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REVIEW

Calcium Signaling Dysregulation as a Convergent Mechanism in Anesthetic-Induced Developmental Neurotoxicity

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Abstract: Exposure to general anesthetics during critical periods of brain development is associated with altered neurogenesis and long-term neurobehavioral abnormalities in preclinical models, although clinical evidence remains inconclusive. Dysregulation of intracellular calcium signaling has emerged as an important convergent mechanism underlying anesthetic-induced developmental neurotoxicity (AIDN). Calcium serves as a pivotal second messenger regulating neural stem cell (NSC) quiescence, proliferation, fate specification, neuronal maturation; its precise spatiotemporal dynamics are essential for normal brain development. Common anesthetics including propofol, ketamine, sevoflurane, isoflurane, and midazolam act primarily as $GABA_A$ receptor agonists and/or NMDA receptor antagonists, thereby disrupting calcium homeostasis by altering calcium influx, increasing intracellular release from the endoplasmic reticulum and mitochondria, or disrupting calcium oscillations. These alterations involve key molecular pathways, including inositol-1,4,5-trisphosphate receptors ($InsP_3Rs$) and ryanodine receptors (RyR) mediated calcium release, mitochondrial calcium overload, and activation of calcium-dependent signaling cascades such as CaMK, CREB, and calcineurin/NFAT pathways. Sustained cytosolic calcium elevation triggers mitochondrial dysfunction, oxidative stress, apoptosis, autophagy, and neurogenesis. This review summarizes evidence linking anesthetic exposure to calcium dysregulation, with an emphasis on neurogenesis and NSC biology. Importantly, it highlights calcium signaling as a potential mechanistic bridge between anesthetic exposure and neurodevelopmental outcomes. Despite substantial preclinical evidence, the translation of these findings to clinical pediatric anesthesia remains limited, underscoring a critical knowledge gap. A better understanding of calcium-dependent mechanisms may inform the development of targeted neuroprotective strategies and improve the safety of anesthetic exposure during early life.

Plain Language Summary: General anesthesia is often used when young children need surgery. There are concerns about whether these medicines could affect how the brain develops. Calcium is an important signal inside brain cells and helps cells grow, develop, and communicate. For the brain to develop normally, calcium levels need to stay well balanced and follow regular patterns. Some anesthetic drugs may disturb these signals. They can cause calcium levels to become too high or disrupt normal patterns. This may affect how brain cells grow and mature. The most current evidence comes from laboratory and animal studies. Studies in children have not shown clear long-term harm after a single, short exposure, but questions remain about repeated or longer exposures. Better understanding of these changes may help guide safer use of anesthesia in early life.

Keywords: developmental neurotoxicity, anesthetic, calcium homeostasis, neural stem cell, NSC, neurogenesis

Introduction

General anesthesia (GA) is widely used in pediatric clinical practice, with millions of infants and young children exposed each year during surgical and diagnostic procedures. In the United States, approximately 2–3 million children under 36 months and 1.5 million infants under 12 months undergo GA annually.[1] While anesthetic agents are essential for ensuring procedural

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safety and comfort, growing preclinical evidence has raised concerns regarding the potential impact of anesthetic exposure on the developing brain.[2,3] Repeated or prolonged exposure to anesthetics during critical developmental periods has been associated with long-term alterations in cognition, behavior, and neurodevelopmental outcomes.[4–8]

Anesthetic-induced developmental neurotoxicity (AIDN) encompasses a spectrum of structural and functional changes in the immature brain following exposure to anesthetic agents. These changes include increased neuronal apoptosis, impaired neurogenesis, disrupted synaptic development, and long-term neurobehavioral abnormalities.[3] Although large-scale clinical studies suggest limited harm from single exposures, risks associated with multiple or prolonged exposures remain debated, underscoring the need for a mechanistic framework linking anesthetic exposure to developmental outcomes.[3,9]

Among the various mechanisms proposed to underlie AIDN,[10–14] dysregulation of intracellular calcium (Ca^{2+}) signaling has emerged as a convergent pathway.[10–13,15] Calcium is a critical second messenger that regulates diverse cellular aspects of neurodevelopment, including neural stem cell (NSC) proliferation, differentiation, migration, and synaptic maturation.[16,17] NSCs are self-renewing multipotent cells that generate neurons and glia during brain development, while neurogenesis encompasses the coordinated processes of NSC activation, fate determination, neuronal maturation, and circuit integration.[18–21] Precise spatio-temporal control of calcium dynamics, particularly calcium oscillation is essential for coordinating gene expression and cellular behavior during brain development.[22,23] Disruption of the finely tuned calcium signaling processes therefore has profound consequences for neurodevelopmental integrity.[24]

General anesthetics, including γ-aminobutyric acid type A ($GABA_A$) receptor agonists and N-methyl-D-aspartate receptor (NMDAR) antagonists, perturb calcium homeostasis by altering both calcium influx and intracellular calcium release, leading to sustained cytosolic calcium elevation, disruption of calcium oscillations, and activation of downstream signaling pathways regulating cell survival and neurogenesis.[25] Anesthetic-induced calcium dysregulation further interfaces with mitochondrial function,[26] oxidative stress,[27,28] and transcriptional regulation,[29] positioning it as a mechanistic bridge linking anesthetic exposure to diverse neurodevelopmental outcomes. This review provides a structured mechanistic synthesis of current evidence, with emphasis on how calcium dynamics alterations affect NSC and neurogenesis, and discusses translational implications for improving pediatric anesthetic safety.

Anesthetic-Induced Developmental Neurotoxicity

Extensive evidence from rodents and non-human primates suggest that repeated or prolonged postnatal GA exposure impairs neurogenesis and produces cognitive deficits.[5–8,30,31] Commonly used anesthetics, including propofol, ketamine, sevoflurane, isoflurane, midazolam, and etomidate exert their pharmacological effects through modulation of $GABA_A$ receptors and NMDARs.[25] Critically, GABAergic signaling is depolarizing in immature neurons,[32] and NMDAR activity is essential for normal brain development.[33] Because these receptor systems play fundamentally different roles in the developing versus the mature brain, anesthetic disruption of their activity may exert disproportionate and long-lasting consequences during early developmental stages.

The vulnerability to AIDN is developmentally restricted to the brain growth spurt (BGS), a period characterized by rapid neurogenesis, synaptogenesis, and circuit formation extending from late gestation to approximately age three in humans.[34] During this window, NSCs and neural progenitor cells (NPCs) actively proliferate and differentiate, rendering them particularly sensitive to intracellular signaling perturbations. The convergence of rapid cellular proliferation and immature homeostatic mechanisms underlies the heightened vulnerability of the developing brain to anesthetic insult.[35–37]

Clinical evidence regarding neurodevelopmental consequences of early anesthetic exposure remains inconsistent and difficult to interpret. Observational studies associate even single GA exposures with subtle alterations in specific neurodevelopmental domains, though confounding cannot be excluded.[38–40] In contrast, large-scale Pediatric Anesthesia Neurodevelopmental Assessment (PANDA) and General Anesthesia compared to Spinal anesthesia (GAS) trials found that a single, short GA exposure does not significantly impair general cognitive function.[9,41] Subsequent studies, however, indicate that multiple or prolonged exposures (≥2 exposures or ≥120 minutes) before age four are associated with elevated risks of learning disabilities (LDs),[42] attention-deficit/hyperactivity disorder (ADHD),[43] and behavioral abnormalities.[44] All available clinical studies are subject to confounding by pre-existing medical conditions, surgical stress, and socioeconomic variables, leaving the precise contribution of anesthetic exposure per se unresolved.

