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Targeting G protein-coupled receptor for pain management

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Abstract:

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Great progress has been made in understanding the important roles of various G protein-coupled receptors in the regulation of pain transmission. However, many important questions remain uncertain about the precise signal transduction mechanisms. This review focuses opioid receptor and CXC receptor 4 on the effects and mechanisms of pain. Taken together, chemokines and their receptors are potential targets for the development of novel pain management and therapy.

Keywords:

Chemokine receptors, chemokines, CXC receptor 4, opioid receptor, pain

Introduction

The heterotrimeric G protein-coupled receptors (GPCRs) are the largest family of cell surface receptors. In spite of their diverse functions, all GPCRs consist of seven transmembrane domains linked by intracellular and extracellular loops.[1] The binding of ligands to their receptors induces the conformation change of the receptor and allows to interact to the specific heterotrimeric G proteins with their intracellular domains.[2] This, in turn, leads to coupling to and signaling through activation of one or more G proteins inside the cell.

GPCRs can block pain upon targeting opioid, cannabinoid, α2-adrenergic, muscarinic acetylcholine, gamma-aminobutyric acid$_B$ (GABA$_B$), Group II and III metabotropic glutamate, and somatostatin receptors. Therefore, we focus GPCRs, especially opioid receptor and CXC receptor 4 (CXCR4), on the mechanisms and targets of pain management.

The heterotrimeric GPCRs are the largest, most diverse receptor families in the mammalian cells. The G proteins consist of three subunits: Gα, Gβ, and Gγ. It has been demonstrated that 5 genes encode the β subunits, 12 genes encode the γ subunits, and 17 genes encode the α subunits.[3] GPCRs interact with heterotrimeric G proteins composed of α, β and γ subunits that are GDP bound in the resting state. Agonist binding triggers a conformational change in the receptor, which catalyses the dissociation of GDP from the α subunit followed by GTP-binding to Gα and the dissociation of Gα from Gαγ subunits. Gβγ subunits activate a diverse array of effectors, such as enzymes and ion channels.[4] Moreover, Gα subunits have a key role in determining the receptor coupling specificity and influencing the efficiency of ion channel modulated by Gβγ subunits.[5] Gα subunits can be broadly classified into four major subfamilies: Gαs-, Gαi/o-, Gαq/11-, and Gα12/13-coupled receptors.[3]

GPCRs regulate and are involved in diverse diseases, including cancer, kidney, inflammatory, central nervous system (CNS), and chronic diseases. GPCRs

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play an important role in pain transduction, especially cancer pain and chronic pain. They regulate the pathways and mechanisms during pain progress. Almost all GPCR agonists that have an analgesic action are coupled to Gi/o proteins. Therefore, they become a new target in blocking pain. Here, we focus opioid receptor and CXCR4 on the effects and mechanisms of pain.

Opioid Receptors and Pain

Opioid receptors are members of the Gi protein-linked GPCRs. These receptors, as well as the chemokine and opioid peptide ligands, are widely distributed in the brain tissue and the periphery. Four major opioid receptors have been cloned: μ-, δ-, κ-, and nociceptin/orphanin FQ receptors (opioid receptor-like 1 [ORL1]).[6] Each of the opioid receptor genes expressed in brain tissue and immune cells has been cloned and sequenced.[7-12] Stimulation of opioid receptors promotes Ca^{2+} release of intracellular Ca^{2+} stores through activation of phospholipase C.[13] The expression level of μ-, δ-, and κ-opioid receptors is correlated to the pain conditions. In a diabetic neuropathy rat model, the expression of μ-opioid receptor is attenuated in the spinal dorsal horn.[14,15] μ-opioid receptor has been reduced by injury in the spinal dorsal horn.[16] On the other hand, an increased expression of δ-opioid receptor of dorsal root ganglion (DRG) neurons is detected in chronic inflammatory pain rat model.[17] Consistent with above, the level of κ-opioid receptor is upregulated in the DRG neurons of mice following nerve injury.[18]

