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The role of voltage-gated calcium channels in the mechanisms of anesthesia and perioperative analgesia

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Abstract

Purpose of review—A family of neuronal voltage-gated calcium channels (VGCCs) have received only recently a significant consideration regarding the mechanisms of anesthesia because VGCC inhibition may be important in anesthetic action by decreasing neuronal excitability and presynaptic excitatory transmission. The T-type VGCCs channels (T-channels), although rarely involved in synaptic neurotransmitter release, play an important role in controlling neuronal excitability and in generating spontaneous oscillatory bursting of groups of neurons in the thalamus thought to be involved in regulating the state of arousal and sleep. Furthermore, these channels are important regulators of neuronal excitability in pain pathway. This review will provide an overview of historic perspective and the recent literature on the role of VGCCs and T-channel inhibition in particular in the mechanisms of action of anesthetics and analgesics.

Recent findings—Recent research in the field of novel mechanisms of hypnotic action of anesthetics revealed significant contribution of the $Ca_V3.1$ isoform of T-channels expressed in the thalamus. Furthermore, perioperative analgesia can be achieved by targeting $Ca_V3.2$ isoform of these channels that is abundantly expressed in pain pathways.

Summary—The review summarizes current knowledge regarding the contribution of T-channels in hypnosis and analgesia. Further preclinical and clinical studies are needed to validate their potential for developing novel anesthetics and new perioperative pain therapies.

Keywords

T-type channels; calcium; anesthetics; thalamus; analgesia

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Introduction.

General anesthetics (GAs) have been clinically used for nearly two centuries, but the mechanisms whereby different classes of these agents achieve different clinical effects remains poorly understood. A complete anesthetic state involves loss of consciousness (sedation and hypnosis) and movement (immobilization), as well as loss of both pain sensation (analgesia) and recollection of the event (amnesia). An early theory proposed that nonspecific alteration of the lipid membrane in nerve cells accounts for the different components of anesthetic states (1,2). However, research advances in the last three decades have disputed the nonspecific lipid membrane theory (3) and strongly suggest that GAs act through specific sites on the neuronal membrane and that different ion channels that control neuronal excitability may mediate their clinical effects (4,5). Overall scope of this review is to summarize the role of different families of ion channels in clinically useful effects of GAs such as hypnosis and analgesia, with the main emphasis on the particular subtypes of voltage-gated calcium channels.

Ion channels as targets for anesthetics.

Of the various families of ion channels, most emphasis has been placed on the ligand-gated receptor-channel complex, such as γ-aminobutyric acid A ($GABA_A$), N-methyl-D-aspartate receptors (NMDARs), and neuronal acetylcholine receptors (nAChRs). These proteins are transmembrane heterooligomers of five subunits arranged around a central pore that passes either chloride ions ($GABA_A$) or nonspecific sodium/potassium ions (NMDARs and nAChRs). A variety of GAs potentiate $GABA_A$-mediated chloride currents that in turn enhance widespread neuronal inhibition in the central nervous system (CNS) due to membrane hyperpolarization. In addition, GAs may inhibit excitatory NMDARs and/or nAChR currents, perhaps by promoting the desensitized state via cooperative binding with the agonist (glutamate and acetylcholine, respectively).

In recent years, it has been shown that other families of voltage-gated ion channels are also sensitive to GAs. In clinically relevant concentrations, some inhaled anesthetics directly activate TREK 1, a two-pore-domain potassium (K2P) channel (6,7) that in turn leads to hyperpolarization of membranes and neuronal inhibition. Consistent with these findings, global genetic ablation of this channels in mice leads to reduced susceptibility of these animals to anesthetic-induced hypnosis (8). Furthermore, the role of inhibition of voltage-gated sodium channels (VGSCs) in the mechanisms of anesthetic effects has been recognized. For example, in a recent study, Speigel and Hemmings (9) demonstrated that isoflurane inhibited synaptic vesicle exocytosis from hippocampal glutamatergic neurons and GABAergic interneurons in a cell-type-specific manner. This was dependent on their expression of different subtypes of VGSCs such as $Na_V1.1$ (associated with lower sensitivity) and $Na_V1.6$ (associated with higher sensitivity). It is reasonable to speculate that even modest decrease in “conduction safety” of axons in CNS produced by inhibition of VGSCs could lead to loss of consciousness caused by GAs.

The role of voltage-gated calcium channel in anesthesia.