At the mechanistic level, AIDN has been linked to mitochondrial dysfunction, oxidative stress, neuroinflammation, and epigenetic dysregulation.[2] Given that calcium homeostasis is intimately linked to mitochondrial function, transcriptional regulation, and cell fate determination, its disruption can simultaneously engage multiple pathogenic pathways. Dysregulation of intracellular calcium signaling is increasingly recognized as an important convergent upstream event that coordinates and amplifies these downstream injury cascades and developmental outcomes.,[45,46] providing a unifying mechanistic framework for diverse neurodevelopmental consequences of anesthetic exposure.

Calcium Signaling in Neural Development

Molecular Basis of Calcium Signaling

Intracellular Ca^{2+} homeostasis is maintained through coordinated regulation of plasma membrane influx, intracellular store release, inter-organelle transfer, and active clearance, particularly the endoplasmic reticulum (ER) and mitochondria.[47,48] Calcium influx across the plasma membrane is mediated by voltage-dependent calcium channels (VDCCs) and ionotropic glutamate receptors (NMDARs and AMPARs), and the transient receptor potential channels (TRPCs).[16] Intracellular calcium release is predominantly controlled by the ER through inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$) and ryanodine receptors (RyRs), which are central to shaping cytosolic calcium signals during development. Calcium signaling is further coupled to mitochondrial function via mitochondria-associated membranes (MAMs): Controlled ER-to-mitochondria calcium transfer supports ATP production and metabolic homeostasis, whereas excessive transfer precipitates mitochondrial overload and cell death.[49–51] Cytosolic calcium clearance is accomplished by plasma membrane Ca^{2+} ATPases (PMCA) and sarco/endoplasmic reticulum Ca^{2+} ATPases (SERCA) pumps, which restore basal calcium levels and enable cyclical signaling[16] (Figure 1).

Calcium Dynamics and Signal Decoding

The functional specificity of calcium signaling also critically depends on its spatiotemporal dynamics.[52] In developing neural systems, calcium signals characteristically occur as oscillations, recurring transients varying in frequency, amplitude, and duration, rather than sustained elevations, and these patterns encode distinct biological information that is selectively decoded by downstream effector molecules.[52] High-frequency calcium oscillations preferentially activate Ca^{2+}/calmodulin-dependent protein kinases (CaMKs),[53] leading to phosphorylation of cAMP response element-binding protein (CREB) and induction of pro-neuronal gene expression. In contrast, sustained or low-frequency calcium signals tend to activate calcineurin, a calcium-dependent phosphatase that promotes dephosphorylation and nuclear translocation of nuclear factor of activated T-cells (NFAT), thereby regulating alternative transcriptional programs governing cell fate and progenitor maintenance.[54] This frequency-dependent decoding mechanism has important implications for understanding calcium dysregulation in the context of anesthetic exposure. Subtle alterations in calcium oscillatory dynamics can redirect downstream transcriptional programs and thereby alter neural cell fate outcomes, even without overt calcium toxicity.

Role of Calcium Signaling in Neural Development

Calcium signaling regulates virtually most stages of neural development, encompassing NSC quiescence and activation, proliferation, differentiation, neuronal migration, axonal growth, dendritic elaboration, and synaptic maturation.[16,17] (Figure 2) NSCs transition between quiescent and activated states is tightly regulated by intracellular calcium dynamics.[55] In the adult mouse subventricular zone (SVZ), quiescent NSCs (qNSCs) show higher Ca^{2+} oscillation frequency and amplitude but lower basal cytoplasmic Ca^{2+} levels compared with activated NSCs (aNSCs).[55] Epidermal growth factor (EGF) promotes qNSC activation by decreasing oscillation frequency while elevating basal cytoplasmic Ca^{2+}, whereas melatonin exerts opposing effects, reinforcing quiescence.[52] ER Ca^{2+} release and store-operated Ca^{2+} entry (SOCE) are also key regulators of NSC state transitions.[56]

Calcium regulates NSC proliferation through modulation of cell-cycle progression.[57] Transient Ca^{2+} elevations activate the CaMK-CREB pathway and support G_1/S transition, whereas sustained or excessive signals may engage calcineurin-dependent pathways that arrest the cell cycle.[57] $InsP_3R$- or RyR-mediated calcium oscillations are required for NPC cell-cycle progression; $InsP_3R$ activation promotes proliferation by reducing p27-mediated inhibition.[58–60] The maintenance of precisely controlled calcium dynamics is important to sustain normal progenitor expansion during development.

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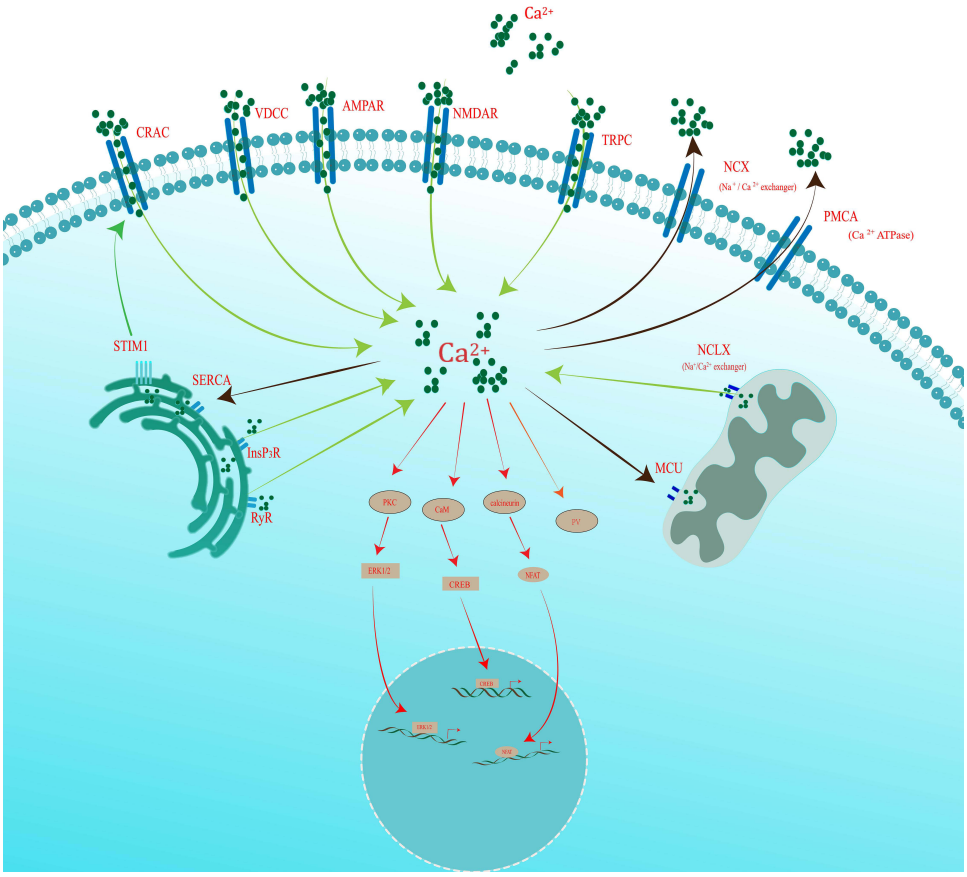