The μ-opioid agonists are still the gold standard for the treatment of moderate and severe pain. μ-opioid receptor is probably coupled to different signaling pathways and heterogeneously expressed in different phenotypes of DRG neurons.[19] Intrathecal injection of μ-opioid receptor antagonists abolishes the inhibitory effect on dorsal horn neurons and the analgesic action produced by μ-opioids administered systemically,[20,21] indicating that μ-opioid receptor in the DRG and spinal cord is involved in pain transmission. However, the heterodimerization of the κ-and δ-opioid receptors synergistically increases the binding of their selective agonists. On the contrary, co-expression of μ- and δ-opioid receptors decreases the binding of their selective agonists.[22] In contrast to the individually expressed μ- and δ-opioid receptors, the co-expressed receptors are insensitive to pertussis toxin in COS cells.[22] Therefore, co-activation of both Gq and Gi/o may be required for this opioid excitatory effect. However, the functional outcome of this effect is not clear, but it may play a role in opioid-induced hyperalgesia reducing pain. The μ-, δ-, κ-, and ORL1-opioid receptor agonists inhibit neuronal activity through (1) inhibition of voltage-gated calcium channels in the DRG neurons[23-25] and (2) suppression of neuronal excitability through activation of GIRK channels in the postsynaptic neurons in the spinal cord.[26] Above all, opioid receptor novel inhibitors will be a potential treatment target for pain management.

CXC Receptor 4 and Pain Neurotransmission

Chemokines are responsible for the recruitment of leukocytes during inflammation and disease. Chemokines, based on the position of conserved cysteines, have been classified into four families: C, CC, CXC, and CX3C.[27] Besides their well-known role in the immune system, they are highly expressed in the nervous system, indicating that they might play roles in the regulation of stem cell migration and neurotransmission. Chemokine signaling is also of key importance in the regulation of neuroinflammatory responses. Many chemokines and their receptors may play a distinct role in chronic pain syndromes.[28] Although it is uncertain of the exact mechanism by which chemokines and their receptors act in these pain states, pain strategies aimed at limiting the actions of chemokines may result in an important new direction of therapies on pain.

GPCR also involved the chemotaxis and inflammatory pathway signaling. A common response of all nonexcitable cells by chemokine stimulation is chemotaxis. The presence of chemokine receptors on neurons often triggers downstream signaling cascades through dissociation of G proteins which induce the phosphoinositide 3-kinase pathway or activates phospholipase C resulting in Ca^{2+} influx and protein kinase C activation.[28] It is important to note that most responses toward chemokines are blocked with pertussis toxin, indicating that many chemokine receptors are Gi/o coupled. Recent functional characterizations of chemokine receptors suggest that these proteins form dimers that could further regulate their signaling.[29,30] In addition, chemokines may activate mitogen-activated protein kinase by either Ga or G-protein independent signaling.[29,31]

The chemokine CXC motif receptor 4 (CXCR4) is a major GPCR for CXCL12. CXCL12/CXCR4 chemokine signaling plays a critical role in modulating various nervous system developmental processes and in regulating synaptic plasticity. CXCR4 is highly expressed in the peripheral nervous system (PNS) and CNS and exerts functions as modulation of neurotransmission, synaptic plasticity, and neuroglial interactions.[32] In pain processing, CXCR4 is overexpressed on primary sensory neurons, satellite cells, Schwann cells, and endothelial cells in the peripheral nociceptive structure.[33-39] Besides functions in PNS, CXCR4 is involved in the CNS pain signaling. In a central neuropathic pain model, CXCL12/CXCR4 was upregulated in neurons, astrocytes,

microglia/macrophages, and leukocytes in the lumbar spinal cord.[40] However, the role of CXCR4 in pain transduction remains largely unknown. A few studies evaluate the effects of pharmacological inhibition of CXCR4 on central pain signal processing. Increased signaling by stromal-derived factor-1 (SDF-1/CXCL12) and its receptor, CXCR4, has been shown to contribute to chronic pain behavior.[35] Specific chemokine receptor antagonists for CXCR4 successfully may reverse nociceptive pain behaviors.[37]

