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Calcium channels in anesthesia management: A molecular and clinical review

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Abstract

Calcium channels play an essential role in the molecular and physiological mechanisms underlying anesthesia by mediating intracellular calcium ion (Ca^{2+}) flux, which regulates key processes such as neurotransmitter release, neuronal excitability, and immune responses. Voltage-gated calcium channels (VGCCs) and ligand-gated calcium channels (LGCCs) are integral to the anesthetic process, with subtypes such as T-type VGCCs and NMDA receptors influencing consciousness and pain perception. This review emphasizes current evidence to highlight how anesthetic agents interact with calcium channels via direct inhibition and modulation of intracellular signaling pathways, such as phosphatidylinositol metabolism. Additionally, calcium channelopathies – genetic or acquired dysfunctions affecting VGCCs and LGCCs – pose challenges in anesthetic management, including arrhythmias, malignant hyperthermia, and altered anesthetic sensitivity. These findings underscore the critical need for precision medicine approaches tailored to patients with these conditions. While significant progress has been made in understanding the roles of calcium channels in anesthesia, knowledge gaps remain regarding the long-term implications of anesthetic interactions on calcium signaling and clinical outcomes. This review bridges foundational science with clinical practice, emphasizing the translational potential of calcium channel research for optimizing anesthetic strategies. By integrating molecular insights with emerging pharmacogenomic approaches, it provides a pathway for developing safer and more effective anesthesia protocols that enhance patient outcomes.

Keywords

Anesthesia, anesthetic mechanisms, calcium channels, calcium channelopathies

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Highlights

1. Calcium channels are pivotal mediators of anesthetic effects, influencing consciousness, pain perception, and synaptic activity.
2. T-type VGCCs and NMDA receptors play critical roles in thalamocortical oscillations and neuronal signaling during anesthesia.
3. Calcium channelopathies pose significant challenges in anesthesia, necessitating personalized approaches for affected patients.
4. Advancing knowledge of calcium channel interactions with anesthetics can optimize perioperative care and patient safety.

Introduction

General anesthesia, a cornerstone of modern medicine, provides a temporary suppression of consciousness, memory, pain perception, and motor responses, enabling complex surgical interventions.[1] Despite its transformative role, the molecular and cellular mechanisms underlying anesthesia remain incompletely understood. Among the numerous physiological systems implicated, calcium channels have emerged as key mediators, playing pivotal roles in translating the effects of anesthetics at the cellular level.[2] These channels, particularly voltage-gated calcium channels (VGCCs) and ligand-gated calcium channels (LGCCs), regulate intracellular calcium ion (Ca^{2+}) influx, a critical second messenger in

processes such as neurotransmitter release, synaptic plasticity, muscle contraction, and immune signaling.[3,4] The intricate regulation of calcium homeostasis underscores the relevance of these channels in anesthesia and their potential impact on perioperative outcomes.

The importance of VGCCs and LGCCs in the anesthetic mechanism has been highlighted by extensive research.[2] VGCCs, including L-, N-, P/Q-, R-, and T-type channels, are central to neuronal excitability and vascular tone regulation, while LGCCs, such as NMDA and P2X receptors, facilitate rapid calcium signaling in synaptic communication and immune responses.[5,6] Notably, T-type VGCCs play a pivotal role in thalamocortical oscillations, a mechanism that directly modulates consciousness and the depth of anesthesia.[7] Additionally, anesthetic agents such as propofol interact with intracellular signaling pathways, including phosphatidylinositol 4,5-bisphosphate (PIP2) metabolism, demonstrating that their mechanisms of action extend beyond direct channel inhibition.[8] These findings reveal the multifaceted influence of anesthetics on cellular signaling and highlight the need for further exploration.

However, significant gaps in understanding remain. For instance, while VGCC inhibition has been linked to key anesthetic effects, the long-term consequences of these interactions on neuronal function and recovery are poorly characterized.[9] Furthermore, calcium channelopathies – genetic or acquired dysfunctions of calcium channels – introduce additional complexity to anesthetic management.[10] These conditions, including mutations in VGCC subtypes and dysregulation of LGCCs, are associated with altered anesthetic responses, heightened susceptibility to arrhythmias, malignant hyperthermia, and challenges in perioperative care.[11] The prevalence of these conditions underscores the critical need for tailored anesthetic protocols to address the unique physiological and pharmacological challenges they present.

The exploration of calcium channels in anesthetic research has evolved over decades, shifting from a primary focus on sodium channels to a broader appreciation of calcium channels' diverse roles in neuronal and systemic physiology.[11] The discovery of T-type VGCC involvement in thalamocortical regulation marked a turning point, illuminating their critical contribution to the modulation of consciousness.[7] More recently, the intersection of calcium channel function with pharmacogenomics and personalized medicine has emerged as a promising avenue for improving anesthetic safety and efficacy.[12]

This review synthesizes the existing literature on the roles of calcium channels in anesthesia, emphasizing their dual function as mediators of anesthetic effects and contributors to potential perioperative complications. By integrating findings from molecular, physiological, and clinical studies, this study highlights the translational potential of calcium channel research in refining anesthetic strategies. It also underscores the need for a deeper understanding of calcium signaling dynamics to develop more precise and effective perioperative management protocols.

By addressing these critical aspects, this review aims to bridge the gap between basic science and clinical practice, offering insights into the nuanced interactions between anesthetic agents and calcium channels. The ultimate goal is to contribute to a foundation for innovative approaches that optimize patient care and ensure the safety and efficacy of anesthetic interventions.

Voltage-gated calcium channels (VGCCs)

Voltage-gated calcium channels (VGCCs) are essential membrane proteins that mediate the entry of calcium ions (Ca^{2+}) into cells in response to changes in membrane potential.[13] These channels play a pivotal role in converting electrical signals into biochemical responses, influencing processes such as neurotransmitter release,[14] muscle contraction,[15] gene expression,[16] and synaptic plasticity.[17]

Structurally, VGCCs are heteromultimeric complexes composed of several subunits. The α_1 subunit forms the central pore and determines the channel's ion selectivity and gating properties. This subunit contains four homologous domains (I–IV), each with six transmembrane segments (S1–S6). The S4 segment acts as the voltage sensor, while the S5–S6 segments contribute to the ion-conducting pore. The auxiliary subunits (β, γ, $\alpha_2\delta$) play critical roles in modulating the biophysical properties, surface expression, and trafficking of the α_1 subunit.[18] Among these, the β subunit interacts directly with the α_1 subunit via a conserved binding site, influencing voltage dependence and kinetics. The $\alpha_2\delta$ subunit, a disulfide-linked complex, enhances current density and channel stability.[19] The process of action potential generation and propagation in the presynaptic neuron, along with the crucial role of VGCCs in triggering neurotransmitter release and the modulatory effects of anesthetics, is illustrated in Figure 1.

