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Potential therapeutic targets for the treatment of opioid abuse and pain

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Abstract

Although **μ**-opioid peptide (MOP) receptor agonists are effective analgesics available in clinical settings, their serious adverse effects put limits on their use. The marked increase in abuse and misuse of prescription opioids for pain relief and opioid overdose mortality in the past decade has seriously impacted society. Therefore, safe analgesics that produce potent analgesic effects without causing MOP receptor-related adverse effects are needed. This review highlights the potential therapeutic targets for the treatment of opioid abuse and pain based on available evidence generated through preclinical studies and clinical trials. To ameliorate the abuse-related effects of opioids, orexin-1 receptor antagonists and mixed nociceptin/MOP partial agonists have shown promising results in translational aspects of animal models. There are several promising non-opioid targets for selectively inhibiting pain-related responses, including nerve growth factor inhibitors, voltage-gated sodium channel inhibitors, and cannabinoid- and nociceptin-related ligands. We have also discussed several emerging and novel targets. The current medications for opioid abuse are opioid receptor-based ligands. Although neurobiological studies in rodents have discovered several non-opioid targets, there is a translational gap between rodents and primates. Given that the neuroanatomical aspects underlying opioid abuse and pain are different between rodents and primates, it is pivotal to investigate the functional profiles of these non-opioid compounds compared to those of clinically used drugs in non-human primate models before initiating clinical trials. More pharmacological studies of the functional efficacy, selectivity, and tolerability of these newly discovered compounds in non-human primates will accelerate the development of effective medications for opioid abuse and pain.

1. Introduction

Although nociceptive somatosensory systems, such as pain, are indispensable to detect abnormalities or disorders in organs and protect tissue damage, intractable pain associated with several chronic diseases should be effectively relieved. Pain is considered a burden that

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largely reduces quality of life and impairs productivity globally (Cohen, Vase, & Hooten, 2021; Collaborators et al., 2018). In the US, over 100 million adults experience chronic pain annually, and the annual total cost of pain, including direct costs, decreased wages, and lost productivity, largely eclipsed that of any other diseases such as heart diseases, cancer, and diabetes (Holmes, 2016). Thus, there is an unmet need to establish effective treatment strategies for intractable pain. People recognized different types of pain, such as burning and stabbing, and the opium poppy (*Papaver somniferum* L.) was used to relieve pain for thousands of years (Brook, Bennett, & Desai, 2017). In 1805, morphine was identified as the active pain-killing ingredient of the opium poppy. The discovery of morphine has had a huge impact that contributed to not only scientific knowledge but also human lives (Pain, 2016). Till date, this ingredient remains one of the most potent analgesics, and several of its derivatives or related compounds that act on μ-opioid peptide (MOP) receptors are widely used for the management of severe pain associated with serious diseases, such as cancer and myocardial infarction (Degenhardt et al., 2019; Kreek, Reed, & Butelman, 2019).

Opioid receptors were identified and cloned in the 1990s after several years of biochemical, physiological, and pharmacological research (Chen, Mestek, Liu, Hurley, & Yu, 1993; Evans, Keith, Morrison, Magendzo, & Edwards, 1992; Yasuda et al., 1993). Classical opioid receptors consist of three subtypes—MOP, δ-opioid peptide (DOP), and κ-opioid peptide (KOP) receptors. These receptors are widely distributed in the peripheral and central nervous system (CNS) and are particularly located in pain-processing regions, such as the dorsal root ganglia (DRG), spinal dorsal horn (SDH), and brain in mammals (Corder, Castro, Bruchas, & Scherrer, 2018; Fields, 2004). Under physiological conditions, endogenous opioid peptides activate cognate opioid receptors to reduce pain and influence reward processing and mood through Gi-protein coupled receptor (GPCR) signaling. This in turn inhibits adenylate cyclase and voltage-gated calcium channels and activates inward potassium channels, resulting in a reduction in synaptic transmission (Darcq & Kieffer, 2018). Among the opioid receptors, the MOP receptor is known to be the sole receptor responsible for the analgesic effects of morphine. This observation is based on rodent studies that demonstrated that the deletion of the MOP receptor eliminates the analgesic effects of morphine (Matthes et al., 1996). The MOP receptor is also a key therapeutic target for clinically used opioids (such as oxycodone, fentanyl, methadone, buprenorphine), indicating that activation of the MOP receptor has substantial utility to relieve severe pain. However, MOP receptors also produce serious dose-limiting adverse effects such as abuse liability, respiratory depression, constipation, itching sensation, and physical dependence (Gunther et al., 2018). Although MOP receptor ligands are the strongest analgesics currently known to humans, these adverse effects often compromise therapeutic effects and cause serious problems, such as opioid use disorder (OUD).

Recently, an epidemic of opioid abuse and overdoses emerged in North America and a part of Europe. The marked increase in abuse and misuse of prescription opioids for pain relief and opioid overdose mortality in the past decade has had considerable impact on society (Dart et al., 2015; Degenhardt et al., 2014). Given that MOP receptor agonists are the only drugs that can relieve unbearable pain associated with cancer or some other medical conditions, it is pivotal to develop novel safe opioid analgesics that produce potent analgesic effects without causing MOP receptor-related adverse effects (Volkow & Collins, 2017). In

this review, we have compiled evidence from preclinical and clinical studies to uncover the regulatory mechanisms of opioid abuse and analgesia and propose newly discovered targets as potential therapeutics for the treatment of opioid abuse and pain.

2. Opioid abuse

2.1 Background of opioid abuse

Opioid abuse is a brain disorder associated with behavioral, psychological, and neurochemical manifestations (Kreek et al., 2019). Although a break-through finding in the 1970s revealed the importance of dopamine systems, for several decades, key components of drug addiction have been considered responsible for dysregulation of dopaminergic neurotransmitter systems (Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015). Dopamine systems normally contribute to various brain functions. Further, dopamine neurons play an important role in attention and working memory and are necessary for regulating motivation, reward, and similar motor functions (Bromberg-Martin, Matsumoto, & Hikosaka, 2010). Moreover, dopamine is associated with the pathogenesis of a proportion of psychosis and involved in positive mood in humans (Cousins, Butts, & Young, 2009). Notably, the mesolimbic dopaminergic system, known as the reward system, originates from the ventral tegmental area (VTA) and projects into the corticolimbic regions, such as the nucleus accumbens (NAC) and the prefrontal cortex (PFC) (Kourrich, Calu, & Bonci, 2015). The majority of NAC neurons are medium spiny neurons that receive excitatory glutamatergic inputs from the PFC, thalamus, amygdala, and VTA; therefore, they are considered key reward-related neural circuits (Kourrich et al., 2015). Based on these data, drug addiction is hypothesized to be due to drugs that induce dopamine release and they are considered to have a risk of abuse. There is a significant causal link between dopamine levels and actions in the brain and addiction to psychostimulants (such as amphetamine and cocaine) (Bello et al., 2011; Sulzer, 2011). However, studies in rodents have demonstrated that blockade of dopamine receptors do not attenuate the rewarding effects of opioids (Fields & Margolis, 2015; Hnasko, Sotak, & Palmiter, 2005), and clinical trials could not support that this blockade was effective for the treatment of drug addiction in humans (Lingford-Hughes, Welch, Peters, Nutt, & British Association for Psychopharmacology, 2012; Rothman, 1994).

