Current and emerging “at-site” pain medications: a review

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Abstract: The myriad pain pathophysiology has intrigued and challenged humanity for centuries. In this regard, the traditional pain therapies such as opioids and nonsteroidal anti-inflammatory drugs have been highly successful in treating acute and chronic pain. However, their drawback includes adverse events such as psychotropic effects, addiction potential, and gastrointestinal toxicities, to mention a few. These factors combined with the likelihood of an increase in chronic pain conditions due to an aging population calls for the development of novel mechanism-based or “site-specific” agents to target novel pain pathways. In this regard, rapid progress has been made in understanding the molecular mechanisms of novel pain targets such as cannabinoid receptors, fatty acid hydrolase, voltage-gated and ligand-gated ion channels such as P2 receptors, transient receptor potential channels and glial cell modulators. Accordingly, preclinical studies indicate that the site-specific/selective agents exhibit sufficient efficacy and reduced side effects such as lack of psychotropic effects indicating their clinical potential. This review provides a brief summary of some “at-site” pain targets and their role in the pain pathophysiology, and describes the efforts in developing some small molecules as novel pain therapeutics.

Keywords: opioids, nonsteroidal anti-inflammatory drugs, cannabinoid receptors, P2X receptors, transient receptor potential channels, glial cells

Introduction

The word “pain” is simple, yet complex. The quest of humans to conquer pain by investigating the underlying cause is a challenging and ongoing process. According to the International Association for the Study of Pain, the definition of pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” indicates the subjective nature of pain.¹ It is the most common complaint for which patients seek medical attention, lose productivity, and incur health care costs.² The epidemic status of pain across the globe is highlighted by a recent study which showed that nearly 37.3% and 41.1% of the adult population in the developed and developing countries, respectively, experience chronic pain due to diseases or disorders or injuries.³ Pain is characterized by both physical and psychological symptoms. Based on clinical characteristics, pain can be classified as nociceptive, neuropathic, or psychogenic/idiopathic.^{2,4-6} The mechanical, chemical, or thermal stimulation of peripheral sensory nerves due to surgery or trauma in a well localized area is described as nociceptive pain, whereas neuropathic pain is defined as an abnormal signaling resulting from injury or dysfunction of the peripheral or central nervous system (CNS) leading to pain. In addition, the latter is less localized and can

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Figure 1 Summary of pain pathophysiology and some pain targets.
Abbreviations: CB, cannabinoid; COX, cyclooxygenase; NMDA, N-Methyl-D-aspartate.

persist in the absence of visible injury or inflammation.⁷⁻¹¹ Pain perception/assessment in patients with personality disorders, mood disorders, or substance abuse indicates the influence of psychiatric disorders on pain etiology.^{12,13} Traditional pain-management therapies involve analgesics such as acetaminophen and aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and indomethacin, and narcotics such as morphine.^{14,15} However, there is a growing concern on the risks of overdose, abuse, and addiction potential of these agents. For example, in the United States alone,

about 30,000 hospitalizations are attributed to acetaminophen overdose, whereas NSAID therapy is associated with fatal gastrointestinal bleeding and potential cardiovascular risks.¹⁶⁻¹⁸ In addition, narcotic analgesic abuse and addiction is a serious concern.¹⁹ These facts mandate the need to look beyond traditional pain targets such as cyclooxygenases and opioid receptors. The complexity in understanding the pain mechanisms listed in Figure 1 will go a long way in developing new therapies. Current research efforts are ongoing to discover agents with superior efficacy and safety profiles that target novel pathological routes as pain therapeutics (Figure 1). Emerging pain targets include cannabinoid (CB) receptors, fatty acid amide hydrolase (FAAH), voltage- and ligand-gated ion channels (sodium channels, T-type calcium channels, N-type calcium channels, P2 receptors, transient receptor potential [TRP] channels), peptide receptor antagonists, nerve growth factor (NGF), and glial cell modulators. This review describes recent developments in the discovery of CB₂ agonists, TRP vanilloid-1 (TRPV1) channel antagonists, P2 receptor antagonists, and agents that target activated glia.

The CB receptors

The CB receptors are part of the endocannabinoid system and are G-protein coupled receptors. Their role in the modulation of pain and inflammation is well documented.²⁰⁻²²

Figure 2 Chemical structures of some nonselective CB receptor modulators.
Abbreviations: CB, cannabinoid; K_i , inhibition constant.

