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Analgesic Mechanism and Research Progress on Improved Preparations and New Dosage Forms of Lappaconitine

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Abstract: ***Lappaconitine is a non-addictive central analgesic independently developed in China with prominent analgesic activity. However, its further clinical application is restricted by poor water solubility, insufficient stability, narrow therapeutic window, and potential cardiotoxicity. In recent years, research on lappaconitine has gradually shifted from pharmacodynamic observations to mechanistic investigations, structural optimization, and novel formulation development. This review summarizes the analgesic mechanisms, pharmacokinetic characteristics, clinical limitations, as well as advances in modified drugs and novel dosage forms of lappaconitine. Current evidence indicates that lappaconitine exerts analgesic effects through multiple pathways, including regulating neurotransmitters, interfering with pain signal transmission in the spinal cord and dorsal root ganglia, inhibiting peripheral ion channel activity, and suppressing neuroinflammation. To overcome its suboptimal druggability, structural modification and formulation optimization have shown considerable potential in improving efficacy, safety, and pharmacokinetic profiles. Overall, lappaconitine remains a promising candidate for further research and development, but its detailed analgesic mechanisms, structure–activity relationships, and clinical translation still require in-depth exploration.***

Keywords: Lappaconitine, Analgesic mechanism, Pharmacokinetics, Structural optimization, Novel dosage forms**.**

1. Introduction

Pain is one of the most common clinical symptoms and a major cause of reduced quality of life and functional impairment [1-3]. Chronic pain, defined as persistent or recurrent pain lasting more than 3 months, not only causes long-term physical discomfort but is also frequently accompanied by emotional disorders such as depression and anxiety, imposing a heavy burden on patients and society [4]. Pharmacological management of pain still faces many limitations: long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) tends to cause gastrointestinal, liver, and kidney damage; opioids have significant analgesic effects but carry risks of addiction, tolerance, and dependence; and some antidepressants and anticonvulsants are limited by insufficient efficacy and numerous adverse reactions [5-6]. Therefore, the development of novel analgesics with high efficacy, safety, and no addiction risk has become an important research direction in this field.

Lappaconitine (LA), a typical representative of C18-diterpenoid alkaloids, is a non-addictive central analgesic with analgesic, anti-inflammatory, antiarrhythmic, and antitumor activities [7]. It was first approved for marketing in China in 1989 and is indicated for moderate to severe acute and chronic pain, including cancer-related pain, postoperative pain, and neuropathic pain [8]. It is clinically used for postoperative pain in anorectal, gynecological, and gastrointestinal surgeries and exhibits preemptive analgesic effects [9]. The analgesic effect of LA is 7 times that of aminopyrine and comparable to pethidine, with advantages of no teratogenicity, no mutagenicity, and no accumulation [7]. Compared with other central analgesics, LA has a lower incidence of central nervous system adverse reactions such as sedation and tolerance [8]. Nevertheless, its further clinical application is restricted by poor water solubility, insufficient chemical stability, narrow therapeutic window [10], and potential cardiotoxicity.

In recent years, research on lappaconitine has gradually shifted from early pharmacodynamic observation to elucidation of action mechanism, rational structural optimization design, and development of novel dosage forms. Clarifying its analgesic mechanism and potential molecular targets, combined with rational structural modification and modern pharmaceutical techniques to improve its physicochemical properties, pharmacokinetic behavior, and safety, is of great significance for enhancing its clinical application value. Accordingly, this paper reviews the analgesic mechanism, pharmacokinetic characteristics, clinical limitations, and research progress of improved drugs of lappaconitine, aiming to provide a reference for its further development and clinical translation.

2. Analgesic Mechanism of Lappaconitine

The analgesic mechanism of lappaconitine is complex and not yet fully elucidated. Available evidence indicates that its analgesic effect relies on multiple synergistic pathways in the central nervous system, spinal cord/dorsal root ganglion (DRG), and periphery, mainly involving regulation of central transmitters and descending inhibitory systems, suppression of pain signal transduction in the spinal cord and DRG [8,11-17], and modulation of peripheral ion channels and neuroinflammation [18].