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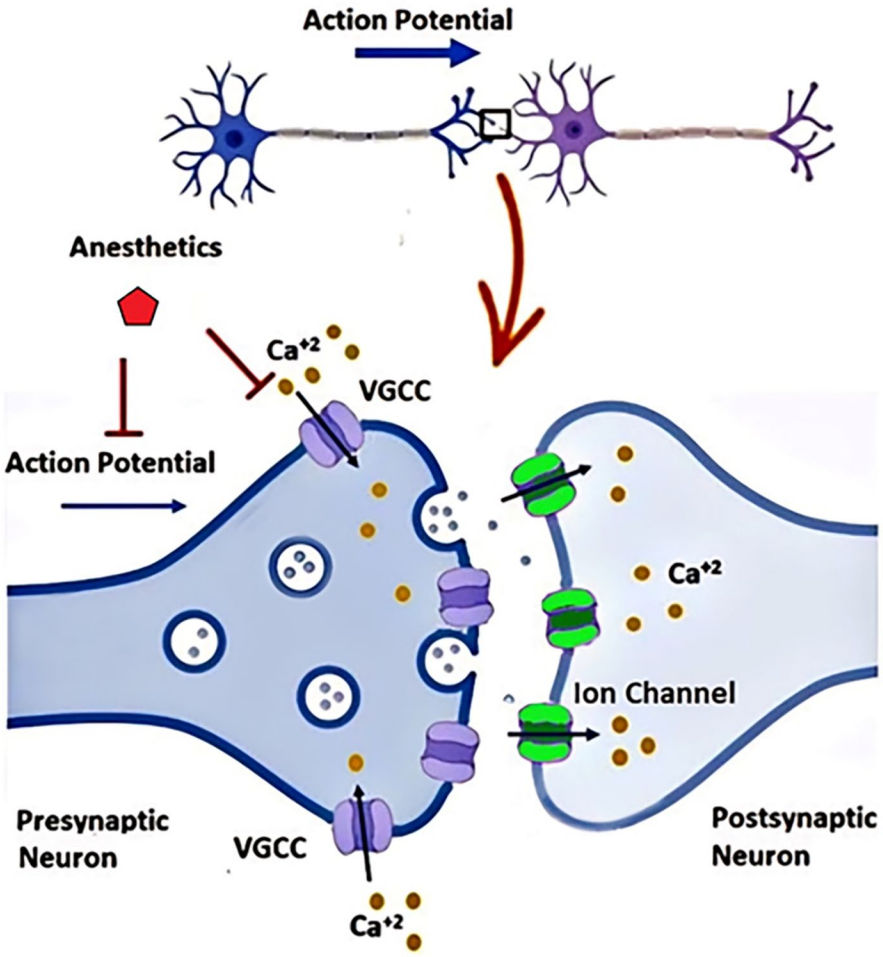

Figure 1. Schematic representation of action potential generation and propagation in the presynaptic neuron, illustrating the vital role of voltage-gated calcium channels (VGCCs) in neurotransmitter release and the modulatory effects of anesthetics. Upon arrival of the action potential at the presynaptic terminal, VGCCs open and permit calcium influx, triggering synaptic vesicle fusion and neurotransmitter release into the synaptic cleft. These neurotransmitters subsequently bind to postsynaptic receptors, eliciting a cellular response. By blocking or modulating VGCCs and other ion channels, anesthetics diminish neurotransmitter release and attenuate synaptic transmission, thereby exerting their anesthetic effect (The figure was drown by *Biorender*).

Types of VGCCs and cellular and molecular mechanisms

VGCCs are classified into two main categories based on their activation threshold and kinetic properties: high-voltage-activated (HVA) and low-voltage-activated (LVA) channels. HVA channels include:

L-type channels: Found in cardiac, skeletal, and smooth muscle, as well as neurons, they are key to excitation-contraction coupling and long-lasting Ca^{2+} signaling.[20]
N-type channels: Predominantly located in neurons, they regulate neurotransmitter release at synaptic terminals.[21]
P/Q-type channels: Highly expressed in presynaptic terminals, they are involved in fast synaptic transmission.[22]
R-type channels: Found in neurons and other tissues, their precise roles remain less defined but include contributions to synaptic plasticity.[23]

LVA channels, represented by T-type channels, are activated by small depolarizations and are involved in rhythmic firing, pacemaker activity, and neuronal excitability. These channels are particularly abundant in the thalamus and contribute to oscillatory activity.[24]

At the cellular and molecular level, VGCCs function through a highly coordinated mechanism. Depolarization of the membrane potential triggers a conformational change in the voltage-sensing domains of the α_1 subunit, leading to the opening of the channel pore.[25] This allows extracellular Ca^{2+} to flow into the cytoplasm, resulting in a localized increase in intracellular Ca^{2+} concentration. The influx of Ca^{2+} serves

Table 1. Overview of calcium channels, anesthetic drugs, and associated channelopathies.

