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Mechanisms of G Protein-Coupled Receptors (GPCRs) in Inflammatory Pain and Their Therapeutic Targets

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Abstract: Inflammatory pain is a common and complex clinical symptom closely associated with many chronic inflammatory diseases, and its treatment has always faced significant challenges. As a receptor family playing a key role in cell signaling, G protein-coupled receptors (GPCRs) play an important role in the occurrence, development, and regulation of inflammatory pain. GPCRs not only regulate inflammatory responses and pain sensitivity through cell membrane signaling pathways but also interact complexly with ion channels, immune cells, and metabolites, affecting the dynamic balance of the neuro-inflammatory-immune network. Studies have shown that specific GPCR subtypes (such as Mrgpr, GPR37, etc.) play a unique role in inflammatory pain perception and inflammation resolution, providing targets for the development of new analgesic drugs. In addition, biased ligands of GPCRs and their endosome targeting effects open up new directions for reducing drug side effects and improving efficacy. This article systematically summarizes the biological functions of GPCRs in inflammatory pain, potential drug targets, and future research directions.

Keywords: G protein-coupled receptors; Inflammatory pain; Biased ligands; Endosome-targeted drugs

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1. Clinical significance of inflammatory pain

Inflammatory pain is a common type of pain seen in clinical settings, often associated with tissue damage or inflammatory responses. Patients may experience symptoms such as persistent pain, tenderness, and limited movement. This type of pain not only affects the physical function of patients but also severely disrupts their daily lives, including sleep quality, emotional state, and social interactions [1]. For example, various diseases such as osteoarthritis, rheumatoid arthritis, and inflammatory bowel disease are accompanied by significant inflammatory pain symptoms, affecting the health of millions of people globally [2]. The clinical significance of inflammatory

pain lies not only in its widespread incidence and high disability rate but also in its complexity and difficulty to eradicate. The inflammatory response is the body's defense mechanism against harmful stimuli, but when it is excessive or persistent, it can lead to tissue damage and pain sensitization, resulting in inflammatory pain [3]. This type of pain involves not only the activation of the peripheral nervous system but also the participation of the central nervous system, forming a complex neural circuit.

2. Signal transduction characteristics and research status of G protein-coupled receptors

The basic structural feature of G protein-coupled receptors (GPCRs) is their seven transmembrane helix (7TM) structure. These helices consist of approximately 20–30 hydrophobic amino acids that pass through the cell membrane in an α-helical form, forming a transmembrane domain. GPCRs recognize various signaling molecules in the extracellular environment, such as neurotransmitters, hormones, chemokines, and inflammatory mediators, and convert these signals into intracellular biological effects. These receptors are widely distributed in the human body and are involved in almost all physiological processes, including neurotransmission, immune response, inflammatory response, cardiovascular function, and metabolic regulation [4]. The widespread distribution and diverse functions of GPCRs make them important therapeutic targets for many diseases. In recent years, significant progress has been made in studying the role of GPCRs in inflammatory pain. Increasing evidence suggests that multiple GPCRs play important roles in the occurrence and development of inflammatory pain. For example, certain GPCRs can activate inflammatory cells (such as macrophages and mast cells) to release inflammatory mediators, exacerbating inflammatory responses and pain sensitization [5]. Researchers have found that targeting these specific GPCRs can effectively relieve inflammatory pain. For instance, antagonists targeting the capsaicin receptor (TRPV1) can reduce pain caused by inflammation [6].

3. Mechanisms of GPCRs in inflammatory pain

3.1. Cell membrane surface signal transduction

3.1.1. Early signaling events after GPCR binding with ligands

The activation of GPCRs is a critical initiating step in cell membrane surface signal transduction. This process begins with the specific binding of ligands to GPCRs. Ligands are diverse, including peptides, small molecules, lipids, etc., and they interact with the transmembrane region of GPCRs through unique molecular structures. The high specificity of this interaction determines the accuracy of signal transmission. After ligands bind to GPCRs, it leads to conformational changes in the receptors, which are dynamic and crucial for downstream signaling pathways. For example, studies on the neurokinin 1 receptor (NK1R) have found that the binding of substance P (SP) to NK1R causes conformational changes in the receptor, activating downstream signaling pathways, including the activation of G proteins and the recruitment of β-arrestin [7].

