International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 16, No. 2, 2026

Research Progress on the Mechanism of Action of Modern Anesthetic Drugs

Hanting Wang *

Guangdong Medical University, Zhanjiang, Guangdong, China
*** Corresponding author Email:** 898645630@qq.com

Abstract: Anesthesiology, as an important part of the modern surgical system, is widely applied in surgical operations, first aid, cardiopulmonary resuscitation, as well as the research and treatment of pain and many other fields. This article is mainly divided into the following sections; Objective: By summarizing the action mechanisms of diverse anesthetics, this article explores the functional mechanisms and existing limitations of contemporary anesthetics, alongside current improvement strategies and research directions proposed to tackle these drawbacks. Methods: Systematically elaborate from the perspective of mechanism of action. Result: Every drug has its own target receptors. Conclusion: The Necessity of Combining Intravenous Anesthesia with Inhalation Anesthesia and the demand for the development of new anesthetics.

Keywords: Intravenous Anesthesia; Inhalation Anesthesia; Analgesia; New-type Anesthetics; Precise Drug Administration.

1. Introduction

Background: Anesthesiology, as an important part of the modern surgical system, is widely applied in surgical operations, first aid, cardiopulmonary resuscitation, as well as the research and treatment of pain and many other fields. Challenges of Precision Anesthesia and Individualized Medication: There are challenges in the management of persistent postoperative pain and neuropathic pain: Single injections of conventional local anesthetics (such as ropivacaine) only provide analgesia for several hours and cannot cover the pain period ranging from several days to months after surgery. Continuous drug administration via indwelling catheters is prone to causing infections and tissue damage. Microsphere and nano-formulations also have drawbacks including difficult injection, local toxicity and inflammation. Deficiencies of existing reviews: Lack of comparison across drug mechanisms. The scope and organizational logic of this paper: This article will elaborate on the mechanisms of different types of these drugs respectively, as well as the research progress concerning anesthetic drug mechanisms covering novel anesthetics and precise targeted drug delivery technologies. It starts with propofol to discuss the mechanisms underlying the anesthetic effects of intravenous anesthetics.

2. Relevant Mechanisms of Propofol in Intravenous Anesthesia

2.1. Propofol Alleviates Pain-related Anxiety and the Elevation of Stress Hormones

Behavioral evidence: In acute (CFA) and chronic (SNI) pain models, 100 mg/kg propofol markedly increases the residence time of mice in the open arms of the EPM and the central zone of the OF, alleviating anxiety-like behaviors with effects lasting for at least 3 days; propofol fails to elevate the mechanical pain threshold, indicating it targets pain-associated emotional abnormalities rather than exerting an analgesic effect.

Endocrine regulation: Propofol significantly reduces serum levels of CORT, CRH and NE in pain-model mice and reverses stress dysregulation.

2.2. Propofol Inhibits Excessive Activation of PVN CRH Neurons

In pain models (CFA/SNI), calcium signals in PVN CRH neurons are markedly enhanced (verified via fiber photometry), accompanied by an increased firing frequency of action potentials (detected by patch-clamp recording). Propofol (100 mg/kg) rapidly reverses the excessive activation of these neurons, and local injection into the PVN yields anxiolytic effects. Chemogenetic activation of PVN CRH neurons completely abolishes the anxiolytic efficacy of propofol, confirming these neurons as the critical target of propofol.

2.3. Synaptic Mechanism: Propofol Restores the Excitation-Inhibition Balance of PVN CRH Neurons

Under painful conditions, the frequency and amplitude of inhibitory postsynaptic currents (SIPSCs) in PVN CRH neurons are decreased, while the frequency of excitatory postsynaptic currents (sEPSCs) is elevated, resulting in excitation-inhibition (E-I) imbalance. Propofol restores E-I balance by increasing the frequency and amplitude of SIPSCs without affecting sEPSCs, indicating that it predominantly enhances inhibitory synaptic transmission.

