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Research Progress on Opioid Receptors and Ion Channels in Dorsal Root Ganglion Neurons

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Abstract

Dorsal root ganglion (DRG) neurons play a crucial role in the perception and modulation of pain signals, making them a critical focus in pain mechanism research. Opioid receptors, as classical analgesic targets, inhibit pain signals by regulating ion channels such as calcium channels, while ion channels are directly involved in the generation and transmission of pain signals. In recent years, the synergistic interaction between opioid receptors and ion channels has become a research hotspot, particularly under pathological pain conditions, where their complex interplay provides key insights into analgesic drug development. This paper systematically reviews the distribution and functional mechanisms of opioid receptors and ion channels in DRG neurons, explores their interaction in pain modulation, and discusses functional changes under inflammatory and neuropathic pain conditions. Additionally, it examines potential targeted therapeutic strategies based on their synergy and outlines their clinical application prospects.

Keywords: dorsal root ganglion neurons, opioid receptors, ion channels, pain modulation, analgesic mechanism

1. Introduction

Pain is a common clinical complaint and a protective response to injury or stimulation. However, chronic and neuropathic pain mechanisms present challenges for effective treatment. Dorsal root ganglion (DRG) neurons, as key components of the peripheral nervous system, are crucial for pain signal perception, transmission, and modulation. They serve as primary pathways for pain information entering the central nervous system and as cellular models for studying pain mechanisms.Opioid receptors, known for their strong analgesic effects, are widely used as clinical analgesic targets. They inhibit pain primarily by regulating calcium channels and intracellular signaling pathways. However, prolonged opioid use can lead to tolerance, dependence, and other limitations. Meanwhile, ion channels—sodium, calcium, and potassium—play central roles in pain signal generation and transmission. Their changes in expression and function under acute and chronic pain conditions provide new opportunities for therapeutic intervention.The interaction between opioid receptors and ion channels, modulated via G protein-coupled mechanisms, has become a key focus in pain research. This interplay offers insights into pain modulation and supports the development of novel analgesics and combination therapies. This paper reviews opioid receptor and ion channel distribution, their synergistic interactions, and therapeutic strategies for inflammatory and neuropathic pain, providing guidance for pain research and treatment.

2. Opioid Receptors in Dorsal Root Ganglion Neurons

2.1 Types of Opioid Receptors and Their Distribution in DRG Neurons

Opioid receptors, key members of the G protein-coupled receptor family, are widely distributed in the central and peripheral nervous systems and are essential molecules for pain modulation. In DRG neurons, three classical opioid receptor subtypes are primarily present: μ-opioid receptors (MOR), δ-opioid receptors (DOR), and κ-opioid receptors (KOR)[1]. Each receptor subtype exhibits distinct distribution patterns and functions in DRG neurons, reflecting their varied roles in pain signal transmission.MOR, the most well-known opioid receptor subtype, is closely associated with the analgesic effects of opioid drugs such as morphine and fentanyl. In DRG neurons, MOR expression is predominantly found in small-diameter sensory neurons, which are closely linked to nociceptive stimuli. Activation of MOR inhibits calcium ion influx and reduces cyclic adenosine monophosphate

(cAMP) levels, suppressing pain signal transmission. Additionally, MOR modulates potassium channel activity to hyperpolarize neurons, further attenuating pain signals.DOR is more broadly expressed in DRG neurons, mainly in medium-diameter neurons associated with mechanosensation. Activation of DOR also inhibits voltage-gated calcium channels and regulates intracellular signaling pathways, effectively reducing pain transmission. Compared with MOR, DOR activation shows greater efficacy in modulating chronic pain, making it a promising new analgesic target.KOR is relatively less expressed in DRG neurons, primarily located in a subset of small- and medium-diameter neurons. KOR activation is typically associated with alleviating inflammatory pain and plays a role in sensing non-noxious stimuli. However, the clinical application of KOR agonists is limited by potential side effects, such as mood alterations.Recent research has also identified non-classical opioid receptor subtypes, such as the nociceptin/orphanin FQ receptor (NOP), in DRG neurons. These receptors provide alternative analgesic pathways distinct from classical opioid receptors. Additionally, endogenous opioid peptides, such as β-endorphins and enkephalins, bind to these receptors and play critical roles in modulating pain signals. Overall, the diverse distribution and functions of opioid receptors in DRG neurons underscore their complexity and significance in pain modulation. Further exploration of receptor distribution may facilitate the development of more precise analgesic interventions[2].

