of gut microbiota (dysbiosis) due to perioperative stress can increase intestinal permeability, allowing pro-inflammatory bacterial byproducts to enter systemic circulation and exacerbate neuroinflammation [78]. In parallel, research at the molecular level indicates that anesthetic exposure can trigger persistent epigenetic changes, such as histone modification and the dysregulation of non-coding RNAs (ncRNAs), which alter the long-term transcription of genes involved in synaptic plasticity and immune responses [79]. Furthermore, intercellular communication via exosomes carrying pro-inflammatory molecular cargo, as well as failures in the cellular clearance process of autophagy, have also been identified as novel mechanisms contributing to the postoperative neurotoxic environment [80]. The interconnectedness of these pathways confirms that POCD is a complex syndrome arising from a systemic failure to maintain homeostasis, demanding the development of multi-targeted neuroprotective strategies [81].

The future direction in this field is shifting from a reactive approach to a proactive, preventative strategy encapsulated in the concept of "brain-protective perioperative care" [82]. In the preoperative phase, the primary focus is on developing robust

risk-stratification models that integrate clinical factors such as age and frailty with fluid biomarkers to identify patients with the highest cerebral vulnerability before surgery [83]. During the intraoperative phase, research continues to validate more "brain-friendly" anesthetic regimens, such as anesthesia guided by processed EEG to avoid burst suppression, as well as clinical trials of neuroprotective agents administered personally based on the patient's risk profile [84]. In the postoperative phase, strong emphasis is placed on evidence-based, non-pharmacological interventions, such as the Hospital Elder Life Program (HELP), which has been proven effective in preventing delirium through reorientation, sleep-wake cycle maintenance, and early mobilization [85]. This convergence of molecular biology, biomarker technology, and clinical protocols is ultimately paving the way for a new era of precision anesthesiology, where safeguarding long-term cognitive function is a priority equivalent to maintaining hemodynamic stability during surgery [86].

In addition to mitochondria, the endoplasmic reticulum (ER) is also a primary target [11]. The ER serves as the quality control hub for protein synthesis and folding [46]. Anesthetics can disrupt the sensitive ER environment, primarily by disturbing its internal calcium homeostasis [47]. This disruption causes newly synthesized proteins to fail to fold correctly, triggering a condition known as ER stress [48]. In response, the cell activates a defense mechanism called the unfolded protein response (UPR) [12]. Initially, the UPR aims to halt the production of new proteins and increase protein-folding capacity [49]. However, if ER stress from prolonged anesthetic exposure persists, the UPR will switch from a rescue mode to an execution mode [50]. The PERK sensor pathway activates the transcription factor CHOP, a molecular "switch" that actively turns off pro-survival genes (like Bcl-2) and activates pro-apoptotic genes (like Bim), ultimately triggering the activation of caspase-3, the primary executioner of programmed cell death [51].

Neuronal damage occurs not only from internal cellular processes but is also exacerbated by the immune response within the brain, or neuroinflammation [13]. Under normal conditions, microglia, the brain's resident immune cells, function as vigilant sentinels [52]. However, anesthetics can act as non-infectious triggers that shift microglia from a resting surveillance phenotype (M0) to an aggressive, pro-inflammatory phenotype (M1) [53]. These activated microglia release a storm of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [14]. These cytokines have widespread damaging effects: TNF-α can directly trigger apoptosis in neurons and disrupt synaptic plasticity, while IL-1β can enhance glutamate toxicity [54]. This process creates a neurotoxic environment that amplifies the initial injury and is highly relevant to the pathophysiology of postoperative delirium, where systemic inflammation from surgery "leaks" into the brain and collaborates with already activated microglia [6, 55].

The ultimate functional impact of the mechanisms described above is synaptic dysregulation [4]. The synapse is the communication point between neurons and the foundation of memory and cognition [56]. Studies show that anesthetics can decrease the expression of key synaptic proteins, such as PSD-95 (at the post-synaptic terminal) and synaptophysin (in pre-synaptic vesicles), which effectively weaken neuronal connections [57]. More alarmingly, findings have linked anesthetic exposure to the hallmark pathologies of Alzheimer's disease [15]. Anesthetics have been shown to disrupt the balance between kinases (like GSK-3β) and phosphatases, leading to the hyperphosphorylation of the Tau protein [16]. This abnormal Tau then detaches from microtubules and forms neurofibrillary tangles within the neuron [58]. Additionally, several anesthetic agents have been reported to increase the production and aggregation of amyloid-beta peptide, the main component of the senile plaques found in the brains of Alzheimer's patients [59].