2.4. Molecular Target: The GABAAB3 Subunit Serves as a Key Mediator

In pain models, the expression of the GABAAB3 subunit in the PVN region is markedly reduced, and propofol can reverse such downregulation. After specific local knockdown of the GABAAB3 subunit in PVN CRH neurons, the anxiolytic effect of propofol is completely abolished, verifying that this effect depends on the GABAAB3 subunit. The mechanism of action of sevoflurane is associated with pro-apoptotic and pro-inflammatory pathways.[1]

3. Relevant Mechanisms of Sevoflurane in Inhalation Anesthesia

3.1. Pro-apoptotic Mechanism of Cognitive Inhibition Induced by Sevoflurane

The cognitive inhibitory effect of sevoflurane is time-dependent and partially reversible within 72 hours. This recovery trend is highly consistent with the dynamic expression of key molecules (PI3K and p-AKT) in the PI3K/AKT pathway. As a vital neuroprotective signaling axis, the activated PI3K/AKT pathway sustains neuronal survival and synaptic function by blocking the Bcl-2-associated X protein (Bax)/Bcl-2-mediated apoptotic pathway, alleviating oxidative stress and regulating the expression of synaptic proteins. Sevoflurane may transiently suppress the activity of this pathway to delay the initiation of compensatory repair mechanisms in hippocampal neurons; as time elapses, the restoration of pathway activity facilitates the gradual repair of neurological functions.

3.2. Pro-inflammatory Mechanism of Cognitive Impairment Induced by Sevoflurane

Sevoflurane may affect cognitive function by regulating the PI3K/AKT signaling pathway. Studies have verified that inactivation of the PI3K/AKT pathway can activate downstream GSK-3β, aggravate the hyperphosphorylation of tau protein and facilitate the formation of neurofibrillary tangles, consequently resulting in impaired synaptic transmission. In addition, inhibition of the PI3K/AKT pathway may upregulate the expression of pro-inflammatory factors via the NF-κB pathway and trigger neuroinflammatory responses.

3.3. Cognitive Inhibition of Sevoflurane and Its Clinical Relevance

Although downstream inflammatory factors were not directly detected in this study, combined with the finding that cognitive function and PI3K/AKT expression decreased simultaneously in the 2-hour post-awakening group, it is hypothesized that sevoflurane may impair hippocampus-dependent memory function via dual mechanisms of pro-apoptosis and pro-inflammation. While its inhibitory effect on cognition can be partially reversed within 72 hours, early postoperative cognitive risks should be cautioned in elderly patients or those with insufficient cognitive reserve. In addition, interventions targeting the PI3K/AKT pathway may serve as a novel strategy for the prevention and treatment of postoperative cognitive dysfunction. Sedative medications alone cannot provide adequate anesthetic depth for surgical procedures; analgesics are additionally required to mitigate pain-induced disturbances to anesthetic depth. Hence, sedatives and analgesics are frequently administered in combination.[2]

4. Mechanisms Related to the Anesthetic and Analgesic Effects of Sufentanil

4.1. Analgesic Mechanism of Sufentanil in the Central Nervous System

As a potent opioid analgesic, sufentanil produces stronger analgesic effects than fentanyl and morphine. It features rapid onset of action, mild respiratory depression, low addiction potential and a low incidence of nausea and vomiting, making it safer than fentanyl and morphine and widely adopted in clinical practice. Sufentanil relieves pain by inhibiting the activation of neuronal cells, the release of excitatory neurotransmitters and the expression of N-methyl-D-aspartate receptors, as well as modulating sodium channels on postsynaptic membranes.

4.2. Sufentanil Alleviates Pain Hypersensitivity Via Anti-Inflammatory and Anti-Oxidative Stress Effects

Studies have shown that sufentanil can downregulate the expression of purinergic ligand-gated non-selective ion channel (P2X)3 receptors in the rat spinal cord, participate in neural synaptic remodeling, and thereby alleviate neuropathic pain (NP). It can also reduce pain hypersensitivity and sciatic nerve cell apoptosis in NP rats by suppressing inflammation and oxidative stress. These findings demonstrate that sufentanil alleviates oxidative stress and inflammatory injury in spinal cord tissues and attenuates allodynia in rats.Sufentanil activates the Nrf2 signaling pathway. Administration of the Nrf2 signaling inhibitor ML385 to chronic constriction injury (CCI) model rats exacerbates painful symptoms, indicating that inhibition of the Nrf2/HO-1 signaling pathway weakens the antioxidant and anti-inflammatory effects of sufentanil, impairs its protective effect on dorsal root ganglion neurons, and partially reverses the analgesic efficacy of sufentanil in NP rats without completely abolishing its analgesic action. Relevant research verifies that blocking Nrf2/HO-1 signaling activation partially reverses the analgesic effect of sufentanil on NP rats, confirming that sufentanil relieves pain in NP rats at least partially via Nrf2 signaling activation and implying that sufentanil may exert analgesic effects through alternative pathways. Sedation during the induction phase is critical, and rapid achievement of sedation is essential for favorable anesthetic outcomes. The following elaborates that midazolam reduces PVT neuronal activity by inhibiting the cAMP-PKA-CREB signaling cascade, consequently inducing depressed consciousness and profound sedation.[3]

5. Mechanisms underlying the anesthetic and sedative effects of midazolam

Midazolam has extensive clinical applications with the characteristics of rapid sedation, anterograde amnesia and oral availability. The paraventricular thalamic nucleus (PVT) is a critical brain region governing the sleep-wake cycle and maintaining bodily arousal, and the inactivity of its neurons is closely correlated with the level of consciousness; the cAMP-PKA-CREB signaling pathway modulates neuronal activity.