2.2 Mechanisms of Opioid Receptors in Pain Signal Modulation

Opioid receptors exert crucial roles in pain modulation through complex signaling pathways, particularly in DRG neurons. As G protein-coupled receptors, opioid receptors primarily activate Gi/Go proteins to inhibit cAMP production, thereby affecting downstream signal transmission. First, opioid receptors suppress voltage-gated calcium channel (VGCC) activity, reducing calcium ion influx and significantly lowering presynaptic neurotransmitter release. This mechanism is notably prominent in MOR and DOR. Second, opioid receptor activation promotes the opening of G protein-coupled inwardly rectifying potassium (GIRK) channels, allowing potassium ion efflux, leading to neuronal hyperpolarization and reduced excitability. Additionally, opioid receptors indirectly regulate sodium channels, such as Nav1.8, further decreasing neuronal sensitivity to pain stimuli.Beyond peripheral mechanisms in DRG neurons, opioid receptors influence central nervous system processes in pain modulation. Peripherally, opioid receptors inhibit the excitability of primary sensory neurons, reducing pain signal transmission to the spinal dorsal horn. Centrally, opioid receptor activation enhances descending inhibitory pathways, suppressing nociceptive signal transmission and perception. Together, these peripheral and central effects form the foundation of opioid receptor-mediated pain modulation.In pathological pain states, opioid receptor functions may undergo significant changes. For example, chronic pain or prolonged opioid drug use may lead to receptor downregulation or desensitization, diminishing analgesic efficacy. In inflammatory pain, opioid receptor expression may be upregulated, with increased levels of endogenous opioid peptides, serving as a protective mechanism for pain modulation. However, in neuropathic pain, MOR expression may decrease, whereas KOR function may increase, reflecting distinct regulatory adaptations in pathological conditions. Overall, the complex and dynamic mechanisms of opioid receptors in pain signal modulation provide vital insights into pain pathophysiology and novel analgesic drug development.

3. Ion Channels in Dorsal Root Ganglion Neurons

3.1 Overview of Ion Channel Types and Functions

Dorsal root ganglion (DRG) neurons, as critical nodes in peripheral pain signal perception and transmission, rely heavily on the coordinated activity of various ion channels. Ion channels are an essential category of membrane proteins that regulate neuronal excitability and signal transmission by selectively allowing specific ions to cross the membrane[3]. Based on the type of ions they mediate and their functional characteristics, the ion channels in DRG neurons can be broadly categorized into sodium, potassium, and calcium channels, each playing a unique role in pain signal perception and regulation.Sodium channels are vital for the generation and propagation of action potentials in DRG neurons. Among them, voltage-gated sodium channels (Nav) are the most extensively studied, particularly Nav1.7, Nav1.8, and Nav1.9, which play key roles in transmitting nociceptive stimuli. Nav1.7 is highly expressed and closely associated with the amplification of pain signals, Nav1.8 primarily contributes to the maintenance of chronic pain, and Nav1.9 is linked to inflammatory pain and endogenous analgesic mechanisms. The dysfunction of these sodium channels is often implicated in the pathogenesis of chronic and neuropathic pain.Potassium channels primarily exert inhibitory effects by regulating neuronal excitability. In DRG neurons, inwardly rectifying potassium channels (Kir) and voltage-gated potassium channels (Kv) are the two main types. Kir channels are crucial for maintaining the resting membrane potential, while Kv channels regulate the repolarization of action potentials and control neuronal firing frequency. Enhanced potassium channel function is typically associated with the suppression of pain signals, making them promising analgesic targets.Calcium channels play a critical role in the presynaptic release of neurotransmitters and intracellular signal transduction.