Mammalian tissues express two types of CB receptors: CB₁ and CB₂ respectively. CB₁ receptors are primarily expressed in the CNS, whereas CB₂ receptors are primarily located in the periphery such as immune cells, spleen, and tonsils.²³ In this regard, a number of CB receptor agonists were reported. The classic CBs, tetrahydrocannabinol (Δ^9 -THC, Marinol®, Solvay Pharmaceuticals, Ixelles, Brussels, Belgium) (Figure 2, compound (1)) and dimethylheptyl tetrahydrocannabinol (HU-210) (Figure 2, compound (2)) based on a tricyclic terpenoid template are nonselective CB agonists with HU-210 exhibiting a greater degree of binding affinity toward CB receptors (Figure 2). The major drawback of classical CB therapy in pain management is the impairment of cognitive/motor function and altered psychological state.^{24,25} Compound CP-55,940 (Figure 2, compound (3)), a nonclassical CB was developed based on the chemical structure of Δ^9 -THC and played a major role in the discovery of the CB₁ receptor.²⁶ Consequently, the development of an aminoalkyl indole-based small molecule such as WIN55212 (Figure 2, compound (4)) provided some degree of CB₂ selectivity.²⁷ Eicosanoids such as anandamide^{22,28} represent endogenous CBs that exhibit greater affinity toward CB₁ than CB₂. Since centrally acting CB₁ receptor agonists are known to produce CNS side effects such as dizziness and cognitive impairment, current focus is to develop CB₂ receptor agonists that could produce minimal CNS side effects and to target CB₁ receptors at the periphery.^{22,29,30}

A number of small-molecule CB₂ receptor agonists have been developed in the past decade as potential agents to treat nociceptive, inflammatory, and neuropathic pain. The mechanism of CB₂-mediated analgesia is not clearly understood. Some studies suggest that CB₂ agonists could act on immune cells and prevent the associated inflammatory response. A recent investigation by Hsieh and coworkers shows that the dorsal root ganglia and spinal cord regions are the potential sites of CB₂-receptor-mediated analgesia.³¹ In this regard, one of the early CB₂-receptor agonists HU-308 (Figure 3, compound (5), a bicyclic derivative) exhibited high CB₂ selectivity (CB₂ inhibition constant [K_i] = 23 nM) and significant pain relief in the formalin model.³²

A wide range of small molecules with diverse ring templates have been developed as CB₂-selective agonists (Figures 3, 4, and 5). In this regard, several aminoalkyl indole-based derivatives exhibit superior CB₂ receptor binding and selectivity.^{33–36} For example, AM1241 (Figure 3, compound (6)) is a highly selective CB₂-agonist (CB₂ K_i = 3.4 nM; CB₁ K_i = 280 nM) that exhibits *in vivo* peripheral analgesia in inflammatory and neuropathic pain models without exhibiting

Figure 3 Chemical structures of some selective CB₂ receptor modulators.
Abbreviations: CB, cannabinoid; K_i , inhibition constant.

CNS side effects. Furthermore, the aminoalkyl indole (Figure 3, compound (7)) was a highly selective CB₂ receptor agonist (CB₂ K_i = 1.9 nM; CB₁ K_i > 10,000 nM; CB₁/CB₂ selectivity > 5263). In another study, Cheng and coworkers developed a novel series of *N*-arylamide oxadiazoles where they identified an amide-linked quinolone derivative (Figure 4, compound (8)) as a potent and selective CB₂ agonist (CB₂ half-maximal effective concentration [EC_{50}] = 2.2 nM) with excellent oral bioavailability profile in rats.³⁷ In an elegant study, a research team from GlaxoSmithKline discovered compound GW842166X (Figure 4, compound (9)) based on a pyrimidinecarboxamide template as a clinical candidate to treat inflammatory pain. Compound GW842166X was a selective CB₂ receptor agonist (CB₂ EC_{50} = 63 nM; CB₁ EC_{50} > 30 μ M) and exhibited potent oral activity (ED_{50} [half-maximal effective dose] = 0.1 mg/kg) in animal models

Figure 4 Chemical structures of some selective CB₂ receptor modulators.