Calcium channel type	Example channel	Role in anesthetic process	Effects of anesthetic drugs	Associated disorders (channelopathies)
Voltage-gated calcium channels (VGCCs)	L-type, T-type, N-type, P/Q-type, R-type	Regulate neuronal excitability and muscle contraction	Inhibit calcium influx into neurons; reduce synaptic excitability (e.g. propofol, local anesthetics)	Familial hemiplegic migraine, episodic ataxia, sensitivity to anesthetics, malignant hyperthermia
Ligand-gated calcium channels (LGCCs)	NMDA, P2X, nAChR, 5-HT3, RYR1	Facilitate rapid and localized calcium signaling in response to ligands	NMDA receptor inhibition (e.g. ketamine), synaptic modulation, and analgesia (e.g. propofol)	Neurological disorders such as Alzheimer's, chronic pain, cardiac dysrhythmias
Store-operated calcium channels (SOCs)	STIM1/Orai1	Maintain calcium homeostasis and regulate immune responses	Anesthetics can modulate SOC activity, offering neuroprotective or neurotoxic effects depending on dosage	Immune deficiency (e.g. STIM1/Orai1-related), susceptibility to malignant hyperthermia

as a second messenger, activating downstream signaling pathways such as exocytosis, muscle contraction, and activation of calcium-dependent enzymes. The channels rapidly inactivate via voltage-dependent or calcium-dependent mechanisms, which ensure precise control of calcium signaling. Auxiliary subunits modulate these processes, fine-tuning the channel's response to physiological demands.[26]

The physiological significance of VGCCs extends to a wide range of tissues. In the nervous system, they govern synaptic communication by triggering vesicle fusion and neurotransmitter release. In the cardiovascular system, L-type channels drive cardiac muscle contraction and vascular tone regulation.[27] Dysregulation of VGCCs is implicated in various pathologies, including chronic pain, epilepsy, hypertension, and neurodegenerative disorders. For instance, mutations in CACNA1A, the gene encoding the α_1A subunit of P/Q-type channels, are associated with familial hemiplegic migraine and episodic ataxia.[28]

Interaction between anesthetics and VGCCs

Recent investigations have shed light on the intricate relationship between anesthetics and VGCCs, particularly focusing on how these channels mediate the physiological effects of anesthetics. The key findings indicate that VGCCs, especially the T-type VGCCs (CaV3.1 and CaV3.2), play a pivotal role in neuronal excitability control, which is of paramount importance during the administration of anesthetics (Table 1).

Joksimovic et al.[29] emphasize that VGCC inhibition leads to decreased excitatory neurotransmission, an essential aspect when considering the mechanisms underlying anesthetic action and analgesia. This is supported further by Timic Stamenic et al.,[7] who elaborate on how CaV3.1 channels directly influence thalamic activity related to anesthetic-induced hypnosis. For instance, the involvement of T-type channels in oscillatory activity in the thalamus suggests they have an important role in regulating consciousness and depth of anesthesia.

In a detailed review of local anesthetics, Yanagidate and Strichartz[30] outline that local anesthetics primarily inhibit VGCCs alongside their more established action on voltage-gated sodium channels. Their ability to attenuate calcium entry at nerve terminals leads to a decrease in neurotransmitter release, thereby modulating pain pathways effectively. The authors note that this action occurs through a combination of inhibiting excitatory transmission and altering glial responses, crucial for managing pain. Anesthetics influence both presynaptic Ca^{2+} dynamics and postsynaptic receptor function, thereby modulating synaptic efficacy (see Figure 2).

Recent studies also evaluate how anesthetics impact phosphatidylinositol 4,5-bisphosphate (PIP2) signaling pathways. Parikh et al.[8] reveal that the modification of PIP2 signaling by volatile anesthetics and propofol can lead to alterations in VGCC behavior, thereby emphasizing a more complex mechanism of action that extends beyond direct channel inhibition. This interaction suggests a modulatory role of phospholipid signaling in anesthetic efficacy, highlighting the need to consider various molecular mechanisms when developing anesthetic strategies.

Hao et al.[31] contribute by outlining the understanding of synaptic transmission dynamics under the influence of general anesthetics. The evidence indicates that VGCCs serve as key players in synaptic plasticity modulation, which could account for some of the broader behavioral changes observed during anesthesia, such as amnesia and analgesia.

Voltage-gated calcium channel disorders significantly affect patients undergoing anesthesia by potentially contributing to increased cardiac morbidity, perioperative complications, and alterations in anesthetic drug responses. Understanding the implications of voltage-gated calcium channel disorders in the context of anesthesiology is imperative, as these channels play a critical role in various

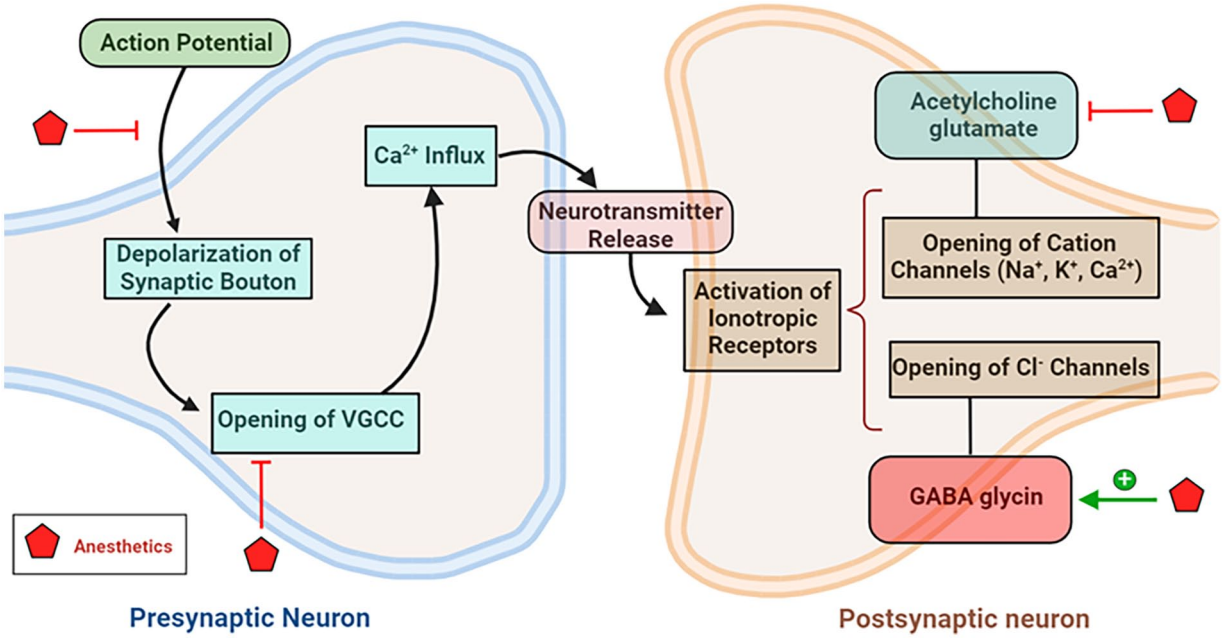

Figure 2. Schematic representation of synaptic transmission and the modulatory effects of anesthetics. Upon arrival of an action potential at the presynaptic terminal, voltage-gated calcium channels (VGCC) open, allowing Ca^{2+} influx and triggering the release of neurotransmitters (e.g. acetylcholine, glutamate, GABA, glycine). These neurotransmitters then bind to ionotropic receptors on the postsynaptic membrane, leading to the opening of either cation channels (Na^+, K^+, Ca^{2+}) and subsequent depolarization (excitatory response), or Cl^- channels and hyperpolarization (inhibitory response). Anesthetics can influence both presynaptic Ca^{2+} dynamics and postsynaptic receptor function, thereby modulating synaptic efficacy and overall neuronal excitability (The figure was drown by *Biorender*).