Six midazolam dosage groups ranging from 40 to 65 mg/kg were established. The optimal dosage and time window for establishing a deep sedation model were screened based on the loss of righting reflex (LORR) and high-performance liquid chromatography (HPLC) quantification of drug concentrations in blood and brain tissues. A normal saline control group and a midazolam model group were set up. Immunofluorescence staining was adopted to count the number of C-fos-positive neurons in the PVT region (an indicator of neuronal activity); Western blot was used to

measure the phosphorylation levels of P-PKA/PKA and P-CREB/CREB proteins; enzyme-linked immunosorbent assay (ELISA) was performed to detect cerebral cAMP concentrations. Mice were pretreated with the cAMP activator rolipram and the PKA inhibitor H-89 respectively to reversely verify the regulatory effects of this pathway on PVT neuronal activity as well as the onset and duration of LORR in mice from the perspectives of pathway activation and inhibition.

Midazolam at 60 mg/kg stably induced deep sedation and complete LORR in all mice; peak plasma drug concentration was achieved at 10 min while peak cerebral drug concentration occurred at 15 min after administration, thereby defining 15 min post-dosing as the tissue collection time, with an ED_{50} value of 59.38 mg/kg.

In deeply sedated mice, the proportion of C-fos-positive neurons in the PVT region was markedly reduced, accompanied by prominent suppression of neuronal activity. Significant declines in cerebral cAMP concentration and the phosphorylation levels of P-PKA and P-CREB were observed in the mouse PVT region, indicating overall inhibition of the signaling pathway, whereas the total protein expression of PKA and CREB remained statistically unchanged.

Rolipram-mediated pathway activation reversed midazolam-induced neuronal suppression in the PVT and restored pathway activity; treated mice exhibited delayed LORR onset, shortened sedation duration and improved arousal capacity.

H-89-induced pathway inhibition further repressed PVT neuronal activity and pathway function, accelerating the onset of sedation and significantly prolonging the LORR duration in mice.

Bidirectional modulation of PVT neuronal activity regulates midazolam-triggered alterations in consciousness: neuronal inhibition aggravates sedation while neuronal activation attenuates sedative effects.

Midazolam reduces consciousness level and induces deep sedation by suppressing the cAMP-PKA-CREB signaling pathway and downregulating PVT neuronal activity. PVT neuronal activity serves as a pivotal modulator of midazolam-induced consciousness variation: neuronal inhibition accelerates and prolongs sedation, and neuronal activation delays and shortens sedation.

Despite widespread clinical utilization, the four categories of conventional anesthetics mentioned above carry adverse effects including sedation, cognitive impairment and respiratory depression. In recent years, subtype-selective affinity-based anesthetics targeting the $GABA_a$ receptor (ENX-102) and neuroactive steroids (NAS) have become prominent research focuses, and their mechanisms of action and potential advantages are reviewed as follows.[4]

6. Research on the Mechanism of Action of Novel Anesthetic Drugs

6.1. Binding Mode and Pharmacodynamic Properties of ENX-102

ENX-102 is a novel subtype-selective positive allosteric modulator (PAM) targeting the α2/3/5 subtypes of the GABAA receptor. Its core mechanism of action is as follows: high subtype selectivity. In vitro, it only exhibits partial agonist activity against α2/3/5 subtypes and barely has any effect on the α1 subtype (Emax=3%), whereas diazepam acts in a non-selective manner. The α2 and α3 subtypes mediate anxiolytic effects, while the α5 subtype is involved in memory modulation. Avoiding activation of the α1 subtype eliminates adverse reactions such as sedation and drowsiness. Accordingly, the target sites of benzodiazepine drugs can be precisely regulated to achieve optimal efficacy.[5]

6.2. Research on Animal Models of Neuroactive Steroids (NAS) and Their Cerebroprotective Mechanisms

Neuroactive steroids represent novel candidate anesthetics featuring higher safety and low neurotoxicity, which are expected to address the damage to developing brains induced by conventional anesthetics. While currently available conventional anesthetics are effective for clinical use, they can trigger neurotoxicity as well as impairments in learning and memory in infants and developing brains, creating an urgent demand for safer alternative agents...