2.1 Central Neurotransmitters and Descending Inhibition

2.1.1 Regulation of noradrenergic and serotonergic systems

As a central analgesic, lappaconitine acts closely on the central pain regulatory network. Studies have shown that

lesioning dopamine, norepinephrine, and serotonin neurons in the central nervous system or administering corresponding receptor antagonists significantly weakens the analgesic effect of lappaconitine [11]. Similarly, selective inhibition of norepinephrine synthesis in the brain markedly reduces its analgesic effect in a rat incisional pain model [12]. These findings suggest that lappaconitine may enhance central descending inhibition by regulating noradrenergic and serotonergic systems, thereby reducing the transmission of nociceptive information to the center.

2.1.2 Upregulation of spinal dynorphin A expression

The dynorphin A/κ-opioid receptor system is an important endogenous analgesic system. Subcutaneous or intrathecal administration of lappaconitine significantly alleviates mechanical hyperalgesia in rats with neuropathic pain, accompanied by increased spinal dynorphin expression [8]. In nerve injury models, intrathecal lappaconitine elevates spinal prodynorphin mRNA expression and dynorphin A content. Pretreatment with specific dynorphin antibodies or κ-opioid receptor antagonists markedly attenuates or even blocks its anti-mechanical hyperalgesic effect. These results indicate that the analgesic effect of lappaconitine may be related to promoting dynorphin A release in the spinal cord and activating κ-opioid receptors.

2.2 Regulation of Spinal/DRG Pain Transmission

2.2.1 Inhibition of substance P- and somatostatin-mediated pain transmission

Substance P and somatostatin are key neuropeptides for pain signal transmission in the spinal dorsal horn [19,20]. In the formalin pain model, lappaconitine inhibits pain signal transduction mediated by substance P and somatostatin. Intraperitoneal injection of lappaconitine dose-dependently reduces the number of substance P-positive neurons in the rat spinal dorsal horn [13,14]. These findings suggest that lappaconitine may attenuate the amplification of nociceptive information at the spinal level by inhibiting neuropeptide-mediated pain signal transduction.

2.2.2 Downregulation of P2X3 receptor expression in DRG neurons

P2X3 receptor, a purinergic receptor in DRG sensory neurons, plays a crucial role in neuropathic pain. In a chronic constriction injury model of the sciatic nerve, lappaconitine significantly reverses mechanical and thermal hyperalgesia and inhibits rapid ATP currents and α,β-meATP-induced currents in DRG neurons. Immunohistochemistry and Western blotting show that lappaconitine decreases P2X3 receptor expression in DRG neurons, and pretreatment with P2X3 receptor antisense oligonucleotides weakens its analgesic effect [15]. Thus, downregulating P2X3 receptor expression and inhibiting its function may be an important mechanism underlying lappaconitine-induced relief of neuropathic pain.

2.2.3 Inhibition of glutamate release

Lappaconitine inhibits glutamate release from nerve terminals by suppressing presynaptic Ca^{2+} influx and reducing protein kinase A phosphorylation [21]. Glutamate is involved in pain transmission and central sensitization, and its inhibition by lappaconitaine may contribute to spinal and central pain regulation.

2.3 Peripheral Ion Channels and Neuroinflammation

2.3.1 Inhibition of Nav1.7 channel activity

Peripheral mechanisms also participate in the analgesic effect of lappaconitine, as its analgesic effect is reduced but not completely abolished in mice with spinal cord transection. Its analgesic activity is related to voltage-gated sodium channels, acting as an irreversible Nav1.7 inhibitor. Lappaconitine dose-dependently inhibits Nav1.7 channel currents, mainly targeting the open state with little effect on resting and inactivated states [18]. Amino acid mutation assays reveal that its binding site partially overlaps with local anesthetics but differs in action characteristics. Notably, poor subtype selectivity of lappaconitine on Nav channels—especially its effect on Nav1.5—may be associated with antiarrhythmic activity and potential cardiotoxicity, requiring close safety monitoring.

2.3.2 Suppression of microglial activation and neuroinflammation

Neuroinflammation is critical for the initiation and maintenance of chronic pain. Lappaconitine alleviates chronic inflammatory pain induced by complete Freund's adjuvant in rats, inhibits microglial activation in vitro and in vivo, and reduces the expression of tumor necrosis factor-α, interleukin-1β, and other inflammatory factors in the spinal cord [16,17]. These results indicate that lappaconitine may exert analgesic effects by suppressing microglial activation and neuroinflammation.