Importantly, a family of neuronal voltage-gated calcium channels (VGCCs) have received only recently a significant consideration in the mechanisms of anesthesia because VGCC inhibition may be important in anesthetic action by decreasing neuronal excitability and presynaptic excitatory transmission (10). VGCCs, which are heteromeric complexes in the plasma membrane of virtually all cell types, show a high level of electrophysiological and pharmacological diversity. These channels consist of a pore-forming α1 subunit and ancillary subunits β, γ, and α2−δ (11). On the basis of the membrane potential at which they activate (12), these channels are subdivided into high voltage-activated (HVA) and low voltage-activated (LVA) or transient T-type Ca^{2+} channels (T-channels). VGCCs in nerve tissue have a central function in sensory, cognitive, and motor pathways, as well as in controlling cell excitability and neurotransmitter release (13). These channels, the products of different genes, give rise to α1 subunits that form the pore of the neuronal VGCCs that passes calcium ions. The HVA VGCCs are members of different families: Ca_V1 (α1C) encoding L-type, $Ca_V2.1$ (α1A) encoding P/Q-type, $Ca_V2.2$ (α1B) encoding N-type, and $Ca_V2.3$ (α1E) encoding R-type HVA current. Similarly, cloning of T-type channels have established that at least 3 isoforms exist based on the structure of α1 subunits: $Ca_V3.1$ (α1G), $Ca_V3.2$ (α1H) and $Ca_V3.3$ (α1I). Because of its importance, intracellular calcium is tightly controlled via many systems, including voltage- and ligand-gated channels, exchangers, ATPases, and soluble binding proteins. Many of these systems have been shown to be influenced by GAs, although early studies have shown that in general the magnitude of effect is modest at clinical concentrations (5,14,15). However, in most instances previous studies studied only one traditional GA such as isoflurane or halothane, did not pharmacologically separate subtypes of VGCCs in native cells, and, in many cases, did not obtain careful concentration-response curves. Nevertheless, small effects on calcium signaling may have large intracellular consequences. Even small blockade of a particular VGCCs by any general anesthetic may produce profound physiological effects. For example, it has been reported that small changes in Ca^{2+} influx into presynaptic terminals can result in profound changes in transmitter release and synaptic efficacy (16). This is related to the fact that presynaptic transmitter release is proportional up to the 4^{th} power of Ca^{2+} entry (17). Thus, even if VGCCs are only partially inhibited by anesthetics in the clinically relevant range, this can profoundly alter neuronal signaling. The effects of volatile anesthetics on even one subset of VGCCs are variable, probably reflecting the molecular heterogeneity of these channels. The T-type VGCCs channels, although rarely involved directly in synaptic neurotransmitter release, play an important role in controlling neuronal excitability and in generating spontaneous oscillatory bursting of groups of neurons in the thalamus thought to be involved in regulating the state of arousal and sleep (18,19,20). Although, it was reported about a decade ago that thalamic T-channels are inhibited by clinically relevant concentrations of volatile GAs such as isoflurane (21), potential clinical significance of these finding was not clear until recently. In a recent study we used mouse genetics, as well as ex vivo and in vivo electrophysiology to demonstrate for the first time that specific $Ca_V3.1$ isoform of T-channels expressed in central medial thalamic (CMT) nucleus is crucial for regulating neuronal excitability and isoflurane-induced oscillations in thalamocortical circuitry in vivo (22). This is important since CMT nucleus is an essential part of arousal

system and considered to be an important target of different classes of GAs, as well drugs that can alter natural sleep-awake states (23, 24, 25).