Animal model researches: experimental systems include tadpoles (for concentration-effect studies), rodents (for mechanism exploration and gene knockout research), and non-human primates (the species closest to humans). Core evaluation indicators consist of loss of righting reflex (indicating loss of consciousness), disappearance of nociceptive reflex (reflecting anesthetic depth), and electroencephalogram burst suppression (marking the surgical anesthesia plane). The consistent research conclusion is that neuroactive steroids deliver rapid onset, smooth recovery and mild cardiopulmonary suppression across multiple species, with a markedly superior therapeutic index compared with conventional anesthetics.

Molecular Mechanism of Action：

Primary Target: $GABA_a$ Receptor

It selectively enhances extrasynaptic $GABA_a$ receptors containing δ subunits to mediate tonic inhibition and reduce neuronal excitability.It features strict stereoselectivity: the 3α-hydroxy isomer acts as a potent agonist, whereas the 3β-hydroxy derivative functions as an antagonist.

Secondary Target: Voltage-Gated Calcium Channels

It blocks T-type calcium channels (Cav3.1/3.2), contributing to hypnotic and analgesic effects; certain compounds concurrently act on high- and low-voltage-activated calcium channels to synergistically produce anesthetic effects.

Electroencephalographic Characteristics: It induces slow-wave/δ oscillations and burst suppression consistent with conventional anesthetics, reflecting the regulatory function of the thalamocortical network.

Key Advantages: Neuroprotective properties and low developmental toxicity. Unlike propofol, ketamine and other agents with evident developmental neurotoxicity, alfaxalone, CDNC24 and 3β-OH do not trigger extensive apoptosis or induce persistent cognitive impairment in neonatal rodents.

Neuroprotective Mechanism: It activates membrane progesterone receptors and pregnane X receptor (PXR) to initiate pro-survival and anti-apoptotic pathways; it mitigates excitotoxicity and upregulates protective factors including BDNF and Bcl-2; it presynaptically modulates GABA release to prevent excessive activation of GABAergic signaling in the developing brain.[6]

6.3. Research on the Awakening Mechanism of Anesthetic Drugs

Conventional theories hold that emergence from anesthesia

is the passive reversal of anesthetic induction, yet recent evidence confirms emergence is regulated by an intrinsic active driving mechanism within the brain. EphB1 functions as a molecular switch for anesthetic emergence, becoming activated exclusively during the MRS phase to specifically govern the emergence process.

Two coordinated signaling pathways work in tandem: phosphorylated NR2B (excitatory effect) plus degraded KCC2 (disinhibitory effect), which jointly activate the VPM-S1 glutamatergic circuit. The emergence mechanism is independent of the molecular targets of anesthetics and constitutes an intrinsic protective driving program of the brain.

Specific activation of EphB1 in the ventral posteromedial thalamic nucleus (VPM) during anesthesia: three distinct anesthetic regimens (120 mg/kg propofol, 250 mg/kg ketamine, and 2% isoflurane administered for 30 minutes) all induce mice to enter the minimum responsive state (MRS, consciousness score ≤3). During the MRS period, the phosphorylation level and protein expression of EphB1 in the VPM rise markedly, while EphB2–B4 and EphB6 remain unchanged.

EphB1 dictates the rate of anesthetic emergence: VPM-specific knockdown of EphB1 delays emergence and prolongs MRS duration; targeted activation of EphB1 within the VPM accelerates emergence and shortens the MRS window; chemogenetic activation of the VPM drastically speeds up emergence, whereas chemogenetic inhibition of the VPM leads to substantial emergence delay.

Two separate molecular pathways: The EphB1-NR2B Y1472 phosphorylation pathway: EphB1 directly phosphorylates the Y1472 residue of the NR2B subunit. This stabilizes the membrane localization of NMDA receptors, facilitates calcium influx, and directly excites VPM neurons. Overexpression of the mutant NR2B (Y1472F) completely abolishes this outcome and postpones emergence. The EphB1-KCC2 ubiquitination and degradation pathway: EphB1 promotes ubiquitin-mediated proteolysis of KCC2 and downregulates its expression, relieving $GABA_a$ receptor-dependent inhibition and triggering disinhibition of VPM neurons. Blockade of KCC2 degradation reverses the emergence-promoting function of EphB1.