3.1.2. Activation mechanism of G protein-dependent signaling pathways

The activation of GPCRs is primarily achieved through interactions with heterotrimeric G proteins, which consist of α, β, and γ subunits. G proteins are classified into multiple subtypes, such as Gs, Gi/o, and Gq/11 based on their α subunits, and each subtype activates different downstream effectors. Gi/o proteins inhibit the activity of AC, reducing cAMP levels. Gq/11 proteins activate phospholipase C (PLC), leading to the hydrolysis of

phosphatidylinositol-4,5-bisphosphate (PIP2) to produce inositol triphosphate (IP3) and diacylglycerol (DAG), thereby increasing intracellular calcium ion concentration and activating protein kinase C (PKC). Changes in these second messenger levels play important roles in inflammatory pain.

3.1.3. β-arrestin-mediated signal transduction

β-arrestin was initially recognized as a key regulator of GPCR desensitization and endocytosis. When GPCRs are activated, β-arrestin is recruited to the receptors through phosphorylation by G protein-coupled receptor kinases (GRKs), preventing further activation of G proteins by the receptors and leading to signal pathway attenuation. Simultaneously, β-arrestin can promote receptor endocytosis, transporting receptors from the cell membrane to endosomes, further reducing the number of receptors on the cell surface and achieving signal termination. However, research has found that β-arrestin not only participates in GPCR desensitization and endocytosis but also acts as a signal adaptor protein, mediating non-canonical signaling pathways. For instance, β-arrestin can activate the MAPK pathway, affecting cell growth, differentiation, and inflammatory responses.

3.2. Receptor endocytosis and endosomal signaling

3.2.1. Signal transduction characteristics of GPCR endocytosis-mediated processes

GPCR endocytosis is a dynamic process where receptors are encapsulated in vesicles through a clathrin-mediated pathway, ultimately forming endosomes. Endosomes are not merely sites for signal termination but can also serve as platforms for signal transduction. During endocytosis, receptors can still bind to signaling molecules such as G proteins and β-arrestin, maintaining or altering signal transmission characteristics. In endosomes, the spatial localization and temporal dynamics of signaling molecules can be regulated, providing more possibilities for signal transduction. This indicates that GPCR endocytosis not only affects signals on the cell membrane surface but also profoundly impacts intracellular signal transmission.

3.2.2. Regulatory role of endocytosis pathways in pain persistence

GPCR endocytosis is a crucial regulator of pain persistence. When GPCRs are activated, endocytosis can lead to the removal of receptors from the cell membrane surface, reducing the sensitivity of cells to painful stimuli. However, if the endocytosis process is abnormal, such as blocked endocytosis or continuous activation of receptors in endosomes, it may result in persistent transmission of pain signals. Additionally, some natural variants of GPCRs exhibit abnormal signal transduction and endocytosis trafficking, leading to the persistent presence of pain.

3.2.3. Potential value of novel endosome-targeted therapies

Due to the significant role of endocytosis pathways in regulating pain persistence, drug development targeting these pathways has emerged as a new research direction. Traditional GPCR antagonists primarily act on receptors on the cell membrane surface, but receptors in endosomes can still transmit signals, limiting the effectiveness of traditional drugs. Therefore, developing novel drugs that can target endosomes is of great importance. Some studies have begun exploring the possibilities of endosome-targeted therapies, such as modifying the lipid solubility and pKa values of GPCR antagonists to make them easier to enter and remain in endosomes, thereby continuously inhibiting endosomal signaling [7]. Additionally, nanoparticle-encapsulated drugs represent a potential endosome-targeted treatment approach, which can precisely deliver drugs to endosomes, enhancing their therapeutic efficacy.

3.3. Interaction with ion channels

3.3.1. GPCR regulation of calcium/sodium channels

GPCRs not only regulate intracellular second messenger levels and signaling pathways through signal molecules like G proteins and β-arrestin, but they also directly modulate neuronal excitability by interacting with ion channels. Calcium and sodium channels are key regulators of neuronal excitability and play crucial roles in pain signal transmission. GPCRs can regulate the function of calcium and sodium channels through various mechanisms.

3.3.2. Connection between ion channels and pain sensitivity

Ion channels play a central role in pain signal transmission. Voltage-gated sodium channels (Nav), particularly the Nav1.7, Nav1.8, and Nav1.9 subtypes, are highly expressed in nociceptive neurons and are involved in pain generation and transmission. Increased activity of these ion channels enhances neuronal excitability, leading to a lowered pain threshold and increased pain sensitivity. By modulating the activity of these ion channels, GPCRs can alter pain thresholds and sensitivity.

