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Review of Advances in Analgesic Peptide Molecules

Pain, particularly chronic and neuropathic pain, represents a significant global health issue and socioeconomic burden. While traditional opioid analgesics like morphine are potent, their long-term use carries serious side effects including addiction, respiratory depression, constipation, and tolerance. Consequently, there is an urgent need to develop novel analgesics that are highly effective with minimal side effects. Analgesic peptide molecules, with their high selectivity, potent efficacy, and relatively low addiction potential, have emerged as one of the most promising frontiers in pain drug development. This review summarizes the mechanisms of action, research progress, and challenges faced by endogenous and exogenous analgesic peptides.

I. Endogenous Analgesic Peptide System

The human body possesses a complex, naturally occurring analgesic system mediated by peptides, primarily categorized into two major classes: opioid peptides and non-opioid peptides.

1. Endogenous Opioid Peptides

This is the most extensively studied endogenous analgesic system, with receptors classified into three primary types: μ, δ, and κ.

Key Components and Limitations:

Includes enkephalins, endorphins, and dynorphins, which exhibit high selectivity for δ, μ, and κ receptors, respectively. They play a crucial role in pain modulation within the central nervous system. However, natural opioids are rapidly degraded by enzymes such as aminopeptidase and enkephalinase, possess extremely short half-lives (measured in seconds), and cannot effectively cross the blood-brain barrier. Consequently, they cannot be used directly as therapeutic agents.

2. Endogenous Non-Opioid Analgesic Systems

These peptides exert analgesic effects through non-opioid receptor pathways, offering potential for avoiding opioid-like side effects.

Neuropeptide Y (NPY): By binding to NTS1 and NTS2 receptors, it produces potent analgesia centrally and peripherally, comparable in strength to morphine but without respiratory depression or addictiveness. Development challenges include hypothermia and hypotension at analgesic doses.

Somatostatin and its analogues: By acting on somatostatin receptors, they inhibit the release of noxious neurotransmitters. Analogs like octreotide are used for cancer pain and headaches, though their analgesic spectrum remains relatively narrow.

Cholcystokinin (CCK): As an “anti-opioid peptide,” CCK expression increases in chronic pain states, antagonizing opioid analgesia. Consequently, CCK receptor antagonists are considered to enhance opioid efficacy and prevent tolerance, though their effects are limited as monotherapies.

II. Exogenous Natural Analgesic Peptides: The Treasure Trove of Animal Venoms

Peptide toxins discovered in the venom of predatory animals (such as cone snails, spiders, and scorpions) have become the primary source for identifying novel analgesic lead compounds due to their evolved ability to precisely target ion channels or receptors.

1. Voltage-gated ion channel inhibitors

These peptides function by blocking the generation and transmission of pain signals in neurons.

Sodium channel blockers: Primarily inhibit subtypes critical for pain signal transmission, such as Nav1.7, Nav1.8, and Nav1.9. For example, μ-conotoxin, discovered from Conus conus, specifically blocks pain-related sodium channel subtypes, delivering potent analgesia without addictive properties. Development challenges lie in achieving absolute selectivity for pain-related subtypes (e.g., Nav1.7) while avoiding interference with cardiac (Nav1.5) or muscular (Nav1.4) function.

Calcium Channel Blockers: Primarily target N-type calcium channels

mediating neurotransmitter release. Qianconotopeptide, the first approved ω-conotoxin-derived drug, treats refractory pain via intrathecal administration with 1000-fold potency over morphine and no opioid side effects. However, it requires precise intrathecal infusion due to a narrow therapeutic window.

Potassium Channel Openers: Activating specific potassium channels stabilizes neuronal membrane potential and reduces excitability. Several spider toxin peptides have been demonstrated as potent openers of Kv or KCa channels, showing promise in neuropathic pain models.

2. Ligand-gated ion channel modulators

NMDA receptor antagonists: Excessive NMDA receptor activation is closely linked to central sensitization and hyperalgesia. Certain peptides can allosterically modulate NMDA receptor function, potentially offering superior subtype selectivity compared to small-molecule antagonists. This may enable analgesia with reduced psychiatric side effects.