Confronted with such a complex series of damage mechanisms, the paradigm in anesthesiology is beginning to shift from merely avoiding harm to active neuroprotective intervention [60]. This concept is based on the understanding that if we can identify the critical points in the damage cascade—be it mitochondrial dysfunction, microglial activation, or apoptotic pathways—we can then design pharmacological strategies to block or attenuate these processes [61]. This approach no longer

views the brain as a passive recipient of anesthetic effects but as an active target to be protected [62]. The goal is to "arm" neurons with stronger biochemical defenses to withstand the dual assault from anesthesia and surgical stress [63].

Among the various neuroprotective agents studied, dexmedetomidine stands out for its ability to target multiple damage pathways simultaneously [17]. Its primary mechanism as an α2-adrenergic receptor agonist on presynaptic nerve terminals suppresses norepinephrine release, thereby effectively "calming" the excessive sympathetic stress response during surgery [18]. This effect extends to the brain, where it suppresses microglial activation and reduces the pro-inflammatory cytokine storm [19]. Even deeper, at the intracellular level, dexmedetomidine has been shown to activate robust pro-survival signaling pathways, such as PI3K/Akt and ERK [41]. These pathways then phosphorylate and inactivate pro-apoptotic proteins (like Bad) while increasing the expression of anti-apoptotic proteins (like Bcl-2), effectively tilting the cellular balance toward survival [64].

Although many agents show remarkable success in the laboratory, the majority fail when tested in humans—a phenomenon known as the translational gap [23]. The reasons for this are highly complex [27]. Rodent models, while valuable, have fundamental differences from humans; their smooth (lissencephalic) brains and sterile, controlled laboratory environments are vastly different from the folded (gyrencephalic) human brain and the physiologically "chaotic" environment of the operating room [24]. Human patients, especially the elderly, often present with multiple comorbidities (diabetes, hypertension, chronic inflammation) that are absent in young, healthy laboratory animals [65]. Furthermore, the anesthetic doses used in animal studies to elicit clear neurotoxicity are often much higher or longer in duration than those used in clinical practice [26].

To bridge the translational gap, objective tools that can detect neuronal injury in patients in real-time are required [5]. This is where the crucial role of biomarkers emerges [30]. Biomarkers are molecules that can be measured in the blood or cerebrospinal fluid that reflect a pathological process in the brain [66]. The two most promising candidates are neurofilament light chain (NfL), a structural protein from the axon that is released into the bloodstream when neurons are damaged, and the Tau protein, whose increase in the blood indicates neuronal cell body injury [67]. By measuring the levels of these biomarkers before and after surgery, clinicians can identify patients who have sustained neuronal injury, quantify the severity of the damage, and objectively assess whether a neuroprotective intervention has successfully protected the brain [68].

The future of safe anesthesia does not lie in the discovery of a single "silver bullet" but rather in the implementation of a personalized, multi-modal approach [31]. This begins with preoperative screening, where biomarkers and clinical risk factors are used to identify patients with the highest cerebral vulnerability [69]. During the intraoperative phase, this approach involves a combination of strategies: selecting potentially safer anesthetic agents, co-administering neuroprotective agents like dexmedetomidine, and maintaining tight physiological monitoring to preserve brain homeostasis [70]. Finally, in the postoperative phase, continuous monitoring with biomarkers can help detect complications earlier and guide interventions to support cognitive recovery [71]. This vision transforms anesthesia from merely "turning off" consciousness into an active, neurocentric process of perioperative management [28].

CONCLUSION

General anesthesia, while indispensable for modern surgical practice, carries the paradox of enabling life-saving interventions while simultaneously posing risks of neurotoxicity, particularly in vulnerable populations such as infants and the elderly. Accumulating evidence highlights that anesthetic agents like sevoflurane and isoflurane can trigger a cascade of molecular events including mitochondrial dysfunction, ER stress, neuroinflammation, and synaptic dysregulation—that culminate in neuronal injury, postoperative delirium, and cognitive decline. Despite significant progress in elucidating these mechanisms, a major translational gap persists between preclinical discoveries and clinical outcomes, largely due to differences in models, dosing, and patient complexity. Promising neuroprotective strategies, such as dexmedetomidine, xenon, and

antioxidant therapies, have demonstrated efficacy in experimental studies but await consistent validation in human trials. The emergence of biomarkers such as neurofilament light chain (NfL) and tau protein offers a transformative opportunity to detect neuronal injury objectively, stratify patient risk, and guide personalized interventions. Moving forward, the paradigm of anesthesiology must shift from passive avoidance of harm toward proactive, precision-based neuroprotection that integrates molecular insights, biomarker monitoring, and tailored clinical strategies across perioperative care. This integrated approach has the potential to safeguard long-term brain health and elevate anesthesiology into a truly neurocentric discipline.

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