physiological functions. Research discussing their impact during anesthesia primarily indicates a connection to cardiovascular stability and drug interactions, underscoring the necessity for anesthesiology to adapt to the unique needs of patients affected by these disorders.

Zhou et al.[32] performed a meta-analysis examining the relationship between preoperative antihypertensive medications, which often include calcium channel blockers (CCBs), and the incidence of postoperative atrial fibrillation (POAF) in 130,087 patients. Their findings demonstrated that patients on CCBs had a significantly higher incidence of POAF ($p < 0.05$), suggesting that while CCBs serve to manage hypertension, they might inadvertently escalate arrhythmic risks during the perioperative period.[32] This correlation necessitates an examination of the patients' underlying calcium channel dysfunctions when considering anesthetic regimens.

Furthermore, Espinosa et al.[33] explored the acute blood pressure management using Clevidipine, a drug acting on L-type calcium channels. Their meta-analysis emphasized the efficacy of Clevidipine in maintaining perioperative blood pressure without significant adverse effects compared to other agents. Notably, the rapid action of Clevidipine highlights the importance of targeting calcium channels for quick hemodynamic stabilization during anesthesia, particularly in patients predisposed to intraoperative hypotension.

In another systematic review, Wijeysundera and Beattie[34] assessed the benefits of CCBs in reducing cardiac complications during noncardiac surgeries. Their analysis of 1007 patients revealed that CCBs significantly reduced ischemia (RR = 0.49, 95% CI: 0.30–0.80) and supraventricular tachyarrhythmias (SVT; RR = 0.52, 95% CI: 0.37–0.72).[34] Although the results advocate for the utility of CCBs in mitigating specific cardiac risks, they also highlight that there is a potential for heightened vulnerability in patients with pre-existing calcium channelopathies, further complicating anesthetic management.

Magnesium's effect as a modulator of calcium channels provides additional context relevant to anesthesia. Soave et al.[35] discussed magnesium's dual role in anesthetic efficacy and cardiovascular stability. Magnesium's interaction with voltage-gated calcium channels might exacerbate or alleviate anesthetic depth – indicating the need for tailored dosing regimens when managing patients with known calcium channel disorders or electrolyte imbalances.[35] This underscores the pressing need for anesthesia providers to be attuned to underlying calcium signaling alterations during surgical interventions.

Further research by Cohen and Dragovich[36] provided perspective on intrathecal analgesia, wherein fluctuations in calcium homeostasis could influence analgesic potency via altered drug interactions with neuronal voltage-gated

calcium channels, thus posing a potential risk for patients with channelopathies. The necessity of understanding these implications emphasizes the delicate balance anesthesiologists must maintain when managing patients with known calcium channel disorders.

Despite the promising evidence, the quality of some studies warrants caution. The investigations range in quality, with a need for further research to establish clear causal links and functional outcomes in clinical settings. For instance, Joksimovic et al. note the variability in VGCC responses among different anesthetic agents and the potential influence of individual patient factors on these mechanisms.

In summary, the collated literature establishes that anesthetics significantly affect VGCC function, contributing to their therapeutic effects. While several studies provide robust evidence regarding T-type channels' role in the anesthetic mechanism, further collaborative multi-disciplinary research involving pharmaceutical sciences and clinical practice is essential for refining anesthetic protocols.

Ligand-gated calcium channels (LGCCs)

Ligand-gated calcium channels (LGCCs) are a distinct class of membrane proteins that facilitate the influx of calcium ions (Ca^{2+}) in response to the binding of specific extracellular ligands.[37] Unlike VGCCs, which are activated by changes in membrane potential, LGCCs are directly gated by chemical signals such as neurotransmitters, hormones, or other small molecules.[38] This property makes them critical mediators of rapid and localized calcium signaling in various cellular contexts.

Structurally, LGCCs are typically composed of multiple subunits that form a central ion-conducting pore.[4] The extracellular domain of these channels contains ligand-binding sites, which, upon activation, induce conformational changes leading to the opening of the channel pore. Prominent examples of LGCCs include N-methyl-D-aspartate (NMDA) receptors, which are activated by glutamate and glycine, and purinergic P2X receptors, which respond to ATP.[39] These channels often exhibit selectivity not only for Ca^{2+} but also for other cations such as Na^+ and K^+, with calcium permeation being a key driver of downstream signaling.

Types of LGCCs and cellular and molecular mechanisms

LGCCs are classified based on their ligand specificity and functional roles:

Ionotropic glutamate receptors: These include NMDA, AMPA, and kainate receptors. NMDA receptors, in particular, are highly permeable to Ca^{2+} and play a central role in synaptic plasticity, learning, and memory.[40]

Purinergic P2X receptors: Found in a variety of tissues, these channels mediate calcium influx in response to extracellular ATP, influencing processes such as inflammation, pain perception, and tissue repair.[41]

Cys-loop receptors: Some members, such as nicotinic acetylcholine receptors (nAChRs) and serotonin type 3 (5-HT3) receptors, allow calcium influx, although they are primarily permeable to other cations.[42]

At the cellular and molecular level, LGCCs operate through ligand-induced activation. Upon ligand binding, conformational changes in the extracellular domain propagate to the transmembrane segments, leading to the opening of the ion-conducting pore. This permits the selective entry of Ca^{2+}, which serves as a second messenger to activate downstream signaling cascades.[43] In neurons, this can result in the activation of calcium-dependent kinases, modulation of gene expression, or initiation of synaptic vesicle release.[44] In non-neuronal tissues, LGCC-mediated calcium influx regulates processes such as muscle contraction, secretion, and immune responses.[45]