High-voltage-activated calcium channels (e.g., Cav2.2) expressed in DRG neurons are closely involved in pain signal transmission, while low-voltage-activated calcium channels (e.g., T-type calcium channels) are primarily associated with the pathophysiology of chronic pain. Cav2.2 has been identified as a key target for the development of calcium channel blockers, with specific inhibitors like ω-conotoxin showing significant analgesic effects.In addition, transient receptor potential (TRP) channels, as non-selective cation channels, are widely expressed in DRG neurons and play an essential role in sensing various nociceptive stimuli, such as heat, cold, and chemical agents. TRPV1, TRPA1, and TRPM8 are the most well-known subtypes, exhibiting high sensitivity to heat, chemical, and cold stimuli, respectively. These channels not only contribute to pain signal perception but are also closely linked to inflammatory and neuropathic pain.In summary, DRG neurons express a diverse array of ion channels with varied functions, which collectively participate in the perception and transmission of pain signals through their coordinated actions. Further research into the functional properties of these ion channels and their alterations in pathological pain conditions provides a solid theoretical foundation for developing novel analgesic drugs[4].

3.2 Interaction Mechanisms Between Ion Channels and Opioid Receptors

Ion channels and opioid receptors interact in DRG neurons through complex mechanisms to regulate the transmission of pain signals. Opioid receptor activation not only directly affects intracellular signaling pathways but also indirectly modulates neuronal excitability by regulating ion channel activity. This interaction plays a pivotal role in alleviating both acute and chronic pain.Firstly, the regulation of calcium channels by opioid receptors is a critical component of their analgesic mechanisms[5]. Voltage-gated calcium channels (VGCC), particularly the Cav2.2 subtype, are primary targets of opioid receptor regulation. Opioid receptors activate Gi/Go proteins, reducing cyclic adenosine monophosphate (cAMP) levels and decreasing the probability of calcium channel opening, thereby suppressing calcium ion influx. This effect directly reduces the release of presynaptic neurotransmitters, effectively blocking nociceptive signal transmission between neurons. Additionally, the regulatory capacity of opioid receptors over calcium channels may undergo adaptive changes under chronic pain conditions, contributing to opioid tolerance.Secondly, opioid receptors reduce neuronal excitability by modulating potassium channels. G protein-coupled inwardly rectifying potassium channels (GIRK) are key targets of opioid receptors. Upon activation of opioid receptors, Gi/Go proteins promote GIRK channel opening, facilitating potassium ion efflux and leading to neuronal hyperpolarization, thereby suppressing action potential generation. This mechanism significantly diminishes the transmission of pain signals. Moreover, voltage-gated potassium channels (Kv) are also indirectly regulated by opioid receptors, influencing the repolarization process of neurons.Thirdly, opioid receptors indirectly regulate sodium channels, which are crucial for action potential propagation. Studies have shown that opioid receptors can modulate downstream signaling pathways involving protein kinase A (PKA) and protein kinase C (PKC), inhibiting the activity of sodium channels such as Nav1.7 and Nav1.8, thereby reducing the firing frequency of action potentials. This mechanism is physiologically significant in both acute and chronic pain conditions.Furthermore, opioid receptors extend their influence to TRP channels, broadening their functional scope across various pain types. By inhibiting the activity of TRPV1 channels, opioid receptor activation reduces neuronal sensitivity to heat and chemical stimuli, alleviating related pain symptoms. This regulatory mechanism is particularly notable in inflammatory and neuropathic pain conditions.Under pathological pain conditions, the interaction mechanisms between opioid receptors and ion channels may undergo adaptive changes. For example, in neuropathic pain, the expression of sodium and calcium channels may increase, while the sensitivity of opioid receptors may decline. These changes weaken the regulatory effect of opioid receptors on ion channels, thereby diminishing their analgesic efficacy. This phenomenon not only explains opioid tolerance but also highlights the necessity of developing combination therapies targeting both receptors and ion channels.In conclusion, opioid receptors regulate ion channel activity to exert synergistic effects on the generation, transmission, and perception of pain signals. These interaction mechanisms provide important theoretical insights into the complex regulatory network of pain and serve as critical targets and strategies for developing novel analgesic drugs[6].