Abbreviations: CB, cannabinoid; EC_{50} , half-maximal effective concentration; K_i , inhibition constant.

of inflammatory pain. Further lead optimization provided the 5-azaindole (Figure 4, compound (10)) with superior CB₂ binding affinity ($CB_2EC_{50} = 5 \text{ nM}$) and efficacy in both acute and chronic pain models.^{38,39} Another study showed that 4-oxo-1,4-dihydropyridines could serve as useful templates to develop selective CB₂ receptor ligands. The phenyl-substituted dihydropyridine (Figure 4, compound (11)) exhibited excellent CB₂-binding affinity and was an inverse agonist ($CB_2 K_i = 4.0 \text{ nM}$; $CB_1 K_i = 592 \text{ nM}$).⁴⁰ Rapid progress has been made in the development of CB₂-selective ligands based on a wide variety of ring templates, and a detailed discussion is beyond the scope of this review.³⁰ The evidence acquired to date, clearly supports targeting CB₂, CB₁/CB₂, or CB₁ receptors and to develop “peripherally restricted” CB (CB₂ selective, dual CB₁/CB₂) agonists that exhibit reduced CNS side effects as novel agents in the pharmacotherapy of pain disorders.

The TRP channels

The TRP channel family belongs to ligand-gated and voltage-dependent ion channels/nociceptors that respond to chemical, mechanical, or thermal noxious stimuli at the periphery. They are divided into subfamilies. Many are located in the central and peripheral sensory neurons and are potential targets to treat neuropathic pain.^{41–43} The TRPV1 channels have been studied extensively and are known to play a critical role in peripheral sensitization of nociceptors and reduce pain threshold when activated by noxious stimuli. Its expression level is high in sensory neurons. The active ingredient of chili

peppers, capsaicin (Figure 5, compound (12)) is a known activator of TRPV1 and is effective as a topical agent to treat pain states. Although opioids are used to treat chronic pain, they exhibit serious side effects such as dizziness, sedation, loss of cognitive function, dependency, respiratory depression, development of tolerance, and constipation. These shortcomings support the need to target novel pathways of pain. In this regard, the role of TRPV1 in peripheral sensitization contributing to acute and chronic pain dictates the need to develop TRPV1 antagonists as potential agents to treat inflammatory and neuropathic pain.^{44–47} One of the early TRPV1 antagonists to enter the clinical trial was SB-705498 (Figure 5, compound (13)) based on a pyrrolidine urea that exhibited excellent oral activity in animal models.⁴⁸ Furthermore, Amgen reported the discovery of a clinical candidate AMG517 (Figure 5, compound (14)) based on a oxopyrimidine ring template. Compound AMG517 exhibited excellent TRPV1 inhibition (half-maximal inhibitory concentration [IC_{50}] = 0.9 nM); however, it had a long half-life and low aqueous solubility. Further lead optimization provided compound AMG628 (Figure, compound (15)), the piperazinympyrimidine derivative that exhibited good TRPV1 inhibition, in vivo half-life, and aqueous solubility and was considered as a clinical candidate.^{49,50} Recently, Abbott Laboratories reported the discovery of an orally active clinical candidate (*R*)-1-(5-*tert*-butyl-2,3-dihydro-1-*H*-inden-1-yl)-3-(1*H*-indazol-4-yl) urea (ABT102, Figure 5, compound (16)) to treat chronic pain. This small molecule exhibited potent TRPV1 binding (TRPV1 $IC_{50} = 4 \text{ nM}$) and

(12) Capsaicin, TRPV1 EC_{50} = 0.7 μ M

(13) SB-705498, TRPV1 IC_{50} = 32 nM

(14) AMG517, TRPV1 IC_{50} = 0.9 nM

(15) AMG628, TRPV1 IC_{50} = 3.7 nM

(16) ABT102, TRPV1 IC_{50} = 4 nM

Figure 5 Chemical structures of some TRPV1 receptor antagonists.
Abbreviations: EC_{50} , half-maximal effective concentration; IC_{50} , half-maximal inhibitory concentration; TRPV1, transient receptor potential vanilloid-1.

was effective in various in vivo pain models such as carrageenan induced postoperative and cancer pain. In addition, this agent did not exhibit side effects such as sedation and constipation commonly seen with opiate therapy, highlighting the fact that selective targeting of TRPV1 should provide agents that lack the adverse side effects of opiates.^{51–53} Accordingly, several small-molecule candidates are being developed by the pharmaceutical companies.^{41,47,54} The representative examples discussed here indicate the enormous

potential of targeting TRPV1 receptors to treat both acute and chronic pain. Compared with peripherally restricted CB agonists, TRPV1 receptor modulators reduce pain by acting on both central and peripheral pain pathways, suggesting their potential to cause CNS side effects. The challenges include recognizing TRPV1 gene polymorphism in patients to predict desired therapeutic responses and identify potential side effects such as hyperthermia.⁴⁶