RYR1 (ryanodine receptor 1) is a crucial component of ligand-gated calcium channels located in the sarcoplasmic reticulum of skeletal muscle. It plays a vital role in excitation-contraction coupling, where it mediates the release of calcium ions (Ca^{2+}) necessary for muscle contraction. RYR1 channels are activated by voltage-dependent calcium channels in the plasma membrane, and their gating can be influenced by accessory proteins such as FKBP12, which stabilizes the channel's open and closed states.[46] The channel's activity is modulated by phosphorylation, particularly by protein kinase A (PKA), which can enhance channel activity by releasing FKBP12, leading to increased calcium release. Overall, RYR1 is essential for proper muscle function, and its dysregulation can lead to significant neuromuscular disorders.[47].

The physiological importance of LGCCs spans diverse systems. In the central nervous system, NMDA receptors are pivotal for synaptic transmission and plasticity, contributing to cognitive functions and neurodevelopment.[48] In the immune system, P2X receptors facilitate calcium-dependent signaling pathways that drive inflammatory and immune responses.[49] Dysregulation of LGCCs has been implicated in several diseases, including neurodegenerative disorders, chronic pain, and immune dysfunctions, highlighting their importance as potential therapeutic targets.[50,51]

Interaction between anesthetics and LGCCs

The discussion surrounding general anesthetics indicates that they primarily act through the potentiation of GABA receptor activity and inhibition of NMDA receptors, but emerging evidence suggests they also influence LGCCs. Anesthetics, particularly propofol, modulate calcium influx

through ligand-gated calcium channels, impacting both central nervous system and cardiac function. Propofol exhibits neuroprotective properties by enhancing GABA(A) receptor activity and inhibiting NMDA receptors, thus providing a protective mechanism against calcium overload.[52] The role of anesthetics in modulating ligand-gated calcium channels is complex and multi-faceted, predominantly characterized by their effects on central nervous system (CNS) function and cardiac physiology. Marik[53] provides a foundational understanding of propofol's neuropharmacological profile, noting its ability to activate GABA(A) receptors directly, leading to enhanced inhibitory synaptic transmission, while concurrently inhibiting NMDA receptors and modulating calcium influx through slow calcium channels. This dual action synergistically augments the anesthetic's sedative effects and contributes to the neuroprotective mechanisms observed during cerebral ischemia and other pathological states, as outlined in Kotani et al.[54] The authors document how propofol's interplay with calcium channels may reverse neuronal excitotoxicity, lending credence to its therapeutic potential in neuroprotection during anesthetic practices (Table 1).

In a complementary vein, Rimola et al.[55] elucidate how specific signaling lipids elicit calcium transients in sensory neurons. Their work accentuates the importance of lysophosphatidylcholine in activating calcium channels, providing insight into how anesthetics may elicit pain responses through calcium signaling modification.[55]

Ligand-gated calcium channel disorders significantly impact patients under anesthesia by contributing to complications such as vasoplegic syndrome after cardiac surgery, hemodynamic instability, and altered anesthetic responses. Effective management of perioperative blood pressure and myopathy associated with calcium channel dysfunction often relies on a combination of vasopressor therapies and proper anesthetic choice and dosing. The literature presents compelling evidence regarding the effects of LGCC disorders on patients undergoing anesthesia, largely highlighting their relevance in scenarios such as vasoplegic syndrome post-cardiac surgery and the pharmacodynamics of calcium channel blockers.[56]

Datt et al.[57] conducted a systematic review on vasoplegic syndrome (VPS) post-cardiac surgery, noting that the disorder occurs in 9%–40% of patients after cardiopulmonary bypass (CPB), with a reported mortality between 30% and 50% despite advances in management strategies. The underlying mechanisms postulated involve resistance to vasopressors, attributed to the inactivation of voltage-gated calcium channels, coupled with dysregulated vasodilator activity. Vasopressors like norepinephrine and vasopressin are indicated as first-line agents in managing VPS, highlighting the critical need to understand calcium channel dynamics in perioperative settings.

The genetic landscape surrounding calcium ion channel functioning offers an avenue for further exploration. Graham et al.[58] delve into ryanodine receptor polymorphisms that alter Ca^{2+} signaling pathways in nematodes, directly correlating these variations to sensitivity toward anesthetics like halothane. This intersection of molecular genetics and pharmacology underscores the nuanced relationship between genetic variance and anesthetic responsiveness. Patients with RYR1-related myopathies, as described by Kushnir et al.,[59] exhibit pathological calcium leaks from ryanodine receptors, leading to oxidative stress and muscle dysfunction. Musculoskeletal complications in these patients may exacerbate anesthetic challenges during surgical procedures, potentially requiring tailored anesthetic strategies. This underscores the broader implications of calcium channel disorders, not only in systemic hemodynamics during anesthesia but also in preoperative assessments and postoperative recovery trajectories. Moreover, the retrospective cohort study by Snoeck et al.[60] provides insights into the phenotypic diversity of RYR1-related myopathies, shedding light on the implications for anesthetic safety due to susceptibility to malignant hyperthermia. Their results emphasize the critical need for preoperative screening for genetic predispositions to ensure safe anesthetic practices for patients with known RYR1 mutations. Figure 3 provides a schematic overview of the pathophysiological mechanism underlying malignant hyperthermia, illustrating how aberrant Ca^{2+} release due to RYR1 dysfunction – especially in response to triggering agents can lead to a hyper metabolic crisis.

Magnesium's role as a calcium channel antagonist also emerges as significant in the context of anesthesia. Best Pract Res Clin Obstet Gynaecol discusses magnesium's vasodilatory properties and its use as an anticonvulsant in obstetric emergencies, indicating its broader role in anesthetic practice.[61] Similarly, Soave et al.[35] highlight magnesium's potential to reduce anesthetic requirements and its cardioprotective effects through modulation of calcium influx. These findings suggest that magnesium supplementation may be beneficial in patients with calcium channel disorders.