Preclinical animal studies have suggested that the opioid system largely contributes to reward and aversion and that dysregulation of opioid neurotransmission is crucial for drug abuse (Darcq & Kieffer, 2018). MOP receptors are widely distributed throughout the mesocorticolimbic circuitry in the brain (Corder et al., 2018). The prevailing disinhibition hypothesis proposes that activation of MOP receptors expressed by GABAergic interneurons in the VTA reduces local inhibition, subsequently resulting in the activation of dopamine neurons (Fields & Margolis, 2015; Morales & Margolis, 2017). However, as discussed above, such a hypothesis has not been confirmed as several brain regions that receive dopaminergic input, such as NAC, have abundant MOP receptors (Cui et al., 2014). Furthermore, dopamine-independent opioid reward based on MOP receptor-expressing neurons driving opioid reward outside the VTA has been demonstrated (Hnasko et al., 2005). MOP and KOP receptors oppositely regulate hedonic homeostasis, and MOP and KOP receptor agonists lead to euphoria and dysphoria, respectively. Unlike MOP receptors,

KOP receptors in dopamine neurons of the VTA counteract MOP receptor-mediated activity in the NAC and PFC (Margolis et al., 2006) and disrupt behaviors. KOP receptors in the medium spiny neurons of the NAC regulate the input to the amygdala to negatively regulate motivational processes (Tejeda et al., 2017). Accumulating evidence suggests that nociceptin/orphanin FQ (N/OFQ) peptide (NOP) and its cognate receptor system, known as the fourth opioid receptor subtype, play unique roles in negatively regulating craving for abused drugs (Kiguchi, Ding, & Ko, 2020; Parker et al., 2019). Although evidence on the contribution of DOP receptors in opioid abuse is limited, four opioid receptor subtypes have been implicated in drug-dependent motivation underlying reward and abuse potential. Given that addiction is a complex mixture of behaviors and other neurological factors, there is no rationale to support that a single neurotransmitter (dopamine) could be associated with all aspects of addiction, suggesting that addiction can be considered a multiple-neurotransmitter disorder (Kreek et al., 2019; Nutt et al., 2015; Rasmussen, White, & Acri, 2019).

2.2 Treatment of opioid abuse

Currently there are three medications available for the treatment of OUD. These medications are methadone (a full MOP receptor agonist), buprenorphine (a low-efficacy partial MOP receptor agonist), and naltrexone (a MOP receptor antagonist). Each of these medications has its own unique pharmacological properties that require considerable knowledge and skills for appropriate prescribing (Kreek et al., 2019; Saxon, 2013; Schuckit, 2016). The appropriate use of these medications has also been limited by stigma, insufficient medical education, and inadequate resources (Kreek et al., 2019). Scientists have developed different strategies to address the opioid crisis. While reviewing the literature, we selected five approaches to update readers with recent findings. It should be noted that given the complex nature of opioid addiction, it is not realistic to expect a magic bullet to treat OUD. Successful treatment outcomes for patients with OUD require integration of both pharmacotherapy and psychosocial interventions (Rasmussen et al., 2019; Volkow & Blanco, 2020). Here, we have focused on opioid-related compounds with improved side-effect profiles and those that could suppress the abuse liability of opioids.

2.3 G protein signaling-biased MOP receptor agonists

MOP receptor activation initiates two different signaling pathways—G protein signaling and β-arrestin recruitment (Whistler, Chuang, Chu, Jan, & von Zastrow, 1999; Zhang et al., 1998). Earlier studies using β-arrestin2 knockout mice have shown that the antinociceptive effect of morphine could be improved, that is, potentiation of morphine can be enhanced, tolerance to it can be slowly developed, and side effects such as respiratory depression and constipation due to its usage can be reduced (Bohn et al., 1999; Bohn, Gainetdinov, Lin, Lefkowitz, & Caron, 2000; Raehal, Walker, & Bohn, 2005). Therefore, a G protein signaling-biased ligand devoid of β-arrestin recruitment may exert enhanced analgesia with improved safety and tolerability (Luttrell, Maudsley, & Bohn, 2015; Schmid & Bohn, 2009; Violin, Crombie, Soergel, & Lark, 2014). Oliceridine (TRV130) was the first reported G protein-biased MOP receptor agonist (Chen et al., 2013). In rodents, oliceridine, a potent analgesic across several pain models, causes less respiratory depression and gastrointestinal dysfunction (DeWire et al., 2013). Although oliceridine has progressed to clinical trials and has been approved by the US Food and Drug Administration (FDA), its therapeutic window

is not as wide as originally expected. Namely, an analgesic effect is seen and accompanied by respiratory depression (Soergel et al., 2014; Viscusi et al., 2016).

Recently, scientists have discovered a series of G protein signaling-biased MOP agonists as new chemical entities with different bias factors, i.e., the degree of separation measured in the G protein signaling and β-arrestin2 recruitment assays. Through computational docking of over 3 million molecules against the MOP receptor structure and further optimization, PZM21 was discovered as a G protein-biased MOP receptor agonist. This compound exerted antinociceptive effects without rewarding effects and respiratory depression in mice (Manglik et al., 2016). Studies have also shown that PZM21 produces morphine-like respiratory depression in mice (Hill et al., 2018) and oxycodone-like reinforcing effects in monkeys (Ding et al., 2020), indicating that there is no difference in the two major side effects of opioids (respiratory depression and abuse liability) between PZM21 and the other clinically used opioid analgesics.

SR-17018 was identified as a G protein-biased MOP agonist with the highest bias factor and minimal respiratory depression even at higher doses (Schmid et al., 2017). However, in another study, SR-17018, PZM21, and oliceridine displayed low intrinsic efficacy similar to that of buprenorphine in MOP receptor regulation, regardless of the downstream signaling pathways (Gillis et al., 2020). Given the correlation between the therapeutic windows and their intrinsic efficacies at the MOP receptor, it is reasonable to attribute the improved side-effect profile of G protein-biased MOP agonists to their low intrinsic efficacy (Azevedo Neto et al., 2020; Gillis et al., 2020). In particular, these G protein-biased MOP agonists with low intrinsic efficacy can function like buprenorphine, which explains their effectiveness in attenuating the abuse-related effects of opioids in animal models. Although substitution with SR-17018 in morphine-tolerant mice restored the antinociceptive effect of morphine in the hot plate test (Grim et al., 2020), additional studies are required to investigate the degree to which SR-17018 is different from buprenorphine in terms of its analgesic and adverse effects in different animal models. With regard to the retained abuse liability of G protein-biased MOP agonists (Ding et al., 2020; Zamarripa et al., 2018), it is difficult to ascertain how biased G protein signaling can substantially refine opioid therapeutics in response to the opioid crisis.