4. Novel therapeutic strategies in inflammatory pain

4.1. Clinical research and applicability of traditional GPCR blockers

GPCRs have a long history as drug targets, and many early drugs, such as antihistamines and beta-blockers, are actually GPCR antagonists or agonists widely used in clinical practice with demonstrated efficacy. In the field of inflammatory pain treatment, the development of traditional GPCR blockers has been accompanied by challenges. Although these drugs can provide pain relief in certain cases, their efficacy is often unsatisfactory, and they are frequently associated with side effects, especially in the management of chronic pain [8]. Therefore, in clinical practice, it is essential to select appropriate drugs based on the specific conditions of patients and closely monitor their efficacy and adverse reactions to facilitate timely treatment adjustments.

4.2. Biased ligands and other novel drug development directions

4.2.1. Research progress of biased ligands

Biased ligands represent a significant advancement in GPCR drug development in recent years. These ligands can selectively activate specific signaling pathways of GPCRs, achieving more precise drug effects [9]. Unlike traditional drugs that simply block or activate the entire GPCR, biased ligands bind to different regions of the receptor, preferentially activating certain downstream signaling pathways while avoiding the activation of undesired pathways. This approach reduces side effects and enhances therapeutic efficacy. The development of biased ligands has brought new hope to the treatment of inflammatory pain. By screening and designing ligands that preferentially activate specific signaling pathways, researchers can develop safer and more effective analgesics.

4.2.2. Development and advantages of endosome-targeted drugs

Endosome-targeted drugs represent another emerging direction in GPCR drug development. This strategy involves delivering drugs to intracellular endosomes, where they exert their effects. Compared to traditional drugs, endosome-targeted drugs offer multiple advantages, including more precise regulation of GPCR activity and reduced systemic exposure, thereby lowering the risk of side effects.

4.2.3. Potential applications of natural products and toxin-based drugs

Natural products and toxin-based drugs hold potential value in the treatment of inflammatory pain. Numerous biologically active compounds exist in nature, such as plant extracts, marine biotoxins, and microbial metabolites. These compounds can interact with GPCRs to produce analgesic and anti-inflammatory effects [10]. Currently, researchers are actively exploring the potential applications of natural products and toxin-based drugs in inflammatory pain treatment. By screening, modifying, and optimizing these compounds, new drug candidates can be developed. Some studies have successfully transformed natural products or toxin-based drugs into clinical medications. For instance, certain capsaicin-like compounds have been used to treat neuropathic pain. However, research on natural products and toxin-based drugs still faces challenges, including compound extraction, purification, pharmacological activity evaluation, and toxicity assessment.

4.3. GPCR gene polymorphism and precision medicine

4.3.1. Differences in GPCR expression profiles and individualized drug strategies

GPCR gene polymorphism refers to individual differences in *GPCR* gene sequences. These differences can affect GPCR expression levels, structures, and functions, leading to variations in responses to the same drug among different individuals. For example, certain *GPCR* gene polymorphisms can result in increased or decreased receptor expression levels, altered ligand binding capabilities, or modified signal transduction efficiency.

In the treatment of inflammatory pain, *GPCR* gene polymorphism can directly influence drug efficacy. For instance, studies have found that polymorphisms in opioid receptor genes are associated with the analgesic effects and side effects of opioids. Patients carrying certain gene polymorphisms may respond poorly to opioids, requiring higher doses to achieve the same analgesic effect. Understanding the impact of *GPCR* gene polymorphism on drug responses can assist doctors in developing more personalized treatment plans. By testing patients' GPCR genotypes, it is possible to predict their responses to specific drugs, allowing for the selection of the most appropriate medication and dosage.

4.3.2. Challenges and opportunities from the perspective of precision medicine

Precision medicine based on *GPCR* gene polymorphism represents a significant development direction in the field of inflammatory pain treatment. However, several challenges still need to be addressed to achieve this goal. Firstly, technical limitations pose a challenge. Although gene detection technology has matured considerably, further technological advancements are needed to comprehensively understand the impact of *GPCR* gene polymorphism on drug responses. This includes developing faster and more accurate gene detection methods and establishing large-scale gene databases. Additionally, functional studies on *GPCR* gene polymorphism remain challenging and require the use of high-throughput screening and bioinformatics approaches to deeply analyze the biological significance of different gene polymorphisms.

Secondly, ethical considerations are crucial in the development of precision medicine. Issues such as privacy protection in gene testing, misuse of genetic information, and genetic discrimination need to be addressed through appropriate laws, regulations, and ethical guidelines. Furthermore, the high cost of precision medicine must be considered, ensuring that all patients can equally benefit from its advantages.

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