Figure 1 Schematic diagram of the intracellular calcium signaling pathway. Plasma membrane calcium channels include Voltage-dependent calcium channel (VDCC), Ionotropic glutamate receptors (NMDAR and AMPAR), Transient receptor punctuated channel (TRPC), Ca^{2+} release-activated Ca^{2+} (CRAC) channel, NCX (Na^{+}/Ca^{2+} exchanger) and PMCA (plasma membrane Ca^{2+} ATPase). Organelle membrane calcium channels include: Inositol-1,4,5-triphosphate receptors ($InsP_3R$), Ryanodine receptors (RyRs), Sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPases (SERCAs), Na^{+}/Ca^{2+} exchange (NCLX), Mitochondrial Ca^{2+} uniporter (MCU) complex. Stromal interaction molecule 1(STIM1) senses endoplasmic reticulum (ER) calcium levels. Cytoplasmic calcium-binding proteins (Calcineurin, Calmodulin (CaM), Parvalbumins) activate downstream transcription factors including ERK1/2, CREB, NFAT.

Physiologically patterned calcium signals promote neuronal differentiation through CREB and NeuroD activation. GABA-induced depolarization of NPCs in the adult dentate gyrus elevates Ca^{2+} and increases NeuroD expression, promoting neuronal commitment,[61,62] and L-type VDCC activation similarly drives NSC-to-neuron differentiation.[62] Notably, oscillation frequency influences neuronal subtype specification: high-frequency oscillations favor GABAergic differentiation, whereas lower frequencies favor glutamatergic identity.[63] Sustained Ca^{2+} elevation or disrupted oscillatory patterns bias lineage commitment toward glial fates, mediated by the relative balance between CaMK-CREB and calcineurin-NFAT transcriptional activity.[64–66]

At later developmental stages, calcium signaling regulates neuronal migration,[67–70] axonal growth, dendritic elaboration, and synapse formation[71,72] through calcium-dependent cytoskeletal remodeling and activity-dependent gene expression. Calcium transients also determine the direction of synaptic plasticity: larger postsynaptic Ca^{2+} rises favor long-term potentiation, while more moderate rises tend to induce long-term depression, acting through postsynaptic receptor trafficking and calcium-dependent kinases such as CaMKII and calcineurin.[73,74] Both excessive Ca^{2+} elevation and pathological oscillation suppression impair maturation, indicating that normal neuronal development requires precisely tuned calcium homeostasis. Calcium signaling coordinates neurodevelopment across every stage from NSC quiescence through synaptic maturation, with both signal magnitude and temporal patterning serving as essential determinants of cellular outcomes. Even

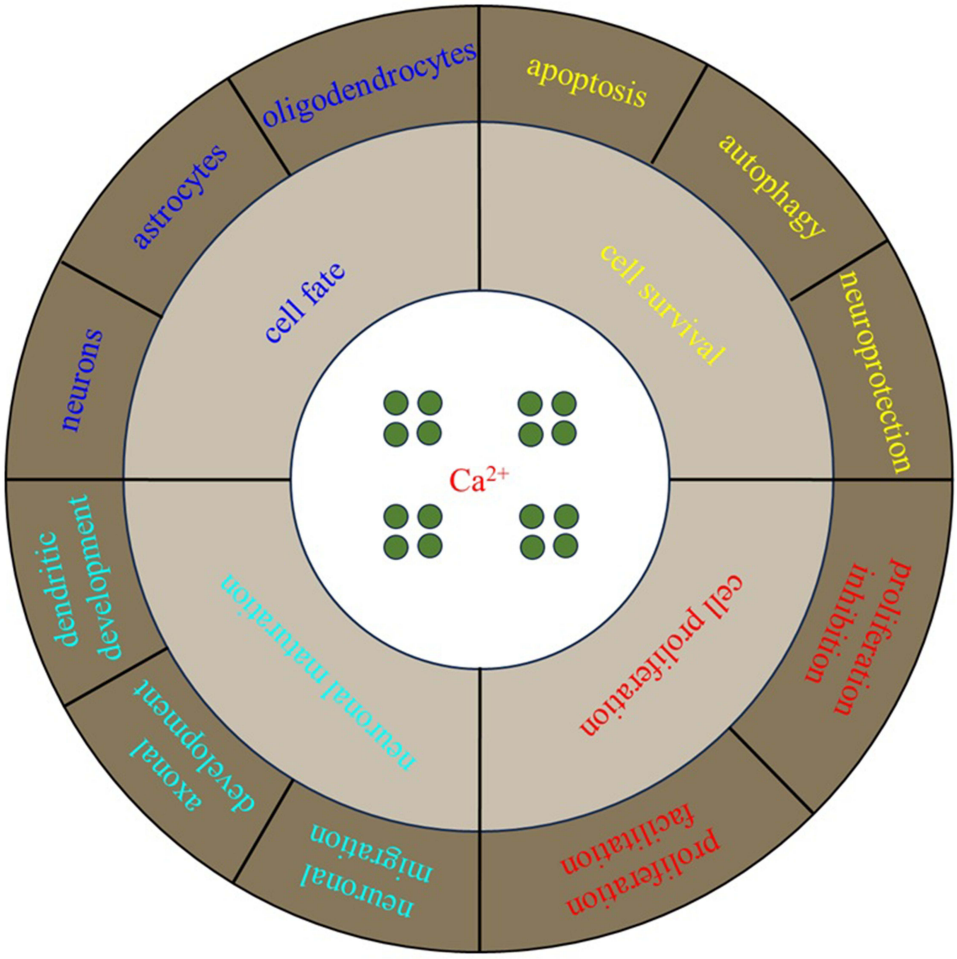

Figure 2 Role of calcium in general anesthetic-associated cell activities. General anesthetics affect nerve cell survival, NSCs proliferation and fate selection, newborn neuronal migration, axonal development, and dendritic growth through disruption of intracellular calcium homeostasis.
Abbreviation: NSCs, neural stem cells.

subtle anesthetic-induced perturbations of calcium signaling therefore can carry the potential to disrupt neurodevelopmental programs at multiple levels simultaneously.

Anesthetic-Induced Calcium Dysregulation

Upstream Mechanism-Receptor Modulation and Calcium Influx

GABAergic anesthetics including propofol, isoflurane, sevoflurane, and midazolam promote membrane depolarization and secondary calcium influx through VDCCs.[32] Propofol elicits dose-dependent increases in cytosolic Ca^{2+} in NSCs and developing neurons, attenuated by VDCC blockers, confirming depolarization-coupled calcium entry.[11,75] Isoflurane and sevoflurane similarly trigger VDCC-mediated Ca^{2+} influx via $GABA_A$ receptor activation, initiating downstream signaling disturbances.[76,77]

NMDAR antagonists such as ketamine reduce baseline calcium influx by blocking glutamate-gated calcium entry. However, sustained NMDAR blockade triggers compensatory receptor upregulation and subunit composition changes. Upon discontinuation of exposure, this receptor upregulation renders neurons transiently hyperexcitable, producing a rebound calcium overload that can paradoxically exceed the initial suppression in magnitude and cellular impact.[78] This withdrawal-associated calcium surge represents a clinically relevant mechanism of delayed neurotoxicity following ketamine exposure.