4. Synergistic Effects of Opioid Receptors and Ion Channels

Opioid receptors regulate the activity of ion channels through various molecular mechanisms, exhibiting significant synergistic effects in pain signal modulation. These molecular mechanisms center around opioid receptors and influence sodium, potassium, and calcium channel activities through downstream signaling pathways, thereby achieving precise control of neuronal excitability and pain signal transmission.The primary mechanism by which opioid receptors regulate ion channel activity is through G protein-coupled signaling pathways. Upon binding to Gi/Go proteins, opioid receptors reduce the activity of adenylyl cyclase (AC), which lowers cyclic adenosine monophosphate (cAMP) levels. This, in turn, inhibits protein kinase A (PKA) activity, modulating the

functions of multiple ion channels. For example, the probability of voltage-gated calcium channel (VGCC) opening is significantly reduced, decreasing calcium ion influx and suppressing presynaptic neurotransmitter release. Notably, the Cav2.2 subtype of calcium channels plays a crucial role in pain signal transmission, and its regulation by opioid receptors is a key mechanism for achieving analgesic effects.Additionally, opioid receptors lower neuronal excitability by modulating G protein-coupled inwardly rectifying potassium channels (GIRK). Upon receptor activation, the Gβγ subunit interacts directly with GIRK channels, promoting their opening and facilitating potassium efflux from the cell. This hyperpolarization effectively inhibits action potential generation, blocking further transmission of pain signals. Opioid receptors also indirectly regulate voltage-gated potassium channels (Kv), influencing action potential repolarization and thereby controlling neuronal firing frequency.For sodium channels (Nav), opioid receptor regulation is primarily mediated through downstream signaling pathways. Opioid receptor activation reduces Nav1.7 and Nav1.8 activities via PKA and protein kinase C (PKC) phosphorylation, diminishing action potential propagation. This mechanism plays a vital role in alleviating both acute and chronic pain, particularly in neuropathic pain conditions.Beyond classical ion channels, opioid receptors also play a role in modulating non-selective cation channels, such as transient receptor potential (TRP) channels. TRPV1 channels, highly sensitive to heat and chemical stimuli, are particularly notable. Opioid receptor activation inhibits TRPV1 channel activity by reducing PKA and PKC activity, mitigating neuronal sensitivity to pain-inducing stimuli. This mechanism is crucial in inflammatory and neuropathic pain, where TRPV1 overactivation is often a key contributor.In pathological pain conditions, the ability of opioid receptors to regulate ion channels may be impaired. Prolonged pain states can lead to desensitization or downregulation of opioid receptors, reducing their inhibitory effects on sodium and calcium channels. Chronic inflammation or nerve injury may also alter ion channel expression levels, further weakening opioid receptor-mediated modulation. Understanding the adaptive changes in the molecular mechanisms between opioid receptors and ion channels under pathological conditions is critical for developing more effective analgesic strategies.In conclusion, opioid receptors regulate ion channel activity through complex molecular mechanisms, with synergistic interactions involving sodium, potassium, and calcium channels providing multi-level modulation of pain signals. These mechanisms are fundamental to understanding the analgesic effects of opioid receptors and offer valuable theoretical support and practical potential for the development of novel analgesic drugs.