The narrative by Wang et al.[62] delves into the hemodynamic effects of calcium channel blockers (CCBs), noting their widespread use in acute care settings. They elucidate the paradox where CCBs lower systemic blood pressure while increasing cardiac output, reflecting the necessity for their judicious use in the anesthetic context. This dual action presents a pertinent consideration in the management of anesthetic agents, especially in the face of varying patient responses attributed to genetic or pathological influences on ion channel functionality.

Taking all these mentioned studies into account, the overall quality of evidence is sound, with systematic reviews and meta-analyses providing robust data. While individual studies present varying methodologies, consistent themes suggest ligand-gated calcium channel dysfunction profoundly influences patient vulnerability during anesthesia. Therefore, comprehensive understanding and vigilant management strategies encompassing pharmacological interventions

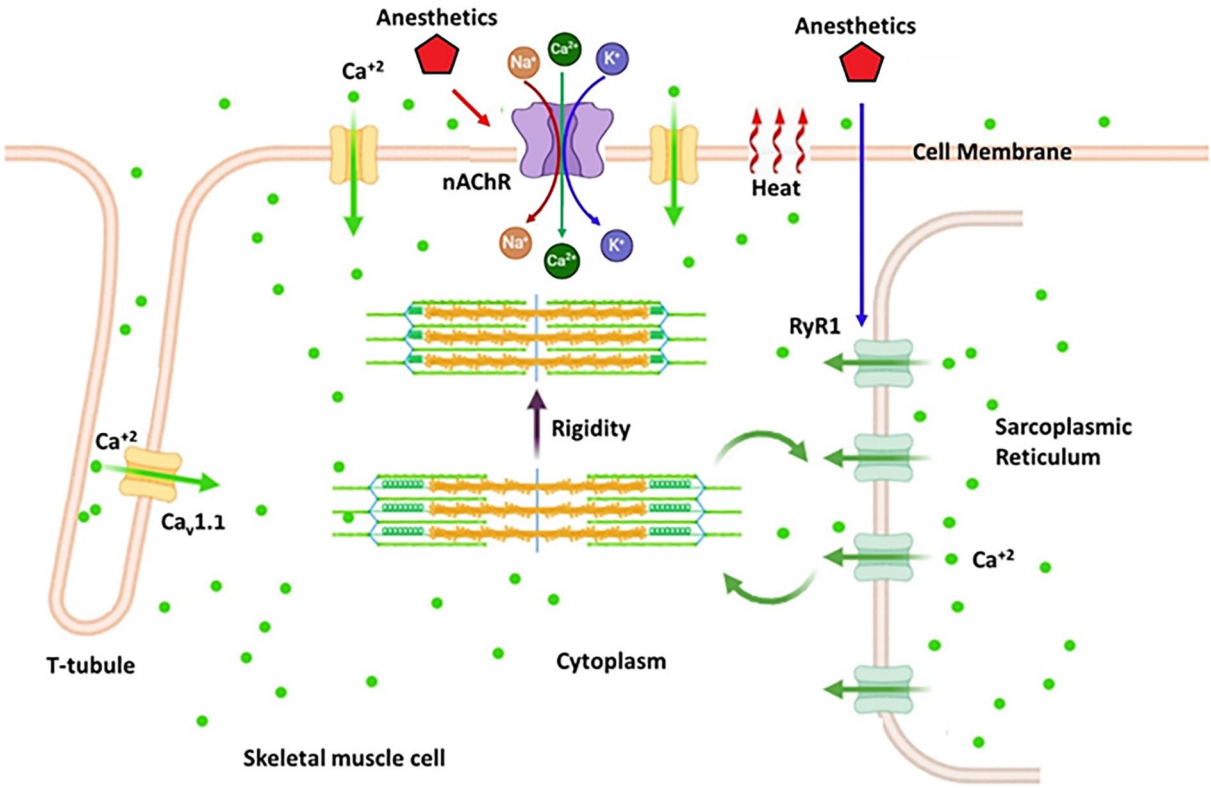

Figure 3. Schematic overview of the pathophysiological mechanism underlying malignant hyperthermia. In individuals harboring mutations in the ryanodine receptor type 1 (RyR1), exposure to triggering agents (e.g. volatile anesthetics or succinylcholine) leads to aberrant calcium (Ca^{2+}) release from the sarcoplasmic reticulum into the skeletal muscle cytoplasm. This excessive intracellular Ca^{2+} promotes sustained muscle contraction, resulting in muscle rigidity and marked heat production. The figure illustrates how succinylcholine acts on nicotinic acetylcholine receptors (nAChRs), facilitating ion flux (Na^+ influx and K^+ efflux), while volatile anesthetics can also potentiate RyR1 dysfunction. The uncontrolled rise in cytosolic Ca^{2+} initiates a hypermetabolic crisis, characterized by elevated CO_2 production, acidosis, and potential multi-organ compromise if not rapidly treated (The figure was drown by *Biorender*).

targeting calcium channels are paramount in the anesthetic care of patients with calcium channel disorders.

Store-operated calcium channels (SOCs)

Store-operated calcium channels (SOCs) are specialized membrane proteins that mediate calcium (Ca^{2+}) influx into cells in response to depletion of intracellular Ca^{2+} stores, particularly from the endoplasmic reticulum (ER).[63] These channels are crucial for maintaining cellular Ca^{2+} homeostasis and regulating various physiological processes, including gene expression, cell proliferation, and immune responses.[64]

Structurally, SOCs are composed of two main components: the stromal interaction molecule (STIM) and the Orai channel. STIM, an ER-resident protein, serves as the Ca^{2+} sensor within the ER lumen.[65] It contains an EF-hand domain that detects changes in luminal Ca^{2+} levels. Upon ER Ca^{2+} depletion, STIM undergoes a conformational change and translocates to ER-plasma membrane junctions, where it directly interacts with and activates Orai channels. Orai proteins, located in the plasma membrane, form the pores of the SOCs. Among the three Orai isoforms (Orai1, Orai2, and Orai3), Orai1 is the most well-characterized and serves as the primary channel for store-operated calcium entry (SOCE).[66]