P2X receptors

The neurotransmitter ATP (adenosine-5'-triphosphate) is known to produce pain through activating the purinergic receptors P1 and P2. The P1 receptors are known as adenosine receptors, whereas P2 receptors are further divided into P2Y (G-protein coupled receptors) and P2X (ligand-gated channels). The P2X receptors are subdivided into seven receptor subtypes (P2X1, P2X2, P2X3, P2X4, P2X5, P2X6, and P2X7 respectively) and have attracted widespread attention as potential targets to develop novel pain therapeutics.^{55–58} Among the P2X family, P2X7 is known to be present in immune cells such as monocytes, macrophages, mast cells, lymphocytes, and microglia, indicating their role in disorders such as pain, neurodegeneration, and inflammatory conditions.^{59,60} In this regard, novel P2X7 receptor antagonists are being developed as clinical candidates to treat acute and chronic pain.⁶¹ Scientists at Abbott Laboratories reported the development of some distinct small molecules as P2X7 receptor antagonists. In this regard, the 1-benzyl-5-phenyltetrazoles (Figure 6, compound (17)) exhibited potent P2X7 inhibition and were effective in a neuropathic pain model. In another study, a series of *N*-acyl hydrazides was reported as a novel series of P2X7 receptor antagonists with in vivo activity. Compound (18) shown in Figure 6 was identified as a potent P2X7 receptor antagonist. Further studies led to the development of a novel series of cyanoguanidines with potent P2X7 inhibition, and compound (19) (Figure 6) was effective in a neuropathic pain model.^{62–64} In addition, researchers from AstraZeneca reported the development of adamantane-based small molecules (eg, compound (20) shown in Figure 6) as P2X7 receptor antagonists with ability to prevent the formation of the pro-inflammatory cytokine interleukin-1 β .⁶⁵ A detailed description of several small-molecule P2X receptor modulators has been reviewed elsewhere.^{61,66}

Targeting glia cells

Recent studies have focused on the role of non-neuronal cells such as astrocytes and glia or glial cells in pain pathophysiology. Under pathological conditions, glial cells

Figure 6 Chemical structures of some P2X7 receptor antagonists.
Abbreviation: pIC_{50} , negative logarithm of the half-maximal inhibitory concentration.

get activated and are known to release pro-inflammatory cytokines, chemokines, and other signaling molecules that contribute to neuropathic pain.^{67–69} Some strategies include blocking glial cell activation, prevent the biosynthesis of pro-inflammatory cytokines, block the action of pro-inflammatory cytokines, and disrupt their signaling. In this regard, the tetracycline antibiotic minocycline (Figure 7, compound (21)) is known to selectively target microglia and could suppress the release of pro-inflammatory cytokines, whereas the xanthine

derivative pentoxifylline (Trental®, Aventis, Strasbourg, France) (Figure 7, compound (22)) currently used to treat chronic occlusive arterial disease and AV411 (Ketas™, Senju Pharmaceutical Co, Osaka, Japan) are known to inhibit pro-inflammatory cytokine biosynthesis. These small molecules are able to cross the blood–brain barrier, indicating their potential to target neuropathic pain. In contrast, biological molecules such as etanercept (Enbrel®, Amgen, Thousand Oaks, CA) and the interleukin-1 β antagonist anakinra (Kineret®, Amgen) are known to exhibit efficacy in neuropathic animal models, suggesting their ability to block glial cell mediated cytokine signaling.⁶⁸ However, these agents are injectables that exhibit poor CNS penetration. In the last decade, glial cells have emerged as attractive targets to prevent chronic pain.^{70,71} In this regard, the neuroprotective nature of glial cells during tissue injury suggests a careful approach toward developing novel glial cell modulators. The molecular mechanisms of glial cell activation and its consequences is still a work in progress.

Figure 7 Chemical structures of some glial cell modulators.

Conclusion

The last decade has seen an unprecedented surge in understanding the complexity of pain pathology. The identification of novel pain targets such as CB receptors, FAAH, voltage- and ligand-gated ion channels (sodium channels, T-type calcium channels, P2X receptors, TRP channels), peptide receptor antagonists, NGF and glial cell modulators to treat nociceptive, inflammatory, and neuropathic pain is highly promising. Preclinical data shows that one can develop

peripherally restricted agents such as CB receptor modulators and FAAH inhibitors that do not exhibit psychotropic effects indicating their superior side-effect profile compared with traditional pain therapies. The challenge is to prove the efficacy seen in preclinical data of novel agents with clinical evidence. The benefit-to-risk ratios of novel pain therapies will come under careful scrutiny of regulatory agencies. Despite the challenges ahead, it is clear that understanding the molecular mechanisms of novel pain targets will go a long way in developing selective or “site specific” agents that exhibit efficacy and superior side-effect profile as pain therapeutics.

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