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Intracellular Calcium Release

A consistent finding across multiple anesthetic agents is their capacity to mobilize calcium from ER stores, independent of or in addition to plasma membrane entry. Propofol activates $InsP_3R$-mediated ER calcium release in a concentration-dependent manner, contributing to cytosolic Ca^{2+} accumulation even at concentrations producing minimal membrane depolarization.[11] Ketamine also sensitizes RyRs and enhances ER calcium release.[79] Isoflurane activates RyR-mediated calcium release in developing neurons, directly linked to mitochondrial overload and apoptotic signaling.[80]

ER calcium release is functionally coupled to mitochondrial calcium uptake at MAMs.[51] Excessive ER-to-mitochondria calcium flux causes mitochondrial membrane potential dissipation, impaired ATP synthesis, and mPTP (mitochondrial permeability transition pore) opening, activating caspase-dependent apoptosis.[49,50] This ER-mitochondria calcium transfer axis directly links early anesthetic-induced calcium dysregulation to the mitochondrial dysfunction characteristic of AIDN. Anesthetic exposure also reduces SERCA pump activity, impairing ER calcium refilling and prolonging cytosolic Ca^{2+} elevation, while compromised PMCA activity further delays restoration of basal calcium levels.[16] The resulting impairment of calcium clearance extends the duration of cytosolic calcium elevation beyond that generated by initial release events, compounding the dysregulatory effect.

Disruption of Calcium Dynamics and Signal Encoding

Anesthetic exposure disrupts physiological calcium oscillatory patterns through two mechanistically distinct routes. First, ER calcium release and VDCC-mediated influx induced by GABAergic anesthetics can convert oscillatory signals into pathological sustained Ca^{2+} elevation, profoundly altering downstream pathway activation. Propofol suppresses oscillation frequency while elevating basal cytosolic Ca^{2+} in NSCs through $InsP_3R$-mediated ER release; isoflurane exerts similar effects via $InsP_3R$- and RyR-dependent pathways; sevoflurane predominantly activates RyR-mediated release with evidence directly linking this to mitochondrial overload and apoptosis.[81,82] Although both volatile agents converge on ER calcium mobilization, differences in relative $InsP_3R$ vs. RyR reliance may produce quantitatively distinct dysregulation profiles warranting systematic comparative investigation.

Second, ketamine exposure reduces calcium influx and attenuate oscillation amplitude, suppressing the physiological calcium transients required for CaMK-CREB pathway activation.[79] Although mechanistically distinct from GABAergic anesthetics, oscillation suppression ultimately converges on impaired pro-neuronal transcription through a distinct route. These dual perturbations (oscillation-to-tonic conversion and oscillation suppression) may occur sequentially or concurrently depending on agent, concentration, duration, and developmental stage, and both result in fundamental disruption of calcium signal encoding.[79]

Downstream Signaling-Imbalance Between CaMK-CREB and Calcineurin-NFAT Pathways

Calcium dynamics disruptions converge on two major calcium-sensitive transcriptional axes: the CaMK-CREB pathway and the calcineurin-NFAT pathway. Under physiological conditions, high-frequency oscillatory calcium signals activate CaMKII and CaMKIV, phosphorylating CREB at Ser^{133} and inducing pro-survival and pro-differentiation genes (BDNF, Bcl-2, c-fos).[63,83] Sustained or low-frequency signals instead preferentially activate calcineurin, promoting NFAT nuclear translocation and alternative gene expression programs including stress responses and, in some contexts, pro-apoptotic signaling.[64–66]

Anesthetic-induced calcium dysregulation disrupts the physiological balance between these two pathways in both agent-specific and context-dependent ways. Ketamine-induced oscillation suppression reduces CaMKII/IV activation and CREB phosphorylation, impairing pro-neuronal gene expression, synaptic development, and neuronal maturation.[79,84] Sustained Ca^{2+} elevation from propofol or volatile anesthetics enhances calcineurin activity, promotes aberrant NFAT-driven transcription,[85,86] and may shift NSC fate decisions away from neuronal commitment. Calcineurin-mediated activation of pro-apoptotic NFAT targets combined with reduced CREB-driven Bcl-2 expression lowers the apoptotic threshold in developing neurons.[87] The relative dominance of each pathway is highly context-dependent, explaining why experimental studies using different agents or paradigms report divergent outcomes ranging from apoptosis to proliferation arrest to altered differentiation, all of which can be mechanistically unified by CaMK-CREB vs. calcineurin-NFAT imbalance.

The evidence supports a multilevel model of anesthetic-induced calcium dysregulation: anesthetics alter calcium entry and intracellular release at the receptor and organelle level, disrupt oscillatory encoding of developmental signals, and destabilize the transcriptional balance between pro-neuronal and alternative programs. These perturbations form an interconnected cascade in which upstream calcium disturbances propagate through ER-mitochondria coupling and signal decoding mechanisms to reshape the transcriptional landscape of developing neural cells.

Effects of Anesthetic-Induced Calcium Dysregulation on Neural Stem Cells and Developing Neurons

Effects on NSC Proliferation

Cell-cycle progression is regulated by the coordinated activity of cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors (CKIs). Cyclin-CDK complexes drive the cell cycle through retinoblastoma protein (pRb) phosphorylation and E2F activation, while CKIs such as p21 and p27 constrain proliferative activity.[88] Calcium signaling is intimately integrated with cell-cycle regulation at multiple checkpoints (Figure 3): transient Ca^{2+} elevations facilitate G_0/G_1 transition, G_1/S progression, and G_2/M entry through calmodulin (CaM), calcineurin, and CaMKs that regulate cyclin/CDK activity.[57,88–90]

Ketamine suppresses NSC proliferation in a dose- and time-dependent manner via the Ca^{2+}-PKCα-ERK1/2 signaling pathway.[91,92] However, many in vitro studies have employed ketamine concentrations (≥200 μM) substantially exceeding clinically relevant plasma levels; at lower concentrations (20–50 μM), proliferative effects are minimal or absent, indicating a threshold-dependent rather than linear dose-response.[92] Current evidence supports an inhibitory effect of suprathreshold ketamine on NSC proliferation via calcium-dependent signaling, but translational significance remains uncertain (Table 1).

Propofol exhibits concentration-dependent biphasic effects on NSC proliferation. At clinically relevant concentrations (~10 μM), propofol promotes proliferation of human neural progenitor cells (hNPCs) and adult rat NSCs through Ca^{2+}-dependent CREB phosphorylation.[11,94] At higher concentrations (≥100-200 μM), it inhibits NSC proliferation through ER calcium release via $InsP_3Rs$ and Ca^{2+}-PKCα-ERK1/2 pathway activation.[95–97] These opposing effects reflect the differential magnitude of ER calcium release: moderate mobilization activates pro-proliferative CaMK-CREB signaling, whereas excessive release engages inhibitory cascades (Table 2).