The role of voltage gated calcium channels in analgesia.—Due to their specific distribution along both peripheral and central pathways involved in pain transmission and modulation, different VGCCs have been recognized as promising targets for the development of analgesic therapeutics (26). Approved and clinically used drugs such as ethosuximide, gabapentin and topiramate are examples of non-selective VGCC blockers used in clinical setting to alleviate painful conditions such as fibromyalgia and migraine. However, since these drugs were initially registered for epilepsy, there is a recognized need to develop VGCC subtype specific channel blockers to improve their safety and tolerability profile. In an effort to achieve this, Ziconotide (Prialt®), a selective N-type calcium channel blocker, has been clinically used intrathecally to alleviate the most intractable chronic pain in cancer patients, and due to its's specific route of administration, the use is limited in conditions where patients are intolerant to conventional systemic analgesics or intrathecal morphine. Pan-T-channel blocker with peripheral efficacy, ABT-639, has shown promising results in pre-clinical studies in rodent pain models (27); however, it failed to exert clinically-relevant pain alleviation in patients with diabetic neuropathy (28,29). It remains to be determined if future development of drugs that inhibit both peripheral and centrally located T-channels may show better efficacy in human trials. One of centrally acting T-channel blockers, Z944 has given promising results in phase Ia and Ib clinical trials. Both oral and systemic injection of Z944 were well tolerated and reduced pain sensitization as well as Visual Analog Scale pain ratings in an experimental pain model in humans (30). The most recent knowledge regarding the role of N- and T-type calcium channels in pain processing mainly suggests that N-type channels predominantly regulate the excitatory synaptic transmission in the dorsal horn of spinal cord, a main pain processing region. In contrast, it is well known that T-channels, particularly $Ca_V3.2$ subtype, contribute to neuronal excitability in both peripheral nociceptive endings and nociceptive dorsal horn neurons (31). In that context, we have recently shown that disruption of the $Ca_V3.2$ channel trafficking and recycling to the membrane (ubiquitination) in peripheral sensory neurons contributes to the development of post-surgical pain in rodents (32). Additionally, in the same pain model, a natural antioxidant and T-type channel blocker such as alpha-lipoic acid alleviated both evoked and spontaneous pain in rats (33). Importantly, it was shown in the same study that alpha-lipoic acid is effective when given systemically, either before or after onset of hyperalgesia induced with surgical paw incision. These findings using clinically-relevant rodent animal models strongly suggest that targeting T-channels would be useful in achieving perioperative analgesia. Furthermore, future development of blockers of VGCCs that have combined inhibitory effect on both T-type and N-type channels would be very promising as a new treatment for various pain disorders.

Neurosteroids in anesthesia and analgesia.—In the recent years there has been increasing interest in the neuroactive steroids (neurosteroids) due to their prominent roles in two important components of anesthesia such as hypnosis/sedation and analgesia. **Alphaxalone** (5α-pregnan-3α-ol-11,20-dione) is a canonical neurosteroid that potentiates neuronal $GABA_A$ currents. Alphaxalone that was used as intravenous GAs in the seventies

but has been withdrawn from clinical use due to a relatively high incidence of anaphylactic reactions to the vehicle used in formulation (Cremophor) (34). However, alphaxalone has been reformulated recently with another vehicle-cyclodextrin, and is used in veterinary medicine (35), as well in clinical trials (36). Related endogenous 3α,5α neurosteroid **allopregnanolone** (5α-pregnan-3α-ol-20-one; 3α-hydroxy-5α-pregnan-20-one or 3α,5α-tetrahydroprogesterone, ALLO) is synthesized in the liver and the brain and exhibits documented hypnotic properties (37,38,39). Although both alphaxalone and ALLO are well known as positive allosteric modulators of $GABA_A$ receptors, we have previously reported that both of these agents are also fairly potent blockers of neuronal $Ca_V3.2$ isoform of T-channels in sensory neurons (40), and display prominent analgesia *in vivo* (41). Over the last decade, our group has extensively studied T-channel blocking properties and analgesic potential of neurosteroids (42,43,44), particularly a novel synthetic 5β-reduced neurosteroid analogue, **3β-OH** ((3β,5β,17β)-3-hydroxyandrostane-17-carbonitrile) (45,46). Interestingly, unlike most other neuroactive steroids, 3β-OH have no direct effect on $GABA_A$ currents activity in native neurons, yet induces potent hypnosis in rats (45) and mice (46) that is at least partly mediated by the inhibition of $Ca_V3.1$ isoform of T-channels. Specifically, we found that hypnotic effect of 3β-OH was greatly diminished in the global $Ca_V3.1$ knock-out (KO) mice when compared to their wild-type littermates (46). In the same study we reported that 3β-OH strongly inhibited spike firing of CMT neurons in thalamic slices from WT mice and the effect was greatly diminished in mutant mice. This effect was confirmed using in vivo recordings of local field potentials (LFPs), where we found that 3β-OH increased slow oscillations that during hypnosis in the WT mice more profoundly than in the $Ca_V3.1$ KO mice (46). Importantly, unlike most other commonly used GAs, our group found that 3β-OH did not induce neurodegeneration in rat pups during critical brain development period (47).

Furthermore, in a post-surgical pain model, when given intraperitoneally 3β-OH alleviated pain in adult rats induced by plantar paw surface surgical incision, and also used in a combination with isoflurane to induce anesthesia in animals undergoing plantar surgical incision. These data indicate that this neurosteroid might be used as a supplementary anesthetic thus reducing the amounts of conventional anesthetics and also reducing the possibility of side effects (42). In the same study we reported that 3β-OH effectively ameliorated incision-induced hyperalgesia in rats when given intrathecally and locally when injected into incised paws. This points to a relatively unique properties of 3β-OH which exerted dose-dependent hypnosis when injected systemically, and reversed hyperalgesia regardless of route of administration (e.g. peripheral, central and systemic). Our ensuing studies using mouse genetics demonstrated that $Ca_V3.2$ isoform of T-channels is important for anti-hyperalgesic properties of 3β-OH in the model of surgical paw incision and contributes to the induction, but not maintenance of neurosteroid-induced hypnosis (36).