2.4 Orexin-1 receptor antagonists

Accumulated evidence on the orexin receptors has opened an exciting avenue for the treatment of drug abuse (Baimel et al., 2015; James, Mahler, Moorman, & Aston-Jones, 2017). Orexin neurons in the lateral hypothalamus project to several brain regions involved in reward and drug-seeking behavior (Harris, Wimmer, & Aston-Jones, 2005; Hopf, 2020). For example, the VTA has been demonstrated to be an important site of orexin signaling in drug abuse (James et al., 2017). Blockade of the orexin-1 receptor (OX1R) in the VTA attenuates the rewarding property of MOP receptor agonists (Zarepour, Fatahi, Sarihi, & Haghparast, 2014). Importantly, SB-334867, an OX1R antagonist, reduced heroin self-administration in rats (Smith & Aston-Jones, 2012). A recent study further demonstrated that SB-334867 decreased oxycodone self-administration, but the orexin-2 receptor (OX2R) antagonist TCSOX229 does not affect oxycodone self-administration in rats (Matzeu

& Martin-Fardon, 2020). In addition, OX1R is critical for the expression of morphine withdrawal, and increased numbers of orexin-producing cells may play a role in maintaining opioid addiction (Georgescu et al., 2003; Sharf, Sarhan, & Dileone, 2008; Thannickal et al., 2018).

Using behavioral economics procedures, preclinical studies have also demonstrated that SB-334867 reduces motivation to consume highly abused opioid fentanyl and attenuates cue-induced reinstatement of fentanyl seeking (Fragale, Pantazis, James, & Aston-Jones, 2019). Considerable evidence supports that orexin-based therapies may represent an effective treatment strategy for addiction across a various drugs of abuse, including opioids, stimulants, alcohol, and nicotine (Fragale et al., 2021; Hopf, 2020). According to the available literature, OX1R antagonists are effective in inhibiting the motivation for drug rewards. In contrast, OX2R antagonists and dual orexin antagonists (DORAs) are useful for facilitating sleep (Fragale et al., 2021; Perrey & Zhang, 2020). Although ample evidence supports the therapeutic potential of OX1R antagonists in the treatment of opioid abuse in animal models, there is currently no FDA-approved OX1R antagonist. Nevertheless, a DORA, suvorexant, has been approved by the FDA for the treatment of insomnia. Several clinical trials have investigated the functional efficacy of suvorexant in patients with OUD and other substance use disorders (Fragale et al., 2021; James et al., 2020). Given that sleep impairment is often associated with OUD, it is worthwhile to wait for results of ongoing clinical trials of suvorexant. Further, preclinical studies rigorously comparing the functional efficacy and therapeutic window of OX1R antagonists and DORAs in the context of OUD-related endpoints will facilitate the future development of orexin-based ligands as a new treatment approach for OUD.

2.5 NOP receptor agonists

Recent research on the NOP receptor has opened another avenue as a potential medication for the dynamic epidemic of opioid abuse (Lin & Ko, 2013; Rasmussen et al., 2019; Toll, Bruchas, Calo, Cox, & Zaveri, 2016). Briefly, activation of the NOP receptor inhibits sensory processing, dopamine release, and neural transmission, which are considered viable targets for both pain and addiction (Kiguchi et al., 2020; Schroder, Lambert, Ko, & Koch, 2014; Toll et al., 2016). NOP agonists alone do not produce rewarding or aversive effects (Ko et al., 2009; Le Pen, Wichmann, Moreau, & Jenck, 2002). In an earlier study, the effects of opioids, measured by conditioned place preference, was blocked by selective NOP receptor agonists (Murphy, Lee, & Maidment, 1999). However, selective NOP receptor agonists did not display functional selectivity, that is, their sedative doses attenuated the reinforcing effects mediated by both opioids and food, measured by the self-administration assay (Podlesnik et al., 2011; Sukhtankar, Lagorio, & Ko, 2014). Given that opioid-induced rewarding and reinforcing effects are not fully mediated by dopamine signaling (Fields & Margolis, 2015; Nutt et al., 2015), selective NOP agonists may have mild-to-moderate efficacy in suppressing the abuse liability of opioids.

Clinical trials have documented that buprenorphine is an effective medication for OUD as it can reduce opioid craving and relapse risk (Kakko et al., 2019; Reimer, Vogelmann, Trümper, & Scherbaum, 2020). However, buprenorphine can produce moderate euphoric

effects and physical dependency. It is also associated with an additional risk of diversion and misuse or abuse of medication (Johanson, Arfken, di Menza, & Schuster, 2012; Lavonas et al., 2014). Nonetheless, added naloxone in the commonly available formulations (e.g., suboxone) is expected to decrease abuse potential (Jones et al., 2017). Given that NOP receptor agonists synergistically enhance the antinociceptive effect of buprenorphine and partially inhibit MOP receptor-mediated reinforcing effects (Cremeans, Gruley, Kyle, & Ko, 2012; Ding et al., 2021), a ligand with mixed NOP/MOP receptor agonist activities may have a wider therapeutic window with fewer side effects (Kiguchi et al., 2020; Lin & Ko, 2013). This hypothesis is supported by the functional profile of BU08028, a buprenorphine analog, with additional NOP receptor binding affinity and efficacy, which shows improved analgesic potency and a lack of reinforcing effects and physical dependency (Ding et al., 2016). The promising therapeutic profile of mixed NOP/MOP partial agonists is not compound specific as this class of compounds in different chemical structures include safe analgesics without abuse potential and physical dependency in non-human primates (NHPs) (Ding et al., 2018; Kiguchi et al., 2019). More importantly, ligands with dual actions (such as partial MOP agonists and NOP agonists) can inhibit the reinforcing effects of oxycodone without affecting the reinforcing effects of food pellets in NHP self-administration models, possessing a functional selectivity for inhibiting opioid abuse-related effects (Ding et al., 2018). Although cebranopadol, a mixed NOP/MOP full agonist, has been developed as a safe analgesic (Calo & Lambert, 2018; Tzschentke, Linz, Koch, & Christoph, 2019), its moderate reinforcing strength may limit its use in a broader therapeutic context (Ding et al., 2021). Nonetheless, given the clinical utility of buprenorphine, its analogs with additional NOP receptor agonist activity and other "*centrally penetrant*" combined NOP/MOP partial agonists possess great potential for treating OUD. In particular, more preclinical studies should be undertaken to further investigate the functional efficacy of such ligands with different brain-penetrant degrees in the context of OUD-related endpoints in NHP models (Ding & Ko, 2021).