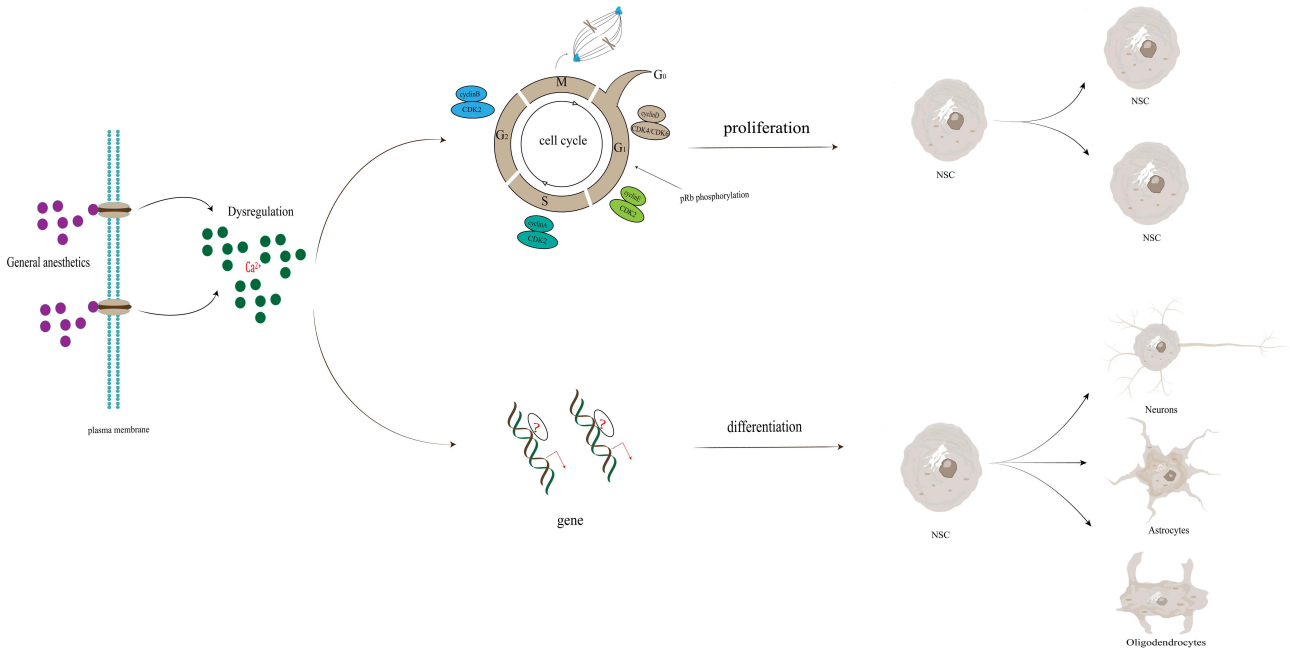

Figure 3 Anesthetic exposure leads to calcium homeostasis dysregulation in NSCs. General anesthetic exposure disrupts calcium homeostasis, interfering with cell-cycle progression and differentiation-related gene expression, thereby affecting NSC proliferation and fate selection.
Abbreviations: NSCs, neural stem cells; CDKs, cyclin-dependent kinases; pRb, retinoblastoma protein.

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Table 1 Calcium Homeostasis Dysregulation Mechanisms of Ketamine and Midazolam Induced Developmental Neurotoxicity

Anesthetic	Animal and Cell Sources	Mechanisms of Calcium Homeostatic Dysregulation	Cell Survival/ Proliferation and Differentiation of NSCs or NPCs/ Neuronal Migration/Axonal and Dendritic Development	References
Ketamine	ED16 SD rat cortical neural stem cells	Elevates calcium concentration in differentiated neurons	Promotes neural stem cell-derived neuronal apoptosis/ / /	[93]
Ketamine	ED19 Wistar rat hippocampal neurons	Increases cytoplasmic calcium concentration, decreases amplitude and frequency of calcium oscillations, downregulates CaMKII, reduces synapsin, and increases caspase-3	Promotes neuronal apoptosis/ / / Affects dendritic and synaptic development	[12]
Ketamine	PND3 SD rat hippocampal neural stem cells	Inhibits of Ca^{2+}-PKCα-ERK1/2 signaling by suppressing of L-type VDCC	/ Inhibits proliferation/ /	[92]
Midazolam	PND1 SD rat hippocampal neural stem cells	Mediates calcium inward flow through $GABA_A$ receptor-dependent.	/ Inhibits proliferation/ /	[15]

Abbreviations: SD, Sprague-Dawley; PND, postnatal day; ED, embryonic day; NSCs, neural stem cells; NPCs, neural progenitor cells; CaMKII, Ca^{2+}/calmodulin-dependent kinase II; L-type VDCC, L-type voltage dependent Ca^{2+} channel; PKCα, protein kinase C-α; ERK, extracellular signal-regulated kinase; $GABA_A$ receptor, γ-aminobutyric acid type A receptor.

Table 2 Calcium Homeostasis Dysregulation Mechanisms of Propofol Induced Developmental Neurotoxicity

Anesthetic	Animal and Cell Sources	Mechanisms of Calcium Homeostatic Dysregulation	Cell Survival/ Proliferation and Differentiation of NSCs or NPCs/ Neuronal Migration/Axonal and DENDRITIC Development	References
Propofol	Rat adult stem cells	Increased cytoplasmic calcium concentration and increased P-CREB	/ Promote proliferation/ /	[94]
Propofol	hNPC	Increases cytoplasmic calcium concentration and activates autophagy via $InsP_3R$ and RyR. Activates autophagy in a concentration dependent manner	Autophagy induces cell death/ Excessive autophagy activation inhibits proliferation and promotes glial cell differentiation/ /	[11]
Propofol	Neurons SY5Y cells	Increases cytoplasmic calcium concentration and activates autophagy via $InsP_3R$ and RyR. Inhibits the mTOR-dependent pathway, impairs autophagic flux, disrupts mitochondrial structure, decrease ATP levels, and increases caspase-3 activation in a concentration dependent manner	Physiological autophagy protects neurons from damage/ / /	[98]
Propofol	PND1 SD rat hippocampal neural stem cells	Reduces cytoplasmic calcium concentration	Promote apoptosis/ Inhibits proliferation and reduces the ratio of neurons to glial cells/ /	[96]

(*Continued*)

Table 2 (Continued).

Anesthetic	Animal and Cell Sources	Mechanisms of Calcium Homeostatic Dysregulation	Cell Survival/ Proliferation and Differentiation of NSCs or NPCs/ Neuronal Migration/Axonal and DENDRITIC Development	References
Propofol	PND3 SD rat hippocampal neural stem cells	Inhibits Ca^{2+}-PKCα-ERK1/2 signaling pathway by suppressing L-type VDCC	/ Inhibits proliferation/ /	[95]
Propofol	ED15.5 Mouse hippocampal neural stem cells	Inhibits CaMKII/pS485/AMPK/ATF5 signaling pathway	/ Inhibits proliferation and differentiation/ Inhibits migration/	[97]

Abbreviations: SD, Sprague-Dawley; PND, postnatal day; ED, embryonic day; NSCs, neural stem cells; NPCs, neural progenitor cells; hNPC, human neural progenitor cells; $InsP_3R$, inositol-1,4,5-triphosphate receptors; RyR, ryanodine receptor; CREB, cAMP response element-binding protein; mTOR, mammalian target of rapamycin; ATP, adenosine triphosphate; L-type VDCC, L-type voltage dependent Ca^{2+} channel; PKCα, protein kinase C-α; ERK, extracellular signal-regulated kinase; pS485, phosphorylation of serine at amino acid position 485; AMPK, 5' adenosine monophosphate-activated protein kinase; ATF5, activating transcription factor 5.