3. Pharmacokinetic Characteristics and Clinical Limitations of Lappaconitine

The analgesic mechanism of lappaconitine involves multiple levels in the central, spinal/DRG, and peripheral regions. However, clinical application is determined not only by pharmacodynamic mechanisms but also by pharmacokinetic properties and druggability. Lappaconitine is characterized by low oral bioavailability, rapid in vivo elimination, wide tissue distribution, and complex metabolism. Meanwhile, poor water solubility, insufficient stability, and narrow therapeutic window limit its clinical use.

3.1 Pharmacokinetic Characteristics

After single intravenous or intragastric administration in experimental animals, the pharmacokinetic profile of lappaconitine generally conforms to a two-compartment model, characterized by rapid distribution into the central compartment followed by transfer to the peripheral compartment and biphasic elimination [7,22]. Transdermal administration in rabbits fits a one-compartment model with a bimodal concentration-time curve (peaks at ~0.5 h and ~3 h) [23].

Non-compartmental analysis shows that the plasma half-life of lappaconitine after single intravenous injection in beagles is 3.31±0.16 h, with an apparent volume of distribution much higher than the theoretical value in whole blood [22]. After high-dose intravenous or intragastric administration in mice, the area under the curve does not increase proportionally, and apparent volume of distribution and clearance decrease significantly. The oral bioavailability of lappaconitine is only approximately 2% [7].

Metabolic studies reveal that the main metabolic pathways of lappaconitine in humans and rats include hydroxylation, N-deacetylation, and O-demethylation, with minor pathways including N-deethylation and hydrolysis. More than 51 metabolites have been identified, including 5'-OH-lappaconitine, 16-O-demethyl-lappaconitine, 16-O-demethyl-N-deacetyl-lappaconitine, and N-deacetyl-lappaconitine; N-deacetyl-lappaconitine is the main toxic metabolite [24,25].

3.2 Clinical Limitations

As the first domestically developed non-addictive central analgesic in China, lappaconitine is mainly used for moderate to severe pain, including postoperative pain, cancer pain, and diabetic peripheral neuropathic pain, and can be combined with opioids, anesthetics, or NSAIDs. Currently marketed dosage forms include injections, tablets, and patches, but further clinical promotion is restricted [26].

Lappaconitine has high liposolubility and low water solubility, leading to slow dissolution and limited bioavailability of conventional oral preparations; short half-life after intravenous administration is not conducive to stable efficacy [27]. It is photosensitive, and its ester bond is prone to oxidation and hydrolysis to form related impurities. Injections may undergo physicochemical changes with inappropriate solvents or preparation conditions.

The LD50 of lappaconitine is 11.7 $mg \cdot kg^{-1}$, and the ED50 in the mouse acetic acid writhing test is 3.5 $mg \cdot kg^{-1}$, giving a therapeutic index of approximately 3.3. Clinical statistics show that adverse reactions involve the gastrointestinal system, skin, and nervous system, with severe cases presenting abnormal liver function and anaphylactic shock [26]. Combined with the production of toxic metabolites [24,25], safety issues require continuous attention, driving subsequent research on structural optimization and new dosage forms.

4. Research Progress on Improved Preparations of Lappaconitine

To address the problems of poor water solubility, insufficient stability, short half-life, narrow therapeutic window, and potential toxicity, recent studies have focused on structural optimization and new dosage form development. Structural modification aims to improve pharmacological activity, target selectivity, and safety, while formulation technologies enhance solubility, bioavailability, stability, and in vivo drug release.

4.1 Structural Optimization

Structural modification is an important approach to obtain highly active and low-toxic derivatives. Key structural moieties of C18-diterpenoid alkaloids are closely related to analgesic activity and toxicity: the ethyl group linked to the tertiary amine on ring A and the saturated state of ring D are essential for analgesic activity, while the 4-O-acetamidobenzoyl group is associated with cardiotoxicity and antiarrhythmic effects [28,29]. Therefore, targeted modification at C-4, N-20, and other key sites has become the main strategy for derivative development.