4.2 Synergistic Mechanisms Under Pathological Pain Conditions

Under pathological pain conditions, the synergistic mechanisms between opioid receptors and ion channels undergo adaptive changes, which can either enhance or diminish the ability to modulate pain signals. Chronic inflammation, neuropathic pain, and other pathological states are often accompanied by abnormal increases in neuronal excitability. In this context, the interplay between opioid receptors and ion channels demonstrates unique regulatory patterns, providing new insights into the pathophysiological mechanisms of pain.In neuropathic pain, the sensitivity and expression levels of opioid receptors often change, affecting their ability to regulate ion channels. For example, prolonged pain states can lead to downregulation or desensitization of μ-opioid receptors (MOR), reducing their inhibitory effects on calcium and sodium channels. Upregulation of Cav2.2 calcium channels is commonly observed under nerve injury conditions, increasing presynaptic neurotransmitter release and amplifying pain signal transmission. Furthermore, the expression of Nav1.7 and Nav1.8 sodium channels may also significantly increase in pathological pain, enhancing neuronal sensitivity to nociceptive stimuli. As MOR function deteriorates, its regulatory capacity over these ion channels diminishes, resulting in uncontrolled pain signal transmission.Conversely, κ-opioid receptors (KOR) may show enhanced functionality under certain pathological pain conditions. Studies indicate that KOR activation effectively inhibits sodium channel activity and restores normal neuronal excitability through potassium channel regulation, such as inwardly rectifying potassium channels. This phenomenon suggests that KOR may play a compensatory role in certain inflammatory pain states. However, the emotional side effects associated with KOR activation may limit its therapeutic potential.In chronic inflammatory pain, the synergistic effects between opioid receptors and ion channels exhibit certain adaptive enhancements. For example, the release of cytokines during inflammation may upregulate MOR expression while increasing the sensitivity of Cav2.2 and Nav1.8 channels[7]. Although these changes enhance the modulation of pain signals by opioid receptors, they may also increase the risk of dependence on opioid drugs. Additionally, inflammatory factors may alter the synergistic regulation of TRP channels by opioid receptors. For instance, opioid receptors mitigate heat hyperalgesia associated with inflammation by inhibiting PKC-mediated TRPV1 channel activation.Under complex pathological pain states, the interaction mechanisms between opioid receptors and ion channels may display dynamic changes. For instance, in the early stages of pain, MOR inhibition of sodium and calcium channels may be effective, alleviating acute pain. However, in prolonged pain, receptor downregulation or desensitization gradually reduces its regulatory capacity, leading to tolerance and diminished analgesic effects. These changes highlight the stage-specific nature of the synergistic effects between opioid receptors and ion

channels, necessitating personalized therapeutic strategies for different pain phases.In summary, the synergistic mechanisms between opioid receptors and ion channels exhibit complex adaptive changes under pathological pain conditions. While certain mechanisms may enhance the inhibition of pain signals, issues such as receptor downregulation and aberrant ion channel expression can undermine the effectiveness of these synergistic effects. Therefore, in-depth research into the pathological characteristics of these mechanisms will aid in developing more targeted pain treatment methods, particularly for chronic and neuropathic pain.

5. Applications and Prospects

5.1 Novel Strategies for Pain Treatment Targeting Opioid Receptors

Opioid receptors, due to their central role in pain signal modulation, have long been a focal point in the development of analgesic drugs. However, traditional opioid medications, such as morphine and fentanyl, often lead to tolerance, dependence, and severe side effects, significantly limiting their clinical application[8].These challenges have spurred the development of innovative strategies targeting opioid receptors, aiming to alleviate pain while minimizing adverse effects.One promising direction is the development of selective agonists, which specifically target certain opioid receptor subtypes, such as δ-opioid receptors (DOR) or κ-opioid receptors (KOR). These selective agonists can achieve potent analgesia without triggering the common side effects associated with μ-opioid receptor (MOR) agonists. Additionally, partial agonists, which maintain effective pain relief while avoiding receptor overstimulation, show potential in reducing addiction risks.Biased agonism has emerged as a major research focus in recent years. This approach involves designing agonists that preferentially activate specific signaling pathways, such as the G protein pathway or the β-arrestin pathway, to precisely modulate opioid receptor functions. G protein-biased agonists, for example, can significantly reduce side effects like respiratory depression and constipation while retaining robust analgesic efficacy. This innovation provides a new avenue for opioid receptor-targeted research.The study and development of endogenous opioid peptides, such as endorphins and enkephalins, offer additional inspiration for novel analgesic drugs. These natural ligands are less prone to causing addiction. By optimizing their structure and designing analogs, researchers aim to enhance their stability and selectivity, reducing adverse effects while maintaining effective pain relief.Combination targeting strategies and multi-target drugs also hold great promise in opioid receptor-based treatments. The synergistic interaction between opioid receptors and ion channels, such as Nav1.7 and Cav2.2, forms the theoretical foundation for combination targeting. For instance, combining opioid receptor agonists with sodium channel blockers can achieve dual inhibition of pain signal generation and transmission, improving analgesic efficacy and reducing side effects.Additionally, the development of long-acting drugs and locally acting opioid medications offers innovative pain management strategies. By integrating opioid receptor agonists with nanocarriers or sustained-release systems, drugs can be released over an extended period, enhancing therapeutic effects and reducing dosing frequency. Locally acting opioid drugs, such as injections or patches, can significantly reduce central nervous system side effects, making them particularly suitable for localized pain treatment.In summary, novel pain treatment strategies targeting opioid receptors integrate the latest advances in molecular biology and medicinal chemistry, offering a pathway to overcome the limitations of traditional opioids[9]. With the further development of biased agonists, combination targeting strategies, and long-acting formulations, opioid receptor-targeted research is poised to open new horizons in pain management.