Isoflurane similarly exhibits concentration- and duration-dependent biphasic effects, promoting proliferation at low concentrations while suppressing it at higher or prolonged exposures through $InsP_3R$- and RyR-dependent ER Ca^{2+} release.[99] Midazolam at clinical concentrations inhibits neonatal rat hippocampal NSC proliferation by increasing calcium influx through $GABA_A$ receptor-mediated depolarization[100] (Tables 1 and 3).

Table 3 Calcium Homeostasis Dysregulation Mechanisms of Inhalational Anesthetic Induced Developmental Neurotoxicity

Anesthetics	Animal and Cell Sources	Mechanisms of Calcium Homeostatic Dysregulation	Cell Survival/ Proliferation and Differentiation of NSCs or NPCs/ Neuronal Migration/Axonal and Dendritic Development	References
Sevoflurane	Hippocampal neurons HT22 cell	Increases cytoplasmic calcium concentration and activates the WNK1/NKCC1/Ca^{2+}/Drp-1 signaling	Promotes apoptosis/ / /	[14]
Isoflurane	E16-17 Mouse cortical hippocampal neuron	Releases calcium from the ER via $InsP_3R$, promotes extracellular calcium influx and mitochondrial calcium overload, and activates caspase-3 and BACE	Promotes apoptosis/ / /	[99]
Sevoflurane	PND8 Mouse hippocampal neurons	Activates GABA receptors and L-type VDCC, Increases cytoplasmic calcium concentration. Induces neuroinflammation via IL-1β, IL-6.	Promotes apoptosis/ Inhibits proliferation/ / Inhibits the growth of dendritic spines	[76]
Isoflurane	PC12 cells	Activation of $InsP_3R$ induces the release of calcium from the ER, leading to an increase in cytoplasmic and mitochondrial calcium concentrations	Promotes apoptosis/ / /	[101]
Sevoflurane	PND1 SD rat hippocampal neurons	Elevates cytoplasmic calcium via L-type VDCC inducing mitochondrial damage, increases expression of ROS and caspase-3, Cyt c release, and Bax/Bcl-2 ratio	Promotes apoptosis/ / /	[77]
Isoflurane	ED16-18 Rat cortical neurons	Releases calcium from the ER via $InsP_3R$, inducing a rapid increase in cytoplasmic calcium concentration	Promote apoptosis/ / /	[102]

(*Continued*)

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Table 3 (Continued).

Anesthetics	Animal and Cell Sources	Mechanisms of Calcium Homeostatic Dysregulation	Cell Survival/ Proliferation and Differentiation of NSCs or NPCs/ Neuronal Migration/Axonal and Dendritic Development	References
Isoflurane	ED15 Mouse cortical neurons	Causes ER stress via RyR, and activates CHOP, caspase-12 and caspase-3	Promote apoptosis/ / /	[80]
Isoflurane	ED15 Mouse cortical neurons	Induces calcium release from the ER, increases ROS and Bax, decreases Bcl-2, and activates caspase9/3	Promotes apoptosis/ / /	[103]
Isoflurane	hNPC	Increases cytoplasmic calcium concentration via $InsP_3R$ and RyR	Excessive increased calcium promotes apoptosis/ Excessive increased calcium elevation inhibits proliferation, suppresses neuronal differentiation/ /	[99]
Isoflurane	ED18 SD rat hippocampal neurons	Increases cytoplasmic calcium via $InsP_3R$ via PLC-γ and induces an increase in HIF-1a	Promotes neuronal death/ / /	[104]

Abbreviations: SD, Sprague-Dawley; PND, postnatal day; ED, embryonic day; NSCs, neural stem cells; NPCs, neural progenitor cells; hNPC, human neural progenitor cells; $InsP_3R$, inositol-1,4,5-triphosphate receptors; RyR, ryanodine receptor; WNK1, lysine deficient protein kinase 1; NKCC1, Na^+-K^+-Cl^- cotransporter 1; Drp1,dynamin-related protein1; BACE, β-site amyloid β precursor protein-cleaving enzyme; ER, endoplasmic reticulum; L-type VDCC, L-type voltage dependent Ca^{2+} channel; IL-1β, interleukine-1β; IL-6, interleukine-6; ROS, reactive oxygen species; Cyt c, cytochrome c; Bax, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma 2; $GABA_A$, γ-aminobutyric acid type A; ROS, reactive oxygen species; CHOP, C/EBP homologous protein; PLC-γ, phosphoinositide phospholipase C; HIF-1a, hypoxia inducible factor-1α protein.

Observed inconsistencies likely reflect genuine biological variability: NSCs from different brain regions, species, or developmental stages exhibit distinct intrinsic calcium properties and may respond differentially to the same anesthetic stimulus. At the transcriptional level, anesthetic-induced calcium dysregulation disrupts NSC proliferation primarily through CaMK-CREB and calcineurin-NFAT imbalance.[11] Oscillation suppression by NMDAR antagonists impairs CREB-driven proliferative gene expression, while sustained Ca^{2+} elevation by GABAergic agents activates calcineurin-dependent upregulation of CKIs and cell-cycle arrest.[11,105]

Effects on NSC Differentiation and Fate Determination

NSC differentiation is a process in which asymmetric divisions progressively give rise to NPCs committing to neuronal, astrocytic, or oligodendrocytic lineages, regulated by intracellular signals and epigenetic modifications.[18,106] Anesthetic-induced calcium dysregulation can divert NSC fate in a concentration- and duration-dependent manner. Propofol exemplifies this dose-dependence: exposure of hNPCs to 10 μM for 24 hours increased Tuj1(β-tubulin III)-positive neurons while reducing glial fibrillary acidic protein (GFAP)-positive glia, indicating pro-neuronal differentiation; conversely, 200 μM propofol produced the opposite-reduced neuronal commitment and increased glial differentiation-through $InsP_3R$-mediated ER calcium release and autophagy activation.[11] (Table 2) Concentrations required to alter lineage specification in vitro (eg., 200 μM propofol) substantially exceed clinically relevant plasma levels; hNPCs versus rodent NSCs introduce biological variability; and differentiation outcomes are assessed by lineage marker immunostaining at single time points, which may not capture full complexity or reversibility. Isoflurane similarly disrupts NSC fate in a duration-dependent manner: prolonged exposure (24 hours at 2.4%) inhibited neuronal differentiation and promoted glial commitment in hNPCs, whereas short exposure (1 hour) had no significant effect on lineage choice-both associated with $InsP_3R$- and RyR-mediated ER calcium release[99] (Table 3).

Mechanistically, fate-altering effects arise from disruption of calcium-dependent transcriptional programs. (Figure 3) Physiologically patterned signals activate CREB-driven NeuroD expression and neuronal commitment; their disruption through excessive Ca^{2+} or oscillation suppression impairs CREB-dependent neuronal gene expression and may redirect

cells toward glial fates through enhanced calcineurin-NFAT signaling. Oscillation frequency further specifies neuronal subtype: high-frequency oscillations favor GABAergic and lower frequencies favor glutamatergic identity. Anesthetic agents that alter oscillation frequency may therefore perturb neuronal subtype specification with consequences for circuit assembly.