3. G-Protein-Coupled Receptor Agonists/Antagonists

Mas-Related GPCR Agonists: Compounds like Mambalgin, derived from black mamba venom, inhibit acid-sensitive ion channels to produce potent opioid-independent analgesia without respiratory depression or tolerance, making them highly attractive novel target ligands.

III. Design and Optimization Strategies for Analgesic Peptides

To overcome the limitations of natural peptides and transform them into

usable drugs, systematic engineering modifications are required.

1. Enhancing Metabolic Stability

Cyclization: Restricting conformation through disulfide bonds, lactam bonds, or head-to-tail cyclization significantly resists proteolytic degradation.

Introduction of non-natural amino acids: Replacing L-amino acids at critical sites with D-amino acids can completely avoid cleavage by corresponding proteases.

Terminal modifications: N-terminal acetylation or C-terminal amidation eliminates sites vulnerable to exopeptidase attack.

2. Enhancing Receptor Selectivity/Reducing Off-Target Toxicity

Domain Grafting and Mutation: Based on structure-function studies, grafting "pharmacophores" with high affinity for target channels from different toxins, or eliminating residues causing off-target effects via alanine scanning to finely tune selectivity.

Multivalent design: Linking two peptides with identical or distinct activities enables simultaneous targeting of different sites on the same receptor or different receptors, enhancing potency and selectivity.

3. Improve delivery and administration routes

Central administration systems: Develop safe intrathecal or epidural continuous infusion devices for potent peptides unable to cross the blood-brain barrier (e.g., for zikano-peptide).

Peripheral-restricted design: Design peptides with positive charges or high molecular weights to hinder blood-brain barrier penetration, enabling targeted peripheral pain treatment while avoiding central side effects.

Novel delivery technologies: Explore intranasal administration, transdermal patches, and carrier systems based on nanoparticles or cell-penetrating peptides to enhance bioavailability and targeting.

4. High-Throughput Screening and Rational Design

Accelerate discovery of novel lead molecules by integrating phage display peptide libraries, animal toxin transcriptomics, and high-throughput electrophysiological screening. Utilize computational modeling and artificial intelligence to predict peptide-target interactions, guiding rational optimization.

IV. Challenges and Future Outlook

Despite significant progress, the clinical translation of analgesic peptides still faces core challenges:

Blood-brain barrier penetration: Most potent peptides struggle to cross the barrier, limiting their application in central pain.

Production costs and scalability: The chemical synthesis of complexly modified long peptides is prohibitively expensive, constraining their accessibility as chronic disease treatments.

Immunogenicity risk: Long-term administration may induce antibody responses, compromising efficacy or triggering allergic reactions.

Administration convenience: Many candidate drugs still require invasive delivery methods (e.g., intrathecal injection).

Future development will focus on:

Exploring new targets and mechanisms: Continued mining of natural venom libraries to identify peptides targeting novel pain pathways.

Smart delivery systems: Developing “intelligent” delivery systems that release drugs in response to pain-related biomarkers.

Multi-target synergistic strategies: Designing multifunctional peptides that simultaneously modulate multiple nodes in pain pathways to achieve superior efficacy and reduced side effects.

Personalized pain therapy: Selecting or designing optimal peptide treatment regimens based on a patient's pain type and genetic background.

Conclusion

Research on analgesic peptide molecules is undergoing a profound shift from natural discovery to rational design. Endogenous systems reveal the physiological blueprint for pain modulation, while animal venoms provide an evolutionarily optimized “molecular toolkit.” Through systematic engineering modifications targeting stability, selectivity, and delivery methods, researchers are striving to transform these highly effective natural templates into usable therapeutics. Although challenges like the blood-brain barrier, production costs, and delivery routes persist, ongoing breakthroughs in peptide chemistry, structural biology, and delivery

technologies suggest that novel peptide-based analgesics may offer safer, more precise alternatives to traditional opioids for acute and chronic pain patients in the future, fundamentally reshaping pain management. Research in this field aims not only to alleviate suffering but also to establish a new equilibrium between potent analgesia and patient safety.