5.2 Ion Channels as Promising Drug Targets

Ion channels are crucial for neuronal signal transmission and have become important targets for developing new analgesics. In dorsal root ganglion (DRG) neurons, sodium, potassium, calcium, and transient receptor potential (TRP) channels play key roles in pain signal generation and transmission. Understanding the physiological and pathological functions of these channels highlights their potential for novel pain therapies.Sodium channels are essential for initiating and propagating pain signals. Among them, Nav1.7, Nav1.8, and Nav1.9 have been widely studied. Nav1.7 is closely associated with increased nociceptive sensitivity, and its mutations causing congenital insensitivity to pain provide strong evidence of its analgesic potential[10]. Selective Nav1.7 blockers have shown effective pain relief in animal models, while Nav1.8 and Nav1.9 offer opportunities for targeting chronic and inflammatory pain.Potassium channels primarily suppress neuronal excitability and are promising analgesic targets. Inwardly rectifying potassium channels (Kir) and voltage-gated potassium channels (Kv) regulate resting membrane potential and action potential repolarization. Drugs enhancing Kir channel activity reduce neuronal excitability and inhibit pain transmission, representing a potential non-opioid approach.Calcium channels, particularly high-voltage-activated Cav2.2, are critical for presynaptic neurotransmitter release and are implicated in chronic and neuropathic pain. While Cav2.2 blockers like ω-conotoxin show strong analgesic effects, their systemic side effects necessitate the development of safer and more selective inhibitors.TRP channels, sensitive to heat, chemicals, and mechanical stress, play unique roles in pain perception. TRPV1, involved in inflammatory

and neuropathic pain, has been effectively targeted in animal models, though thermoregulation challenges persist. TRPA1 and TRPM8 show promise in treating chemically and cold-induced pain.In pathological pain, ion channels may exhibit altered expression and activity, offering opportunities for targeted analgesic development. Combining ion channel modulation with other approaches, such as opioid receptor targeting, or using nanotechnology to deliver localized treatments, could enhance efficacy and reduce systemic side effects.In conclusion, ion channels are promising drug targets, and further research and technology integration may lead to safer and more effective non-opioid analgesics, addressing chronic and neuropathic pain challenges.

6. Conclusion

Opioid receptors and ion channels in dorsal root ganglion neurons play central roles in the perception and modulation of pain signals. Opioid receptors regulate ion channel activity through complex signaling pathways, exhibiting significant synergistic effects that are critical for pain relief. In pathological pain conditions, the interaction mechanisms between opioid receptors and ion channels undergo adaptive changes, providing valuable insights into pain mechanisms and novel analgesic drug development. By leveraging innovative strategies targeting both opioid receptors and ion channels, precise and effective pain management can be achieved, opening new avenues for treating chronic and neuropathic pain.

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