Effects on NSC and Neuronal Survival

Anesthetic-induced calcium dysregulation exerts direct cytotoxic effects on post-mitotic neurons and NSCs, primarily through apoptotic and autophagic pathways. Although both apoptosis and autophagy serve essential roles in normal neurodevelopment,[34,107] pathological calcium overload disrupts this balance: sustained cytosolic Ca^{2+} elevation triggers mitochondrial calcium uptake, impairs ATP synthesis, generates ROS, induces cytochrome c release, and activates caspase-3-dependent apoptosis.[101,103,108,109] Elevated Ca^{2+} also activates autophagy through Ca^{2+}/calmodulin-dependent signaling, and excessive autophagic flux can transition from cytoprotective to cytodestructive.[110]

Sevoflurane induced $GABA_A$ receptor-mediated neuron depolarization, VDCC activation, elevated Ca^{2+}, and apoptosis.[14,76,77,102] In neonatal non-human primates, prolonged ketamine induced apoptosis and necrosis through NMDAR upregulation and subsequent excitotoxic calcium overload upon withdrawal.[111] Propofol produces dose-dependent cell death in hNPCs: clinically relevant concentrations exert minimal cytotoxicity, whereas high concentrations trigger excessive ER Ca^{2+} release via $InsP_3Rs$ or RyRs, leading to pathological autophagy and cell death.[11] (Tables 1 and 2) Both $GABA_A$ receptor agonists and NMDAR antagonists converge on shared downstream calcium entry pathways via L-type VDCCs, $InsP_3R$, and RyRs to elevate cytosolic Ca^{2+} and initiate cell death cascades.[11,76,95,98,104] In immature neurons and NSCs, GABA-induced depolarization directly activates VDCCs,[32] while NMDAR blockade produces delayed overload through compensatory receptor upregulation upon withdrawal.[78,93] The convergence of mechanistically distinct anesthetics on shared calcium-dependent death pathways underscores the centrality of calcium dysregulation in AIDN.

Effects on Neuronal Maturation

Calcium signaling regulates structural and functional maturation of post-mitotic neurons including axonal growth, dendritic elaboration, synapse formation, and synaptic protein expression (Figure 2), with CaMKII playing a particularly prominent role in transducing calcium oscillations into structural neuronal changes.[69,112] Exposure to 25 μM S(+)-ketamine for 24 hours significantly reduced synaptic protein expression in immature neurons, associated with decreased Ca^{2+} oscillation amplitude and frequency and reduced CaMKII expression.[12] Midazolam similarly impaired synaptic integrity: prolonged exposure (100 and 300 nM, 24 hours) reduced synaptic protein expression and disrupted synaptic architecture through $GABA_A$ receptor-mediated suppression of calcium oscillation amplitude and frequency.[15] (Table 1) As both excessive elevation and suppression of calcium signaling impair neuronal maturation, normal neuronal architecture requires a precisely tuned range of calcium oscillatory activity.[67,68,71,72]

Mechanistic Integration

Anesthetic-induced calcium dysregulation propagates through ER-mitochondria coupling, oxidative stress amplification, and calcium-dependent transcriptional imbalance to produce both structural and functional neurodevelopmental abnormalities. Excessive ER calcium release via $InsP_3Rs$ and RyRs drives mitochondrial calcium overload, leading to membrane potential dissipation, impaired ATP synthesis, cytochrome c release, and caspase-dependent apoptosis (Figure 4).

Anesthetic-induced perturbation of calcium dynamics disrupts the physiological CaMK-CREB vs. calcineurin-NFAT transcriptional balance, shifting cellular responses from adaptive toward maladaptive programs. This transcriptional imbalance is further compounded: sustained ROS elevation and prolonged calcium overload progressively suppress CaMKII/IV-mediated CREB phosphorylation while enhancing calcineurin activity, simultaneously removing pro-survival transcriptional support and activating pro-apoptotic and fate-altering programs.

Furthermore, calcium dysregulation impairs synaptic development in neurons that survive the anesthetic insult. CaMKII-mediated phosphorylation of synaptic proteins and CREB-dependent transcription are essential for dendritic elaboration and synapse formation; anesthetic-induced oscillation suppression reduces both, leading to diminished

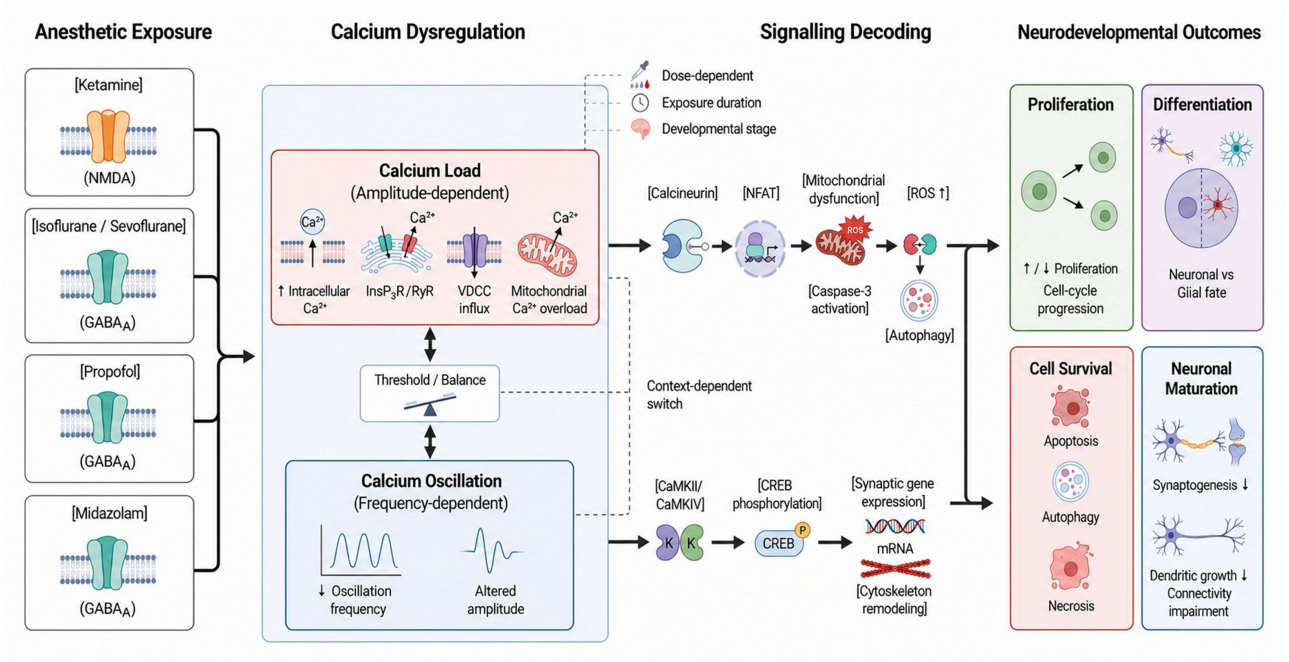

Figure 4 Mechanistic framework of anesthetic-induced developmental neurotoxicity mediated by calcium dysregulation. Anesthetics including ketamine, isoflurane/sevoflurane, propofol, and midazolam act primarily as $GABA_A$ receptor agonists or NMDA receptor antagonist. Anesthetic exposures induce calcium dysregulation by both calcium load and oscillatory calcium dynamics. Intracellular calcium load can be dysregulated by receptor modulation, ER calcium release, VDCC-mediated calcium influx, and mitochondrial calcium overload in an amplitude-dependent manner. Calcium Oscillations are disturbed via changing oscillation frequency and amplitude alteration by anesthetic exposures. Calcium dysregulation activates the calcineurin-NFAT pathway, promoting mitochondrial dysfunction, ROS generation, apoptosis, and autophagy. In contrast, disturbance of physiological calcium load and oscillations also impairs CaMK-CREB signaling, reducing synaptic gene expression and cytoskeletal remodeling. Together, these mechanisms contribute to abnormal proliferation, altered neuronal-glial differentiation, impaired neuronal maturation and synaptogenesis, and reduced cell survival. The final outcome is influenced by anesthetic dose, exposure duration, and developmental stage.