SOCs and cellular and molecular mechanisms

Functionally, SOCs operate through a tightly regulated mechanism. When ER Ca^{2+} levels drop below a critical threshold, the Ca^{2+}-binding EF-hand domain of STIM loses its bound Ca^{2+}, triggering oligomerization and migration of STIM to ER-plasma membrane contact sites. STIM's cytoplasmic domains then interact with Orai channels, inducing their opening.[67] This results in a robust influx of extracellular Ca^{2+} into the cytoplasm, replenishing ER Ca^{2+} stores and activating downstream Ca^{2+}-dependent signaling pathways. Notably, SOC activity is finely modulated by accessory proteins such as CRACR2A and SARAF, which enhance or inhibit channel function as needed.[68]

SOCs are broadly distributed across various cell types and are particularly prominent in non-excitable cells, such as immune and endothelial cells. In the immune system, SOCs

regulate T-cell activation and cytokine production by sustaining Ca^{2+} signals required for nuclear factor of activated T-cells (NFAT) translocation to the nucleus.[69] In endothelial cells, SOC-mediated Ca^{2+} entry contributes to vascular tone regulation and angiogenesis.[70]

Dysfunction of SOCs is implicated in a variety of diseases. For example, loss-of-function mutations in ORAI1 or STIM1 genes lead to immunodeficiency and impaired T-cell function.[71] Conversely, aberrant activation of SOCs is associated with pathological conditions such as cancer, autoimmune diseases, and cardiovascular disorders. Investigating the molecular mechanisms underlying SOC regulation offers promising opportunities for therapeutic development.

Interaction between anesthetics and SOCs

The available literature indicates that anesthetics can differentially influence store-operated calcium channels (SOCs) through various mechanisms. General anesthetics have been shown to both protect and harm neuronal cells by modulating intracellular calcium levels, predominantly via inositol 1,4,5-trisphosphate receptor activity.[72] Specifically, studies demonstrate that certain anesthetics enhance SOC activity, which may contribute to pain mechanisms, but could also introduce neurotoxic effects at high concentrations. The previous studies surrounding the effects of anesthetics on SOCs reveals a multifaceted interaction largely dictated by the concentration and duration of anesthetic exposure (Table 1).

Wei and Inan[73] articulate this dichotomy in their review, positing that while general anesthetics can activate protective mechansims at low concentrations, they can also provoke toxicity via excessive calcium release at high levels. This duality is critical in evaluating the therapeutic windows for anesthetics, especially in vulnerable populations, such as pediatric or geriatric patients.[73]

A pivotal review by Yanagidate and Strichartz[30] underscores how local anesthetics inhibit not only sodium channels but also voltage-gated calcium channels, impacting pain processing and inflammatory signaling pathways. This opens avenues for understanding how local anesthetics might indirectly modulate SOC function in neurons and immune cells.[30]

The current body of evidence highlights the instrumental role of Orai1 and STIM1 in mediating SOC activity. Studies demonstrate that Orai1 is crucial for enhancing SOC-mediated calcium entry in various models of inflammatory pain, as illustrated by Wei et al.,[74] where Orai1 knockout (KO) mice exhibited significantly diminished pain hypersensitivity in response to inflammatory stimuli. Such findings solidify the importance of SOCs in peripheral sensitization during pain signaling.

Moreover, Yao et al.[75] reveal interactions between calcium regulatory pathways and mechanosensitive channels such as Piezo1 within the context of airway hyperreactivity. This is particularly salient for areas influenced by anesthetics during surgical manipulation, wherein mechanosensitive activation may influence calcium dynamics across various cellular compartments, thereby moderating the inflammatory response and influencing anesthetic outcomes.[75]

Liu et al.[76] provide compelling insights into the interplay between glucocorticoids and SOCs, showing that dexamethasone can upregulate PIEZO1 and thereby modulate immune cell activity through enhanced SOCE. This research highlights an innovative avenue where anesthetics might be employed to manipulate immune features in postoperative care.[76]

Additionally, the mechanosensitive pathways triggered by physical stretch in airway smooth muscle cells, discussed by Yao et al.,[77] indicate that mechanical events may also engage SOC pathways that are critical during surgical procedures, where anesthetic effects are often compounded by alterations in mechanical dynamics.

SOCC disorders, specifically those involving RYR1 and STIM1 mutations, significantly impact patients under anesthesia, contributing to complications such as altered calcium homeostasis, muscle weakness, and malignant hyperthermia susceptibility.[78] Management of anesthesia in these patients is complex and necessitates careful consideration of their underlying calcium channel pathologies. The intersection of calcium channel disorders with anesthesia, particularly involving SOCC, has been the subject of several investigations, implicating mechanisms that compromise patient safety and efficacy of anesthetic interventions. Notably, pathological alterations in calcium release channels such as RYR1 and regulatory proteins like STIM1 have become crucial in understanding anesthetic responses.

Kushnir et al.[59] explored the implications of RYR1 mutations in patients with RYR1-related myopathies, documenting a pronounced aberration in calcium release from the sarcoplasmic reticulum (SR) leading to systemic pathologies and a therapeutic rationale for targeting RYR1. The study engaged a cohort of 17 individuals, illuminating the pathology of leaky RYR1 channels and providing empirical support for the utility of Rycal molecules in therapeutic contexts, suggesting that these disruptions could be exacerbated during anesthetic management.

Similarly, Silva-Rojas et al.[79] expanded on this by demonstrating how STIM1 over-activation culminates in multi-systemic manifestations including skeletal muscle dysfunction, a condition pertinent to an anesthetic setting where respiratory failure or malignant hyperthermia are potential outcomes. Utilizing a murine model, the authors delineated the physiological consequences of STIM1 mutations, notably regarding impaired calcium homeostasis.

The work by Niedermirtl et al.,[80] while focusing on nociceptive TRP channels, inadvertently highlighted interactions between anesthetic agents like etomidate and the calcium signaling pathways, demonstrating increased calcium influx via TRPA1 and TRPV1 channels which could lead to complications during anesthesia. The research on the pain induction from etomidate underscores the necessity of understanding the underlying ion channel dynamics that

may influence patient experiences during induction and stabilization.

The synthesis of findings by Dridi et al.[81] emphasized late diaphragm dysfunction attributable to altered ryanodine receptor activity post-extubation, potentially compounding risks in patients susceptible to muscle weakness due to calcium channel dysfunctions. This delayed recovery from mechanical ventilation in the presence of anesthetic-induced diaphragm complications necessitates strategic adjustments in anesthetic approaches for those with pre-existing SOCC disorders.