2.6 Emerging targets

After the discovery of trace amine-associated receptor 1 (TAAR1) and subsequent development of selective small-molecule TAAR1 agonists (Borowsky et al., 2001; Sotnikova, Caron, & Gainetdinov, 2009), there has been a growing interest in the therapeutic potential of this receptor (Tonelli & Cichero, 2020). TAAR1 agonists are known to reduce the firing rate of dopaminergic neurons (Revel et al., 2011) and have great potential as therapeutic targets for neuropsychiatric diseases and drug addiction (Liu & Li, 2018; Schwartz et al., 2018). Although TAAR1 agonists have been extensively demonstrated as a promising pharmacotherapy for psychostimulant addiction (Liu, Wu, & Li, 2020), little is known about whether these agonists can modulate the abuse-related effects of opioids. Importantly, a recent study demonstrated that RO5263397, a TAAR1 partial agonist, attenuates morphine intake and motivation to self-administer morphine and decreases cue- and drug-induced reinstatement of morphine-seeking behavior in rats (Liu et al., 2021). Selective inhibition of the reinforcing effects of morphine by RO5263397 without changing the antinociceptive effect of morphine warrants additional animal and human studies to develop an optimal treatment strategy to curb opioid abuse.

Ibogaine, an alkaloid extracted from plants from the family Apocynaceae such as *Tabernanthe iboga*, is classified as a hallucinogen owing to its psychedelic property (Iyer, Favela, Zhang, & Olson, 2021). Although human studies on the safety and efficacy of ibogaine are lacking, anecdotal reports and animal studies support that it can reduce opioid cravings and prevent relapse (Belgers et al., 2016). Ibogaine has been reported to cause acute motor impairment and cardiotoxicity in animals. However, additional studies are required to determine its risks and potential benefits. As ibogaine is a psychoplastogen that can promote functional and structural neural plasticity in addiction-related circuitry, chemists have concentrated on the function-oriented synthesis of analogs of iboga alkaloids (Iyer et al., 2021). Importantly, tabernanthalog was discovered through a psychoplastogenic pharmacophore of ibogaine; it does not possess the toxicity and hallucinogenic effects of ibogaine (Cameron et al., 2021). Systemic administration of tabernanthalog reduced both heroin and sucrose self-administration, indicating that its inhibitory effect could be due to non-selective disruption of the operant response. Nonetheless, pretreatment with tabernanthalog prevented only cue-induced reinstatement of heroin and not sucrose-seeking behavior in rats (Cameron et al., 2021). These new findings encourage additional behavioral and neurochemical studies on tabernanthalog to determine its functional efficacy and selectivity across different animal models of OUD.

3. Pain

3.1 Background of pain

Primary sensory neurons transmit electrical impulses that encode specific sensory information to the CNS (the SDH and brainstem). Among heterogeneous sensory neurons, C- or Aδ-fibers are nociceptors that respond to noxious (such as thermal, mechanical, and chemical) stimuli that are essential for the recognition of pain, while Aβ-fibers play a role in sensing tactile information (Moehring, Halder, Seal, & Stucky, 2018; Peirs & Seal, 2016). For the detection and transmission of nociceptive information, specialized cation channels, such as transient receptor potential vanilloid 1 (TRPV1) and voltage-gated sodium channels (Na_Vs), are necessary to amplify these signals for generation of action potential (Waxman & Zamponi, 2014). Subsequently, propagation of action potentials to the central terminals of sensory neurons leads to the release of neurotransmitters (such as glutamate and neuropeptides), which activate secondary CNS neurons by binding to postsynaptic cognate receptors. Primary sensory neurons input corresponding laminae in the SDH, which is the region for integration of peripheral input and descending supraspinal regulation. Most C- and Aδ-fibers form synapses in the superficial laminae (I and II), and Aβ-fibers project to deeper laminae (III–V) (Braz, Solorzano, Wang, & Basbaum, 2014; Moehring et al., 2018). The majority of SDH neurons consist of excitatory or inhibitory interneurons that locally modulate pain processing, while the other minor population is neurokinin-1 (NK1) receptor-expressing projection neurons located in laminae I (Peirs & Seal, 2016). Projection neurons convey pain information to several supraspinal areas such as the thalamus, parabrachial nucleus, amygdala, and cortex (Todd, 2010). Recent studies have uncovered complicated pain-processing mechanisms at the peripheral and SDH levels, suggesting that these areas could be reasonable therapeutic targets for pain (Woolf, 2020).

Pain is classified into three types—nociceptive, neuropathic, and nociplastic according to its etiology, pathophysiology, anatomical presentation, intensity, and duration (Raja et al., 2020). Nociceptive pain is caused by the activation of nociceptors and is important for defensive behaviors under physiological conditions, while continued noxious stimuli lead to pathological nociceptive pain. For example, osteoarthritis (OA) causes intense joint pain based on hyperactivation of nociceptors (Basbaum, Bautista, Scherrer, & Julius, 2009). To deal with such pain, a pharmacotherapy directly targeting molecules expressed on nociceptors, for instance, TRPV1 and other cation channels, might be effective (Moran, McAlexander, Biro, & Szallasi, 2011). In the event of tissue injury and inflammation, alterations in nociceptor function cause hypersensitivity and spontaneous pain. Nevertheless, if the inflammation is acute and transient, non-steroidal anti-inflammatory drugs can effectively suppress inflammatory pain (Woolf, 2020). Neuropathic pain is elicited by lesions or disorders in the somatosensory nervous system and present allodynia (pain caused by innoxious stimuli) and hyperalgesia, which are exaggerated responses to noxious stimuli (Attal, Bouhassira, & Baron, 2018). Compared to inflammatory pain, neuropathic pain is normally intractable and long lasting because of structural and functional alterations occurring in the nervous system, at least in part, through neuro-immune mechanisms (Ji, Chamessian, & Zhang, 2016). Nociplastic pain is defined as pain occurring in the absence of noxious stimuli, inflammation, or damage to the nervous system (Fitzcharles et al., 2021). Thus, it is very challenging to appropriately control neuropathic and nociplastic pain because of their complicated mechanisms. To appropriately deal with different types of pain, the extent to which the component of pain is mechanistically linked needs to be determined.

3.2 Treatment of pain

Currently, there are a limited number of options that produce clinically meaningful analgesia, and efforts to develop novel effective analgesics are ongoing (Yekkirala, Roberson, Bean, & Woolf, 2017). Traditionally used analgesics, such as opioids, non-steroidal anti-inflammatory drugs, acetaminophen, and antiepileptics, were discovered first for their analgesic effects, after which the target molecules were identified. In contrast, serotonin-norepinephrine re-uptake inhibitors and gabapentinoids have been identified based on preclinical studies of pain-regulatory mechanisms (Woolf, 2020). Although it is necessary to use these drugs as front-line treatment, they do not sufficiently relieve some types of pain because of their dose-limiting adverse effects or diversity of pathophysiology (Attal & Bouhassira, 2015; Cohen et al., 2021). Given the complicated mechanisms of pain processing, it might be reasonable to discover novel analgesic targets based on preclinical studies. TRPV1, NK1 receptor, Na_Vs, and nerve growth factor (NGF) have been nominated as candidates for analgesics that block excessive input of somatosensory nociceptive information into the SDH. Despite numerous studies demonstrating that such molecules (i.e., TRPV1 and NK1 receptor) significantly contribute to several types of pain in rodents (Nilius & Szallasi, 2014; Steinhoff, von Mentzer, Geppetti, Pothoulakis, & Bunnett, 2014; Yekkirala et al., 2017), inhibitors for TRPV1 or NK1 receptor failed clinical human studies because of their lower efficacy than originally anticipated or unexpected adverse effects. These facts suggest that there are difficulties in developing novel analgesics that are safe and clinically effective. Hence, reliance on this approach alone may not be appropriate to identify clinically effective therapeutic targets. Human diseases and biological responses

are not well simulated in rodents because of anatomical and functional gaps between rodents and humans (Balsters, Zerbi, Sallet, Wenderoth, & Mars, 2020; Seok et al., 2013; Warren et al., 2020). It is very important to conduct preclinical studies that replicate human pain conditions using multiple outcome measures and different species (Fig. 1).