4.1.1 C-4 side chain modification

Modification of the C-4 side chain focuses on retaining analgesic activity while reducing toxicity and expanding pharmacological effects. Derivatives with similar analgesic activity and significantly lower toxicity (including reduced arrhythmia risk) have been obtained by modifying the acetamidobenzoic acid side chain [24]. Introduction of anti-inflammatory fragments at the C-4 position confers strong anti-inflammatory activity [30].

4.1.2 N-20 modification

N-20 is an important site for introducing functional moieties. A series of derivatives have been constructed by linking cinnamic acid, triazole acid, amino acids, and phospholipid backbones. Some N-20-modified compounds show favorable anti-inflammatory activity and inhibit inflammatory factor production by regulating NF-κB and MAPK signaling pathways [31].

4.1.3 Modification at other sites

Systematic optimization at other key sites has also been explored. Introduction of ynone or heterocyclic moieties yields derivatives with low toxicity and favorable analgesic activity [32]. Recently, Nav1.7-targeted optimization has attracted attention: based on pharmacophore analysis, scaffold hopping, and privileged fragment integration, systematic modification of deethylated and deacetylated sites has generated derivatives with potent Nav1.7 inhibitory activity. Some representative compounds show better analgesic activity and longer duration than lappaconitine in postoperative pain models.

4.2 Novel Dosage Form Development

Modern pharmaceutical technologies effectively improve the druggability of lappaconitine by addressing poor solubility, low oral bioavailability, short half-life, and instability.

4.2.1 Oral dosage forms

Phospholipid complexes, solid dispersions, and nanoparticles improve solubility, dissolution rate, and oral bioavailability [33-35]; osmotic pump tablets prolong the duration of action [32].

4.2.2 Topical dosage forms

Transdermal preparations such as liposomes [37] and pressure-sensitive adhesive patches [38] reduce first-pass

metabolism, enhance local drug concentration, and extend analgesic duration based on the transdermal permeability of lappaconitine [36].

4.2.3 Injectable dosage forms

Long-acting injectable systems (proliposomes and lyotropic liquid crystal injections) improve solubility and stability, prolong in vivo retention, and extend analgesic duration [39,40].

4.2.4 Other dosage forms

Microemulsions and other novel drug delivery systems enhance stability and enable sustained release, but most are still in the preclinical stage [41].

5. Conclusion and Perspective

Lappaconitine is a non-addictive central analgesic independently developed in China with favorable analgesic activity and a solid clinical foundation. This review systematically summarizes its analgesic mechanism, pharmacokinetic characteristics, and research progress of improved preparations. Lappaconitine exerts multi-target and multi-level analgesic effects by regulating norepinephrine, serotonin, substance P, and other neurotransmitters, interfering with spinal and DRG pain transmission, and inhibiting peripheral Nav1.7 channel activity and neuroinflammation. However, its clinical application is limited by poor water solubility, insufficient stability, short half-life, narrow therapeutic window, and potential toxicity.

Recent studies have promoted the improvement of lappaconitine through structural optimization and new dosage form development. Targeted modification at C-4, N-20, and other sites improves analgesic activity, reduces toxicity, expands anti-inflammatory effects, and enhances Nav1.7 selectivity. Nav1.7-based design yields promising lead compounds. Modern formulations (solid dispersions, nanoparticles, liposomes, proliposomes, liquid crystal injections) improve solubility, stability, bioavailability, and duration of action.

Current research is mainly focused on in vitro screening, animal experiments, and preliminary pharmaceutical evaluation, with insufficient systematic druggability, safety assessment, and clinical translation. Future research should:

Strengthen structure-activity relationship studies, especially improving Nav1.7 selectivity and reducing off-target inhibition of Nav1.5 to lower cardiotoxicity;

Balance pharmacodynamics, pharmacokinetics, and safety in optimization;

Conduct systematic preclinical evaluation (pharmacokinetics, safety, stability) of promising derivatives and delivery systems to facilitate clinical translation;

Further clarify the synergistic and hierarchical analgesic mechanisms of lappaconitine to support rational application and drug design.

As a unique non-addictive analgesic with Chinese characteristics, lappaconitine has great development potential. Multidisciplinary collaboration (medicinal chemistry, pharmacology, pharmaceutics, clinical medicine) will promote synergistic development of structural optimization and formulation improvement, enhance its clinical value, and provide a reference for the development of safe and effective novel analgesics.

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