The involvement of chemokine and their receptors in neuropathic pain processing has recently been established in animal models. It has been shown that the injection of SDF1α/CXCL12 into the un-inflamed adult rat hind paw produces dose-dependent tactile allodynia, designed regulated on activation, normal T-cell expressed, and secreted (RANTES/CCL5) or macrophage inflammatory protein-1α (MIP1α/CCL3).[34] These behavioral studies in combination with reverse-transcription polymerase chain reaction, calcium imaging, and immunohistochemistry confirmed the presence and functionality of the respective chemokine receptors, CXCR4, CCR5, and CCR4 in rodent DRG sensory neurons.[34] CXCR4-knockout mice show abnormalities in the development of several neuronal structures, such as the dentate gyrus of the hippocampus, the cerebellum, and the DRG.[41,42] These phenotypes result from deficits in the chemokine-mediated migration of neural stem cells. Chemokines are involved in the regulation of neuronal excitability, neurotransmitter release, and neuronal survival.[42] These possibilities are supported by the extensive expression patterns of some chemokines and their receptors throughout the developed brain[43-48] and by the reported actions of chemokines on phenomena such as neuronal excitability and transmitter release in both CNS[49-52] and PNS.[34] Interestingly, although many chemokines are not commonly expressed at high levels in the brain, they can be dramatically upregulated due to neuroinflammatory responses. Increased signaling by SDF-1/CXCL12 and its receptor, CXCR4, has been shown to contribute to chronic pain behaviors. The use of specific chemokine receptor antagonists for CXCR4 successfully reverses nociceptive pain behavior. Taking all this evidence into consideration, drugs that inhibit chemokine receptor function would be predicted to be useful in treating painful neuropathies. In the spinal cord injury-induced central neuropathic pain model, it is demonstrated that SDF1 and CXCR4 expression was continuously increased at the spinal cord level.[53] Moreover, by mapping the cellular and subcellular localization of SDF1 and CXCR4, Reaux-Le *et al.* reported that SDF1/CXCR4 system was closely related to the nociceptive pathway, especially in the primary nociceptive neurons, and they also found that activating the CXCR4 by intrathecal SDF1 injection could induce mechanical allodynia, which could be prevented by the CXCR4-neutralizing antibody.[54] However, the underlying mechanisms of SDF1/CXCR4 involved in the chronic and persistent pain remain unclear. Recently, this chemokine signaling has attracted much attention because of its emerging involvement in nociceptive signal regulation.

In summary, chemokines and their receptors could potentially be important for the development and maintenance of pain. Chemokines can be synthesized by nociceptive neurons and by other cells in response to injury. These chemokines activate receptors on macrophages and microglia, resulting in their migration and enhancing their activation. Importantly, the chemokines, as RANTES, SDF1α, MCP1, and fractalkine,[34,55] can act directly on nociceptive neurons to produce excitation and pain.[34,55] Opioid receptors are members of the Gi protein-linked GPCRs. The μ-opioid agonists are still the gold standard for the treatment of moderate and severe pain. Furthermore, specific chemokines/receptors are upregulated following peripheral nerve injury and appear to participate in neural signal processing, leading to chronic pain states.[56] CXCL12/CXCR4 signaling is now proven to be a potential analgesic target for pain management.

Conclusion

Tissue damage, inflammation, or injury of the nervous system may lead to chronic neuropathic pain characterized by hyperalgesia, allodynia, and spontaneous pain.[57,58] Significant progress has been made in understanding the important roles of various GPCRs in the regulation of pain transmission. However, intracellular signaling is complex and diverse process, and many important questions remain to be answered, especially in the precise signal transduction mechanism that underlies the diverse effects of individual GPCR agonists on ion channels and transmission during the pain. Further studies on the signal transduction pathways and molecular interactions between GPCRs are essential for a better understanding of drugs' action through GPCRs. Drug development by targeting each GPCR will improve the efficacy of traditional GPCR analgesics used to treat acute and chronic pain. The opioid receptor agonists are still the gold standard for the treatment of chronic pain. Furthermore, CXCR4 as a new therapeutic target has the pivotal role for pain managements. GPCRs function, their downstream effectors, and signaling pathways in pain processing need to be further illustrated. Taken together, chemokines and their receptors are potential targets for the development of novel pain management and therapy.

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Conflicts of interest

There are no conflicts of interest.

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