We addressed the role of preemptive use of intrathecal administrations of neurosteroids with inhibitory activity on $Ca_V3.2$ T-type currents and potentiating effect on $GABA_A$ currents using a rat paw incision model (44). We used neurosteroids with distinct effects on $GABA_A$ receptors and/or T-channels such as: alphaxalone (combined GABAergic agent and T-channel inhibitor), ECN (T-channel inhibitor), CDNC24 (GABAergic agent), and compared them with an established analgesic, morphine (an opioid agonist without

known effect on either T-channels or $GABA_A$ receptors). We found that alphaxalone and ECN, but not morphine, were effective in alleviating mechanical hyperalgesia when administered preemptively whereas morphine provides dose-dependent pain relief only when administered once the pain had developed. In contrast, we found that CDNC24 did not offer any analgesic benefit. We concluded that neurosteroids that inhibit $Ca_V3.2$ T-currents are effective preemptive analgesics that may offer a promising therapeutic approach to the treatment of post-incisional pain hypersensitivity.

We also investigated potential hypnotic and analgesic properties of an endogenous analogue of 3β-OH, namely epipregnanolone [(3β,5β)-3-hydroxypregnan-20-one]. We have shown that this neurosteroid exhibited effective peripheral analgesia in healthy rats and mice by blocking $Ca_V3.2$ isoform of T-channels in peripheral sensory neurons while sparing $GABA_A$ currents (48). In our follow-up study we found that intrathecal injections of epipregnanolone effectively reduced mechanical hyperalgesia after intrathecal application in rats after paw incision surgery by blocking both $Ca_V3.2$ T-type currents and unidentified component of HVA calcium currents in sensory neurons (presumably N-type VGCCs) (49). We posit that neurosteroids that have combined inhibitory effects on T-type and HVA calcium currents like epipregnanolone may be suitable for the development of novel pain therapies during the perioperative period.

In a very recent study we used mouse genetics to investigate the hypnotic effects elicited by systemic administration of epipregnanolone and characterized its use as an adjuvant agent to commonly used GAs (50). We found that epipregnanolone induced an hypnotic state in WT mice when injected alone intra-peritoneally (i.p.) and effectively facilitated anesthetic effects of isoflurane and sevoflurane. The global $Ca_V3.1$ KO mice demonstrated decreased sensitivity to epipregnanolone-induced hypnosis when compared to WT mice, whereas no significant difference was noted between global $Ca_V3.2$ KO mice, global $Ca_V3.3$ KO mice and WT mice. Finally, when compared to WT mice, we reported that onset of epipregnanolone-induced hypnosis was delayed in global $Ca_V3.2$ KO mice but not in global $Ca_V3.1$ and $Ca_V3.3$ KO mice. These data are consistent with the idea that different hypnotic and analgesic effects of epipregnanolone are mediate by the inhibition of different isoforms of neuronal T-channels.

CONCLUSION

Collectively, the ongoing use of alphaxalone and recent promising preclinical studies with 3β-OH and related analogues continue to encourage future development of synthetic neurosteroids with hypnotic/anesthetics properties. These preclinical studies strongly suggest that the inhibition of T-type channels by neurosteroids is important for their hypnotic and analgesic properties. Although intraperitoneal injections of hypnotic doses of 3β-OH and epipregnanolone alone did not completely suppress response to painful stimuli in rodents, they turned out to be effective in lowering required amounts of potent volatile GAs (e.g. isoflurane) used to induce hypnosis and surgical levels of anesthesia. However, future pre-clinical and clinical studies are needed to establish potential use of neurosteroids and other drugs that inhibit T-channels as effective anesthetics for intravenous administration and analgesics in the perioperative period.

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Key Points:

- This review summarizes current knowledge on the role of low voltage-gated calcium channels (T-channels) in hypnosis, anesthesia, and analgesia.
- Neurosteroid anesthetics such as alphaxalone 3β-OH, have shown promising preclinical results and continue to encourage future development of novel anesthetics.
- In a preclinical setting, it is possible to alleviate pain and to achieve hypnosis by targeting T-channels with novel synthetic neurosteroids.
- Neuronal T-channels channels could be considered as a potential target for the drug development of novel anesthetics and analgesics in perioperative period.