3.3 Treatment of pain by peripheral actions

3.3.1 NGF inhibitors—Accumulating evidence suggests that neurotrophins, such as NGF and brain-derived neurotrophic factor, largely contribute to several types of pain through peripheral and central mechanisms (Ji, Xu, & Gao, 2014). NGF is the most characterized neurotrophin that activates nociceptive sensory neurons to convey pain signals from the periphery to the CNS, and its effects on pain processing have been well investigated (Denk, Bennett, & McMahon, 2017). Although NGF underlies the development of sensory neurons, it is also required to maintain the homeostasis of neurons and other tissues. NGF forms a ligand-receptor complex with the high-affinity receptor tyrosine kinase A (TrkA), and the complex is translocated to the nuclei of DRG neurons. Subsequently, phosphorylation of the NGF-TrkA complex enhances gene transcription (Denk et al., 2017; Ehlers, Kaplan, Price, & Koliatsos, 1995). In response to nociceptive (such as thermal, mechanical, and chemical) stimuli, substance P and calcitonin gene-related peptide are upregulated by NGF-TrkA signaling. Although these neuropeptides are transported to the central terminals of sensory neurons, they can also be released from peripheral terminals to act as proinflammatory molecules in tissue (Wise, Seidel, & Lane, 2021). Moreover, NGF increases the excitability of DRG neurons when nociceptors, such as TRPV1, are activated, resulting in peripheral sensitization (Ji, Samad, Jin, Schmoll, & Woolf, 2002). Given that NGF is a multifunctional molecule that affects not only the C- and Aδ-fibers of DRG neurons but also the bone and other tissues, musculoskeletal diseases are closely related to NGF signaling among the different types of chronic pain (Lane & Corr, 2017). Notably, NGF plays an important role in bone metabolism and regeneration as documented in animal studies. Peripherally released NGF facilitates bone formation by increasing the number of osteoblasts in mice with bone fractures (Wise et al., 2021).

NGF inhibitors attenuate OA-related pain in mice, suggesting that inhibition of NGF signaling might have favorable effects on musculoskeletal pain in humans (Lane & Corr, 2017; Wise et al., 2021). NGF is expressed on accumulating lymphocytes and monocytes in the synovial fluid in patients with rheumatoid arthritis or OA (Barthel et al., 2009; Stoppiello et al., 2014), which is supported by findings that substance P and pro-inflammatory cytokines upregulate NGF in cultured synovial cells. Furthermore, NGF is expressed in bone-associated cells (such as subchondral mononuclear cells, osteoclasts, and chondrocytes) in tissues of patients with OA. The expression levels of NGF are associated with age and synovitis scores, suggesting a correlation between NGF and chronic pain caused by OA (Aso et al., 2019). Based on these findings, a number of small compounds and antibodies that inhibit NGF and TrkA functions have been tested in both preclinical and clinical studies. Larotrectinib, which inhibits TrkA, TrkB, and TrkC, has been approved for the treatment of solid tumors (Drilon et al., 2018). As the therapeutic potential of NGF antibodies has also been demonstrated in animal models of bone cancer pain, it is pivotal to further undertake clinical studies to assess the effectiveness of NGF inhibitors (Lucchesi

et al., 2017). However, other small molecules, such as ASP7962, a TrkA antagonist, did not show the desired efficacy in patients with knee OA (Watt et al., 2019). Although, several monoclonal antibodies have been investigated, a majority of these molecules have not entered clinical trials because of lower efficacy or unexpected adverse effects, such as osteonecrosis. Tanezumab and fasinumab are currently being evaluated in clinical trials for OA and chronic low back pain with promising results for further consideration (Wise et al., 2021). Therefore, preclinical and clinical studies have supported the therapeutic potential of NGF-TrkA signaling for chronic pain associated with musculoskeletal diseases.

3.3.2 Na_v inhibitors—Among the different types of Na_vs that are expressed in humans, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are localized on DRG neurons and are crucial for peripheral signaling in nociceptive pain (Dib-Hajj, Yang, Black, & Waxman, 2013; Goodwin & McMahon, 2021). Na_vs consist of an ion-conducting pore-forming α subunit and one to two β subunits; their trafficking and gating properties are due to the α subunit. These Na_vs are divided into the tetrodotoxin (TTX)-sensitive subtype (Nav1.7) and the TTX-resistant subtype ($Na_v1.8$ and $Na_v1.9$). TTX-sensitive subtypes are activated more rapidly and show faster kinetics than TTX-resistant subtypes (Zeisel et al., 2018). Previous studies have indicated that mutations in the genes encoding these Na_vs are largely associated with sensitivity to pain in humans. This is because mutation leads to gain of function in $Na_v1.7$, which in turn activates $Na_v1.8$, which enhances pain (Bennett, Clark, Huang, Waxman, & Dib-Hajj, 2019). Furthermore, loss of function in $Na_v1.7$ results in loss of pain sensation due to different nociceptive stimuli without affecting other neurological functions (Cox et al., 2006; Goldberg et al., 2007). Although the mechanisms linking the loss of $Na_v1.7$ function and insensitivity to pain are not fully understood, it may be correlated to the fact that the majority of inactivating mutations of $Na_v1.7$ lead to a complete loss of channel function (Cox et al., 2006; McDermott et al., 2019). $Na_v1.8$ mutations have been identified in individuals with painful peripheral neuropathy (Faber et al., 2012), and a mutation causing a moderate loss of function in $Na_v1.8$ has been associated with reduced pain sensitivity (Duan et al., 2016). Based on preclinical studies in rodent models, $Na_v1.8$ contributes to neuropathic pain (Lai et al., 2002). Given that many preclinical and human studies have emphasized the potential role of $Na_v1.8$ in regulating pain at the peripheral level, it is essential to validate $Na_v1.8$ as a potential therapeutic target for pain (Alsaloum, Higerd, Effraim, & Waxman, 2020).