As discussed in the work of Tammineni et al.,[82] the emergent understanding of calcium dynamics extending to myoblasts illustrates a stress-adaptive response influenced by calcium dysregulation. These findings are critical for practitioners aiming to mitigate hypocalcemia and related systemic effects provoked by anesthetics.

The nuances of these cellular mechanisms become vital when managing patients with established calcium channelopathies, where sedation and anesthesia can exacerbate or unveil underlying conditions. For instance, existing literature regarding malignant hyperthermia, particularly in certain myopathies linked to RYR1 and STAC3 variants,[83] highlights the urgent need for vigilance in anesthetic strategies for predisposed individuals.

Overall, the assessment of these articles emphasizes a theme: The modulation of SOC activity by anesthetics is intricate, involving various pathways and presenting both therapeutic potential and risks. The evidence varies in quality, with controlled preclinical studies providing a robust foundation, but further clinical investigations are warranted to translate these findings into therapeutic applications.

In conclusion, the prevailing body of evidence substantiates the significance of SOCC disorders in the context of anesthesia. The cumulative risk of adverse outcomes, notably mechanical ventilation difficulties and malignant hyperthermia, warrant an informed, cautious, and tailored approach to the anesthesia of patients suffering from these disorders.

Limitations

Although this review provides a comprehensive exploration of calcium channels and their roles in anesthesia, certain limitations must be acknowledged. First, the narrative format limits the ability to systematically assess all available evidence, which may introduce bias in the selection and emphasis of studies, especially given the vast heterogeneity in experimental models and clinical contexts. Second, while significant attention is given to T-type VGCCs and NMDA receptors, the complexity of other subtypes, such as R-type VGCCs and P2X receptors, remains underexplored, leaving potential gaps in understanding their broader contributions to anesthetic mechanisms. Finally, despite the growing recognition of calcium channelopathies in anesthesia, detailed clinical data directly linking specific genetic mutations to perioperative outcomes are sparse, constraining the translational relevance of existing molecular findings. Addressing these gaps requires targeted research that bridges molecular insights with rigorous clinical studies, paving the way for personalized anesthetic strategies.

Conclusion

The interplay between calcium channels and anesthetic agents represents a critical axis in the understanding and advancement of anesthesia practices. As integral mediators of calcium signaling, voltage-gated calcium channels (VGCCs) and ligand-gated calcium channels (LGCCs) contribute to the core physiological mechanisms underlying anesthesia, including neuronal excitability modulation, neurotransmitter release, and immune response regulation. Through their diverse subtypes, such as T-type VGCCs and NMDA receptors, these channels influence consciousness, pain perception, and hemodynamic stability, thereby shaping the depth and efficacy of anesthesia.

This study has synthesized current insights into the dual role of calcium channels as facilitators of anesthetic effects and potential contributors to perioperative complications. It has underscored the multifaceted mechanisms by which anesthetic agents interact with calcium channels, including direct inhibition, modulation of downstream signaling pathways such as phosphatidylinositol metabolism, and impacts on synaptic plasticity. Moreover, the challenges posed by calcium channelopathies – genetic or acquired dysfunctions affecting these channels – highlight the necessity of precision medicine approaches. Personalizing anesthetic protocols based on an individual's genetic and physiological profile could mitigate risks associated with channelopathies, such as arrhythmias and malignant hyperthermia, and enhance patient outcomes.

Despite significant progress, critical gaps in knowledge persist. The complex and often context-dependent nature of calcium channel interactions with anesthetic agents demands further investigation to elucidate their long-term effects on neural and systemic function. Such research has the potential to not only advance fundamental understanding but also pave the way for innovative therapeutic strategies that prioritize patient safety and efficacy.

This review illuminates the critical role of calcium channels in anesthesia, underscoring the necessity for precise management in patients with calcium channelopathies. By integrating molecular and clinical insights, it introduces novel approaches to personalized anesthesia strategies, potentially enhancing patient safety and perioperative outcomes. This work lays the groundwork for future research into calcium channel modulation as an innovative therapeutic avenue in anesthesia.

Abbreviations

Abbreviation	Full Term
VGCCs	Voltage-Gated Calcium Channels
LGCCs	Ligand-Gated Calcium Channels
SOC	Store-Operated Calcium Channels
STIM	Stromal Interaction Molecule
RYR1	Ryanodine Receptor 1
NMDA	N-Methyl-D-Aspartate
P2X	Purinergic Receptor
nAChR	Nicotinic Acetylcholine Receptor
5-HT3	Serotonin Type 3 Receptor
PIP2	Phosphatidylinositol 4,5-Bisphosphate
HVA	High-Voltage-Activated
LVA	Low-Voltage-Activated
POAF	Postoperative Atrial Fibrillation
CCBs	Calcium Channel Blockers
CRAC	Calcium Release-Activated Calcium
NFAT	Nuclear Factor of Activated T-Cells
SVT	Supraventricular Tachyarrhythmias
CPB	Cardiopulmonary Bypass
VPS	Vasoplegic Syndrome
PKA	Protein Kinase A
EF-hand	Helix-Loop-Helix Motif Found in Calcium-Binding Proteins
PGE2	Prostaglandin E2
PIEZO1	Piezo-Type Mechanosensitive Ion Channel Component 1
T-type	Transient-Type Voltage-Gated Calcium Channels
L-type	Long-Lasting-Type Voltage-Gated Calcium Channels
N-type	Neuronal-Type Voltage-Gated Calcium Channels
P/Q-type	Purkinje/Granule-Type Voltage-Gated Calcium Channels
R-type	Residual-Type Voltage-Gated Calcium Channels
GABA	Gamma-Aminobutyric Acid
AMPA	Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ATP	Adenosine Triphosphate
SR	Sarcoplasmic Reticulum
CRACR2A	Calcium Release-Activated Calcium Channel Regulator 2A
SARAF	SOCE-Associated Regulatory Factor

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The study was conducted following the highest ethical standards. The data presented in this manuscript are accurate and authentic.

Declaration of using the generative AI

During the preparation of this work the author(s) used *ChatGPT 4o* only to improve language and readability.

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Availability of data and materials

The datasets collected and/or analyzed during the current study are available from the corresponding author on reasonable request.

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