Abbreviations: NMDA, N-methyl-D-aspartate; $GABA_A$, γ-aminobutyric acid-type A; $InsP_3R$, inositol-1,4,5-trisphosphate receptor; RyR, ryanodine receptor; NFAT, nuclear factor of activated T-cells; ROS, reactive oxygen species; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CaMKIV, Ca^{2+}/calmodulin-dependent protein kinase IV; CREB, cAMP response element-binding protein; CDK, cyclin-dependent kinase; VDCC, voltage-dependent calcium channel.

synaptic protein expression and compromised connectivity independently of cytotoxicity. This dissociation between cell death and functional impairment suggests that surviving neurons may carry lasting deficits in connectivity and circuit function, meaning the neurodevelopmental consequences of early anesthetic exposure may be substantially broader than apoptotic endpoints alone.

Translational Implications

Translation of preclinical calcium dysregulation findings to clinical practice remains substantially limited by a fundamental gap between experimental models and clinical reality. The majority of mechanistic evidence derives from in vitro systems and rodent models employing supraclinical concentrations, raising concerns about physiological relevance and species transferability. This gap is reflected in inconsistent clinical findings and ongoing regulatory debate. In 2016, the FDA issued a Drug Safety Communication warning that repeated or prolonged GA in children under three may affect brain development, while acknowledging an incomplete evidence base.[3] This precautionary posture, informed primarily by preclinical rather than definitive clinical evidence, underscores the urgency of mechanistically grounded translational research.

From a mechanistic standpoint, the calcium signaling cascade offers several potentially tractable therapeutic targets. Pharmacological agents with indirect calcium-modulatory properties including antioxidants, mitochondrial stabilizers, and neurotrophic factor modulators such as BDNF pathway activators, have demonstrated neuroprotective potential in preclinical models, though safety profiles, target specificity, and developmental stage-dependent efficacy remain incompletely characterized, and none has been evaluated in controlled pediatric clinical trials.

A complementary consideration is optimization of anesthetic exposure parameters. Given that anesthetic-induced calcium dysregulation is sensitive to dose, duration, and developmental timing, minimizing unnecessary exposure and avoiding repeated anesthetics during critical neurodevelopmental windows may meaningfully reduce risk without pharmacological intervention. A precision-based approach to anesthetic protocol design, informed by understanding of developmental calcium vulnerability windows, represents a practical near-term strategy.

Conclusions and Perspectives

Current evidence supports calcium signaling dysregulation as an important convergent mechanism linking anesthetic exposure to neurodevelopmental alterations across multiple stages of development. General anesthetics, $GABA_A$ receptor agonists and NMDAR antagonists, disrupt intracellular Ca^{2+} homeostasis through complementary upstream mechanisms, impairing NSC proliferation, differentiation, survival, and neuronal maturation. At the molecular level, these effects are mediated through excessive cytosolic Ca^{2+} elevation, pathological ER-mitochondria calcium transfer, and CaMK-CREB vs. calcineurin-NFAT imbalance, collectively driving mitochondrial dysfunction, oxidative stress, apoptosis, impaired neurogenesis, and neuronal maturation (Figure 4).

Several important knowledge gaps nonetheless remain. The precise role of calcium oscillation dynamics, frequency- and amplitude-dependent encoding, in mediating anesthetic neurotoxicity in vivo is incompletely characterized. The relative contributions of different calcium sources, anesthetic agents, and exposure paradigms to specific neurodevelopmental outcomes require more systematic evaluation. Whether transcriptional and structural deficits observed preclinically are reversible, and under what conditions, remains an open question with direct clinical relevance.

Addressing these gaps requires new experimental approaches. Physiologically relevant in vivo calcium imaging will be essential for directly characterizing spatiotemporal calcium dysregulation in living neural tissue under anesthetic conditions. Human induced pluripotent stem cell (iPSC)-derived NSC models offer a means of bridging the species gap and recapitulating human-specific neurodevelopmental calcium signaling. Clinically relevant dose-response and exposure-duration studies are needed to distinguish adaptive from pathological calcium responses and define genuine neurotoxic thresholds. Targeting calcium signaling at the level of ER calcium release, mitochondrial homeostasis, or downstream transcriptional effectors may ultimately yield neuroprotective strategies that improve the safety of anesthetic agents in early life.

Abbreviations

ADHD, attention-deficit/hyperactivity disorder; AIDN, anesthetic-induced developmental neurotoxicity; AMPARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; aNSCs, activated neural stem cells; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; BDNF, brain-derived neurotrophic factor; BGS, brain growth spurt; Ca^{2+}, calcium ion; CaM, calmodulin; CaMKs, Ca^{2+}/calmodulin-dependent protein kinases; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CDKs, cyclin-dependent kinases; CKIs, cyclin-dependent kinase inhibitors; CREB, cAMP response element-binding protein; CRAC, calcium release-activated calcium; Cyt c, cytochrome c; EGF, epidermal growth factor; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinase 1/2; GA, general anesthesia; GABA, γ-aminobutyric acid; $GABA_A$ receptor, γ-aminobutyric acid type A receptor; GFAP, glial fibrillary acidic protein; hNPCs, human neural progenitor cells; IL-1β, interleukin-1 beta; IL-6, interleukin-6; InsP3, inositol-1,4,5-trisphosphate; InsP3Rs, inositol-1,4,5-trisphosphate receptors; IQ, intelligence quotient; LDs, learning disabilities; MAMs, mitochondria-associated membranes; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; mTOR, mechanistic target of rapamycin; NCX, Na+/Ca^{2+} exchanger; NCLX, mitochondrial Na+/Ca^{2+} exchanger; NFAT, nuclear factor of activated T-cells; NMDARs, N-methyl-D-aspartate receptors; NPCs, neural progenitor cells; NSCs, neural stem cells; pRb, retinoblastoma protein; PKCα, protein kinase C alpha; PMCA, plasma membrane Ca^{2+} ATPase; PND, postnatal day; qNSCs, quiescent neural stem cells; ROS, reactive oxygen species; RyRs, ryanodine receptors; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; SGZ, subgranular zone; SOCE, store-operated Ca^{2+} entry; STIM1, stromal interaction molecule 1; SVZ, subventricular zone; TRPCs, transient receptor potential canonical channels; Tuj1, neuron-specific class III β-tubulin; VDCCs, voltage-dependent calcium channels; VEGFR2, vascular endothelial growth factor receptor 2; WNK1, with-no-lysine kinase 1.

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Disclosure

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