Moreover, locally administered non-selective Na_v blockers, such as lidocaine, suppress pain originating from different nociceptive stimuli. Funapide, an inhibitor of both $Na_v1.7$ and $Na_v1.8$, has been investigated for the treatment of inherited erythromelalgia, neuropathic pain, and postherpetic neuralgia (Goldberg et al., 2012; Price et al., 2017). Although funapide showed promising results in clinical studies, multiple trials have failed to meet the endpoint (Alsaloum et al., 2020). Lacosamide, which is prescribed as an anticonvulsant inhibiting $Na_v1.7$ and $Na_v1.8$, has been tested in clinical studies for $Na_v1.7$-related small fiber neuropathy (de Greef et al., 2019), and currently available data suggest that this compound is effective in the treatment of painful neuropathy (Alsaloum et al., 2020). Moreover, various selective blockers of $Na_v1.7$ have also been tested in patients with chronic pain. For example, vixotrigine was tested for the treatment of lumbosacral radiculopathy

and trigeminal neuralgia. The results of phase II trials suggest that vixotrigine has the potential to be an effective and safe treatment for small fiber neuropathy (Alsaloum et al., 2020). Ambroxol, a widely used mucoactive agent for bronchopulmonary diseases (Malerba & Ragnoli, 2008), inhibits TTX-resistant $Na_v1.8$ and $Na_v1.9$, rather than TTX-sensitive $Na_v1.7$, in DRG neurons (Weiser & Wilson, 2002). Ambroxol not only attenuates neuropathic pain, as seen in preclinical studies using various rodent models (Belkouch et al., 2014; Gaida, Klinder, Arndt, & Weiser, 2005), but also exerts analgesic effects at the peripheral level, as seen in clinical studies (Chenot, Weber, & Friede, 2014). In a recent phase III randomized controlled trial, ambroxol attenuated oropharyngeal pain (Sousa, Lakha, Brette, & Hitier, 2019). Nevertheless, the use of ambroxol for the treatment of neuropathic pain has only been supported by case reports, necessitating controlled clinical trials for neuropathic pain. Furthermore, other $Na_v1.8$ blockers, such as PF-0431082 and VX-150, manufactured by different pharmaceutical companies have also been tested in clinical trials. These new compounds, at least in part, demonstrate reasonable effects on several types of pain, and it is important to keep an eye on the results of the ongoing clinical studies.

3.3.3 Novel targets—More recently, newly discovered molecules regulating sensory processing have been identified in animal models of chronic pain. Importin α3, which is a key regulator of nucleocytoplasmic transport, induces nuclear import of c-Fos in DRG neurons (Marvaldi et al., 2020; Panayotis, Karpova, Kreutz, & Fainzilber, 2015). Importin α3 knockout or sensory neuron-specific knockdown attenuated responses to noxious stimuli and the maintenance phase of neuropathic pain in rodents (Marvaldi et al., 2020). Although c-Fos-related mechanisms underlie both peripheral and central levels of pain processing (Coggeshall, 2005), peripheral sensory neurons are targets of importin α3-dependent regulation of pain. Given that the expression patterns of both importin α3 and c-Fos are conserved between mice and humans (Ray et al., 2018), importin α3 might be a potential target for pain. Stimulator of interferon genes (STING) is an endoplasmic reticulum-bound DNA sensor that induces type I interferons and other cytokines that regulate immune responses (Hopfner & Hornung, 2020; Zhang et al., 1998). As STING is highly expressed in peripheral nociceptors, it was hypothesized that it may regulate nociception through interferon signaling. Although the loss of STING functions exhibited hypersensitivity to nociceptive stimuli and heightened nociceptor excitability, the intrathecal activation of STING exerted analgesic effects in mice with chemotherapy-induced peripheral neuropathy, nerve injury-induced neuropathic pain, and bone cancer pain (Donnelly et al., 2021). Importantly, the STING pathway exerts long-lasting analgesic effects in NHPs, and interferons directly suppress the excitability of nociceptors in mice and that of NHPs in humans through modulation of sodium and calcium channel function (Donnelly et al., 2021), indicating that STING can also be a novel peripheral target for chronic pain. Collectively, these results suggest that novel pain-regulatory molecules exhibiting different peripheral mechanisms are ideal candidates for the development of potent and non-opioid-based analgesics.

4. Treatment of pain by spinal and supraspinal actions

4.1 Cannabinoid receptor agonists

It has been traditionally known that cannabinoids (CBs), such as Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), purified from *Cannabis sativa* have therapeutic effects against several neurological disorders (Friedman, French, & Maccarrone, 2019). Based on binding studies using radiolabeled THC, CB1 and CB2 receptors (CB1R and CB2R, respectively) have been identified as target receptors of naturally isolated CBs (Devane, Dysarz 3rd, Johnson, Melvin, & Howlett, 1988; Matsuda, Lolait, Brownstein, Young, & Bonner, 1990). Subsequently, the biochemical and physiological characteristics of endogenous ligands for CB1R and CB2R, which are anandamide and 2-arachidonoyl-glycerol, have been worked out (Devane et al., 1992; Sugiura et al., 1995). Similar to the opioid receptors, both CB1R and CB2R are GPCRs. Although CB1Rs are abundantly expressed in the brain, CB2Rs are highly expressed in the immune system and involved in several physiological functions (Cristino, Bisogno, & Di Marzo, 2020). As CB1Rs are located on presynaptic terminals of excitatory and inhibitory neurons, activation of CB1R signaling can inhibit voltage-gated calcium channels and vesicular release of neurotransmitters (such as GABA and glutamate) underlying regulation of mood, cognition, and perception in animals and humans (Bara, Ferland, Rompala, Szutorisz, & Hurd, 2021; Cristino et al., 2020). In particular, accumulating evidence from studies using animal models suggests that CB1R agonists produce antinociception through the activation of CB1Rs at spinal or supraspinal levels (Donvito et al., 2018), indicating that CB1R agonists may be potential targets for centrally acting analgesics. Moreover, CB1Rs are also expressed on astrocytes that are not only involved in the regulation of synaptic plasticity in different brain areas and but also further located on progenitor stem cells and differentiate into neurons or astrocytes (Prenderville, Kelly, & Downer, 2015). Given that the patterns of CB1R activation and distribution may be altered in several CNS regions under pathological conditions (Cristino et al., 2020), CB1R may be considered a potential target for the treatment of neurological diseases. In contrast, CB2Rs are mainly expressed in CNS microglia in patients with multiple sclerosis and amyotrophic lateral sclerosis (Aymerich et al., 2018), and the activation of CB2Rs attenuates the expression of inflammatory cytokines associated with neurodegenerative disorders (Cassano et al., 2017). Thus, CB2Rs may have different functional properties and diverse therapeutic mechanisms than CB1Rs.