Pathway independence: Inhibiting NR2B phosphorylation has no impact on KCC2 degradation, and stabilizing KCC2 expression does not interfere with NR2B phosphorylation.A comprehensive understanding of anesthesia encompasses not only neural regulation throughout induction, maintenance and emergence but also how administration modalities shape clinical outcomes. Conventional single-bolus injection frequently fails to sustain long-term analgesia demands, rendering precise drug delivery technology a key focus for refining anesthetic protocols. Taking PLGA nanoparticles and MXene heterostructures as representative examples, this section reviews research advances in long-acting analgesia and stimulus-responsive precise drug delivery.[7]

7. Precision Drug Delivery Technology

7.1. Targeted Delivery Systems such as Ropivacaine Encapsulated in PLGA Nanoparticles

Challenges exist in the management of persistent postoperative pain and neuropathic pain: single injection of conventional local anesthetics (e.g., ropivacaine) only provides analgesia for several hours, failing to cover the pain period ranging from several days post-surgery to chronic pain. Indwelling catheters for continuous drug administration are prone to complications such as infection and tissue injury; microsphere/nanoparticle formulations are plagued by drawbacks including difficult injection, local toxicity and inflammation.

Mechanisms underlying the long-acting, stable and safe performance of PLGA co-loaded microspheres: vasoconstriction, decelerated metabolism and enhanced axonal binding:

0.25% PLGA-encapsulated ropivacaine: mechanical pain relief lasts **≥12 days**, cold allodynia relief lasts **=7 days**.

0.125% PLGA-encapsulated ropivacaine: mechanical pain relief lasts approximately 7 days, cold allodynia relief lasts around 3 days.

0.06% PLGA-encapsulated ropivacaine: no obvious analgesic efficacy.

0.25% free ropivacaine: short-duration analgesia with pain control lasting less than 12 hours.

Blank PLGA: no analgesic effect.

0.25% nanoparticulate ropivacaine: analgesia lasts roughly 2 days, only alleviating thermal pain without improving mechanical pain.

PLGA-encapsulated sustained-release ropivacaine (SRR) delivers long-term analgesia (≥67 days) via single injection, with markedly superior efficacy compared with free ropivacaine and nanoparticle preparations. The formulation is injectable, biodegradable with negligible local or systemic toxicity and favorable safety profiles.[8]

8. Discussion

Common limitations of the current research:Most studies rely on animal models and lack large-sample clinical research.The Future Directions of Precision Anesthesia and Individualized Medication:Over the next 30 years, precision medicine, digital human twins and artificial intelligence will serve as the core driving forces for the transformation of anesthesiology. The integration of these technologies will enable anesthesia to develop in a safer, more efficient, personalized, inclusive and eco-friendly manner, catering to the medical needs brought by population aging and the treatment of patients with complex conditions. Nevertheless, challenges including data standardization, relevant regulations and computing power still need to be addressed step by step. Meanwhile, advances in minimally invasive surgery, surgical robots, nano drug delivery and other technologies will complement precision anesthesia, comprehensively improving the overall level of perioperative medical treatment.[9]Limitations of this review:It only discusses drug types and mechanisms of action without specific analysis based on clinical data, and has a weak connection with clinical practice.

9. Summary and Conclusion

Based on the above chapters, different anesthetic agents have distinct characteristics in terms of action targets, signaling pathways, brain region specificity and administration routes. To facilitate comprehensive understanding, a summary and comparison categorized by drug type and core mechanisms are presented below. The intravenous anesthetic propofol alleviates anxiety induced by pain rather than pain itself and thus possesses no analgesic

effect; it relieves anxiety mainly by inhibiting PVN CRH neurons, and its anxiolytic effect relies on the $GABA_a\beta3$ subunit. The inhaled anesthetic sevoflurane induces cognitive suppression primarily via facilitating apoptosis and triggering inflammatory responses. The analgesic sufentanil produces analgesia by mitigating neuronal inflammation and oxidative stress to reduce pain hypersensitivity. The sedative midazolam reduces consciousness level and induces deep sedation by inhibiting the cAMP-PKA-CREB signaling pathway and suppressing the excitability of PVT neurons. ENX-102 is a novel $GABA_a$ receptor ligand that exerts anxiolytic effects mediated by α2/3 subunits and modulates memory through α5 subunits; avoiding α1 activation eliminates adverse reactions such as sedation and drowsiness, enabling precise regulation of the binding targets of benzodiazepine drugs for optimal efficacy. Neuroactive steroids represent novel candidate anesthetics featuring superior safety and low neurotoxicity, with the potential to address developmental brain damage caused by conventional anesthetics. EphB1 governs the speed of anesthetic emergence: the EphB1-NR2BY1472 phosphorylation pathway delays emergence, whereas the EphB1-KCC2 ubiquitination and degradation pathway accelerates it. Ropivacaine encapsulated in PLGA (SRR) enables long-lasting analgesia with a single injection.

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