In view of the substantial anatomical and neurochemical overlap between opioid and CB systems (Le Foll, 2021; Rios, Gomes, & Devi, 2006), it was hypothesized that there is a therapeutic benefit of combining opioids and CBs for the treatment of pain. In this regard, a number of studies have demonstrated that non-analgesic doses of THC enhance opioid analgesia in rodents and NHPs (Babalonis & Walsh, 2020). The synergistic effects of opioid and CB combinations appeared to be rather selective for pain processing in animals, and the other unfavorable effects of CBs (such as hypothermia and hypoactivity) and opioids (such as respiratory depression) were not potentiated by such a combination (Welch, 2009). However, these findings have not been clearly confirmed in human studies. In fact, a combination of CBs and opioids demonstrated diverse results depending on the experimental setting in humans (Babalonis & Walsh, 2020). In addition, no substantial data

are available to suggest that CBs are highly effective analgesics for different pain conditions, including chronic pain. However, considerable evidence suggests that the expression levels of CB1R and CB2R are altered not only in animal models but also in patients with multiple sclerosis and that the activation of CB1Rs and CB2Rs has a beneficial therapeutic effect (Baker et al., 2000; Cristino et al., 2020; Maresz et al., 2007). Nabiximols, a cannabis extract that includes THC and CBD, has shown promising results in clinical studies and has been approved in several countries for the treatment of neuropathic pain and spasticity in multiple sclerosis (Giacoppo, Bramanti, & Mazzon, 2017). Moreover, as the effects of nabiximols are based on neuroimmune regulation, treatment with nabiximols reduces circulating levels of inflammatory cytokines that usually enhance pathological pain (Orefice et al., 2016). Nabiximols are currently being investigated for the treatment of painful conditions associated with CNS disorders, such as stroke and glioblastoma (Marinelli et al., 2017). Since nabiximols have shown promising therapeutic effects in clinical studies for these diseases (Friedman et al., 2019), it is likely that CBs can also be useful for several types of neurological disorders.

4.2 NOP receptor agonists

As NOP receptors are located on the pain-processing pathways (the DRG, spinal cord, and brain), several studies have been conducted to understand the functional profiles of NOP receptors in regulating pain (Corder et al., 2018; Schroder et al., 2014). Similar to MOP receptors, presynaptic and postsynaptic NOP receptors can inhibit excitatory glutamatergic transmission via GPCR signaling in the SDH and brain (Winters, Christie, & Vaughan, 2019), indicating that NOP receptor activation may produce antinociception. In rodents, NOP receptor activation produces both dose- and pain modality-dependent bi-directional (pronociceptive or antinociceptive) effects at the spinal or supraspinal levels. (Schroder et al., 2014). Nevertheless, as peptidic and non-peptidic NOP receptor agonists suppress neuropathic pain in rodents (Kiguchi, Ding, Kishioka, & Ko, 2020; Toll et al., 2016), NOP receptor-related ligands may be effective for the treatment of neuropathic pain. In contrast, intrathecal, intracisternal, or systemic administration of NOP receptor agonists only produces antinociception in NHPs (Ding et al., 2015; Kiguchi & Ko, 2019; Ko et al., 2009). Notably, N/OFQ was found to be the most potent endogenous peptide among all opioid peptides, such as β-endorphin and enkephalins, for spinal analgesia in inflammatory pain conditions (Lee & Ko, 2015). Importantly, intrathecal administration of NOP receptor agonists produces potent antinociceptive effects without eliciting morphine-like adverse effects, such as itching, in NHPs (Kiguchi et al., 2020). Moreover, the combination of SCH221510, a NOP receptor agonist, and buprenorphine significantly enhanced the analgesic effect and did not cause adverse effects in NHPs (Cremeans et al., 2012). These results indicate the probability of synergistic analgesia by the co-activation of both NOP and MOP receptors in humans.

Given the preferable functional properties of the NOP receptor agonists, it has been hypothesized that mixed NOP/MOP receptor agonists may be safer opioid analgesics, without the undesirable adverse effects. Based on the understanding of the structure-activity relationship of NOP receptors, several candidates for novel ligands, acting on both NOP and MOP receptors with different affinities and partial agonist efficacies, have been investigated

in preclinical studies (Kiguchi, Ding, Kishioka, & Ko, 2020; Zaveri & Meyer, 2019). In rodents, intrathecal administration of BU08028 (Khroyan et al., 2011) and SR16435 exerted antinociceptive and antiallodynic effects through the activation of NOP and MOP receptors (Sukhtankar, Zaveri, Husbands, & Ko, 2013). Recently, BU10038 was developed as a naltrexone-derived bifunctional NOP/MOP receptor agonist. Intrathecal BU10038 produced potent and long-lasting antinociceptive and antiallodynic effects compared to morphine in NHPs, and intrathecal BU10038 did not cause adverse effects, such as itching sensation, and tolerance. Unlike spinal analgesia, systemically administered NOP receptor agonists demonstrate integrated effects of peripheral, spinal, and supraspinal actions (Kiguchi et al., 2019). Systemic administration of BU08028 exerted morphine-comparable antinociceptive effects, but showed rewarding effects in rodents (Khroyan et al., 2011). However, it did not elicit reinforcing effects in NHPs (Ding et al., 2016), indicating that a translational gap exists with respect to the efficacy of mixed NOP/MOP receptor agonists between rodents and NHPs. A non-morphinan NOP/MOP receptor agonist, AT-121, produced potent antinociceptive and antiallodynic effects, which were almost 100-fold more potent than those of morphine, and was antagonized by either NOP or MOP receptor antagonist in NHPs (Ding et al., 2018). Moreover, the systemic administration of AT-121 lacks dose-limiting adverse effects such as abuse liability, itching sensation, respiratory depression, cardiovascular dysfunction, physical dependence, and opioid-induced hyperalgesia (Ding et al., 2018). Although these NOP/MOP receptor agonists have different binding profiles to NOP and MOP receptors (Kiguchi, Ding, Kishioka, & Ko, 2020), mixed NOP/MOP receptor partial agonists seem to have ideal functional profiles and, thus, may be developed as novel non-addictive and safe analgesics.

In rodents, cebranopadol has a half-life of 4.5h and oral bioavailability of 13–23% and exerts dose-dependent antinociceptive effects via NOP and MOP receptor activation after systemic administration (Calo & Lambert, 2018; Linz et al., 2014). Notably, cebranopadol was >100-fold more potent and long-lasting than morphine-induced analgesia, producing potent anti-allodynic effects in different models of neuropathic pain; unlike morphine, it does not affect respiratory and motor functions at analgesic doses (Calo & Lambert, 2018; Linz et al., 2014). The beneficial effects of cebranopadol can be translated to NHPs as it produces potent antinociceptive and antihypersensitive effects compared to fentanyl after systemic or intrathecal administration with reduced side effects, such as a lack of respiratory depression and itching (Ding et al., 2021). Although cebranopadol caused reinforcing effects in the fixed-ratio schedule of self-administration, its reinforcing strength was lower than that of fentanyl (Ding et al., 2021). Given that MOP receptor activation mainly contributes to cebranopadol-induced antinociception in NHPs, it is necessary to consider the detectable reinforcing effects of cebranopadol for clinical use. In phase I and phase II clinical trials for analgesic indications, the pharmacokinetic properties of cebranopadol have been demonstrated in patients (Calo & Lambert, 2018; Kleideiter, Piana, Wang, Nemeth, & Gautrois, 2018). Although oral administration of cebranopadol produced drug-liking effects, they were less or shorter than those of the usual MOP receptor full agonist hydromorphone (Gohler et al., 2019). This observation was consistent with that of preclinical study on NHPs (Ding et al., 2021). In clinical trials, cebranopadol produced significant analgesic efficacy in patients with low back pain, cancer pain, or diabetic neuropathy, with fewer

undesirable side effects such as miosis, respiratory depression, constipation, dizziness, and nausea (Christoph, Eerdekens, Kok, Volkers, & Freynhagen, 2017; Eerdekens et al., 2019; Kiguchi et al., 2020). Collectively, these findings support the concept of coactivation of NOP and MOP receptors for enhanced pain relief with reduced side effects.

5. Conclusions

This review highlights the recent progress in well-known targets and discusses exciting findings of emerging and novel targets for the treatment of opioid abuse and pain. Given that opioids are the most commonly prescribed analgesics for the treatment of moderate-to-severe pain, it is challenging to develop non-opioid analgesics that can replace opioids in clinical settings (Azzam, McDonald, & Lambert, 2019; Corbett, Henderson, McKnight, & Paterson, 2006). Nevertheless, biomedical science has evolved rapidly to discover innovative medications to treat opioid abuse and/or as safe, non-addictive interventions to manage pain (Rasmussen et al., 2019; Volkow & Collins, 2017; Woolf, 2020). There is a translational gap in the development of effective medications for opioid abuse and pain as behavioral and physiological responses to opioid-related ligands in rodents cannot be translated to primates (Ding & Ko, 2021; Kiguchi, Ding, & Ko, 2016). Rhesus macaques have genetic similarities to the human genome (Rhesus Macaque Genome et al., 2007) and this species plays a critical role in modeling human diseases and physiological responses that are not well simulated in rodents (Balsters et al., 2020; Seok et al., 2013; Warren et al., 2020). Although rodent studies have documented promising novel targets, few non-opioid targets have been validated in primates. To date, NHP studies have demonstrated that MOP receptor- or mixed opioid receptor subtype-based ligands are effective in alleviating opioid-induced adverse effects (Ding & Ko, 2021). Given the mounting evidence that neuroanatomical aspects of opioid and non-opioid receptors differ between rodents and primates (Bianchi et al., 2012; Hawkinson et al., 2007; Shiers et al., 2021; Yu et al., 2019), it is important to investigate the functional profiles of novel compounds extensively in NHP models before initiating expensive clinical trials. More pharmacological studies of the functional efficacy, selectivity, and tolerability of the novel compounds in NHP models will accelerate the development of effective medications for opioid abuse and pain to advance human medicine.

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Abbreviations

CB	cannabinoid
CB1R	cannabinoid 1 receptor
CB2R	cannabinoid 2 receptor
CBD	cannabidiol
CNS	central nervous system

DOP	δ-opioid peptide
DORA	dual orexin antagonist
DRG	dorsal root ganglia
FDA	Food and Drug Administration
GPCR	G-protein coupled receptor
KOP	κ-opioid peptide
MOP	μ-opioid peptide
N/OFQ	nociceptin/orphanin FQ
NAC	nucleus accumbens
Nav	voltage-gated sodium channel
NGF	nerve growth factor
NHP	non-human primate
NK1	neurokinin-1
NOP	nociceptin/orphanin FQ peptide
OA	osteoarthritis
OUD	opioid use disorder
OX1R	orexin-1 receptor
OX2R	orexin-2 receptor
PFC	prefrontal cortex
SDH	spinal dorsal horn
STING	stimulator of interferon genes
TAAR1	trace amine-associated receptor 1
THC	Δ9-tetrahydrocannabinol
TrkA	tyrosine kinase A
TRPV1	transient receptor potential vanilloid 1
TTX	tetrodotoxin
VTA	ventral tegmental area

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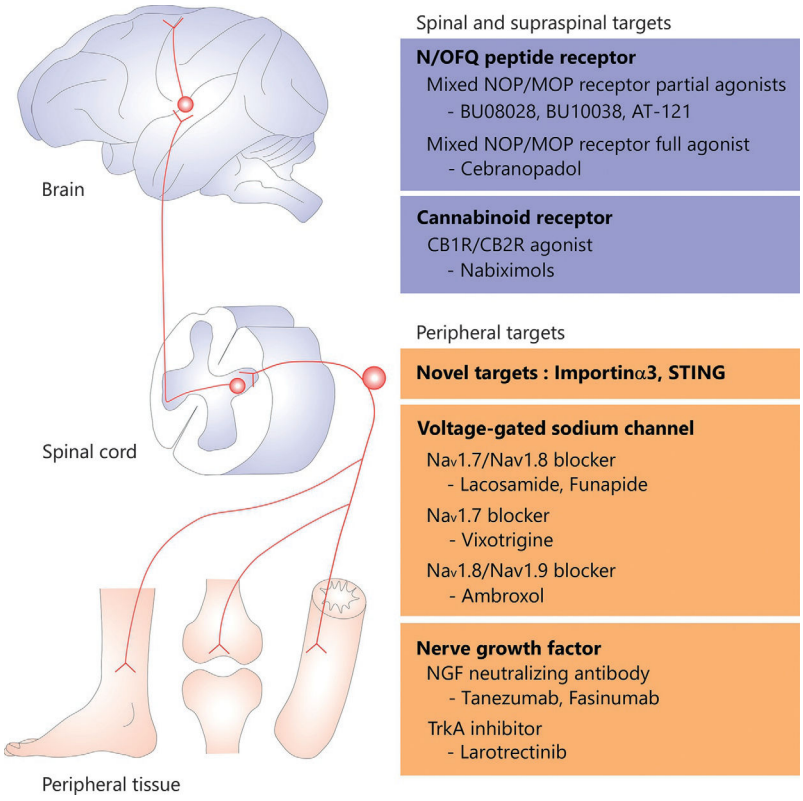

Fig. 1.

Potential therapeutic targets for the treatment of pain. Primary sensory neurons transmit electrical impulses that encode specific sensory information to the spinal cord, subsequently projection neurons in the dorsal horn convey pain information to the brain. Given the complicated mechanisms of pain processing, it might be reasonable to discover novel analgesic targets based on preclinical studies. At the same time, it is also very important to conduct preclinical studies that replicate human pain conditions. CB1R; cannabinoid 1 receptor, CB2R; cannabinoid 2 receptor, MOP; μ- opioid peptide, Na_v; voltage-gated sodium channel, NGF; nerve growth factor, N/OFQ; nociceptin/orphanin FQ, NOP; nociceptin/orphanin FQ peptide, STING; stimulator of interferon genes, TrkA; tyrosine kinase A.