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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Recent Advances in Peripheral Opioid Receptor Therapeutics

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Abstract

Purpose of Review Although opioids are excellent analgesics, they are associated with severe short- and long-term side effects that are especially concerning for the treatment of chronic pain. Peripherally acting opioid receptor agonists promise to mitigate the more serious centrally mediated side effects of opioids, and the goal of this paper is to identify and elaborate on recent advances in these peripheral opioid receptor therapeutics.

Recent Findings Peripheral opioid receptor agonists are effective analgesics that at the same time circumvent the problem of centrally mediated opioid side effects by (1) preferentially targeting peripheral opioid receptors that are often the source of the pain and (2) their markedly diminished permeability or activity across the blood-brain barrier. Recent novel bottom-up approaches have been notable for the design of therapeutics that are either active only at inflamed tissue, as in the case of fentanyl-derived pH-sensitive opioid ligands, or too bulky or hydrophilic to cross the blood-brain barrier, as in the case of morphine covalently bound to hyperbranched polyglycerols.

Summary Recent innovations in peripheral opioid receptor therapeutics of pH-sensitive opioid ligands and limiting opioid permeability across the blood-brain barrier have had promising results in animal models. While this is grounds for optimism that some of these therapeutics will be efficacious in human subjects at a future date, each drug must undergo individualized testing for specific chronic pain syndromes to establish not only the nuances of each drug's therapeutic effect but also a comprehensive safety profile.

Keywords Opioids · Opioid side effects · Peripheral opioid receptor (POR) · Peripheral opioid receptor therapeutics

Introduction

Opioids are potent systemically acting painkillers that have become the mainstay of treatment for both acute and chronic pain [1, 2]. While opioids are considered indispensable for the treatment of acute pain and pain at the end of life, their use for the treatment of long-term chronic pain is increasingly being criticized. Opioids carry a significant risk of serious side effects including sedation, respiratory depression, addiction, the potential for withdrawal, and an unacceptably high death rate for their continued use as the mainstay of treating chronic pain.

Prescription opioids in fact are the major contributor to the ongoing opioid epidemic in the United States [3]. In 2018, 3.6 percent of the US population misused pain relievers—second only to marijuana in the incidence of illicit drug use—with 9.9 million people aged 12 or older misusing prescription pain relievers compared to 808,000 heroin users [4]. An estimated 2.0 million people had an opioid use disorder, again with an overwhelming contribution from prescription pain reliever use disorder at 1.7 million people [4]. There is thus an urgent need for the development of less harmful alternative therapies for the treatment of chronic pain.

Emerging therapies in selective opioid-based analgesia promise to mitigate the problem of serious side effects associated with systemically acting opioids. These include abuse-deterrent formulations of opioids, nanocarrier-based drug delivery systems, biased agonism, the targeting of opioid

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receptor splice variants, multivalent ligands, enkephalinase inhibitors, gene therapy, endomorphin analogs, and allosteric modulators [5••, 6, 7••]. These strategies are motivated by the availability of opioid receptors both centrally and peripherally and preferentially target the latter to varying degrees to mitigate centrally mediated side effects. Tissue-specific opioid ligand activation and reduced opioid entry into the CNS are two more such strategies that aim to directly enhance the peripheral opioid receptor (POR) system. These POR therapeutics, preceded by a review of the POR system, will be discussed in detail in this article.

The Peripheral Opioid Receptor System

Opioid receptors belong to the family of G-protein-coupled receptors (GPCR) with three main types based on three different genes: the mu opioid receptor (μ, MOR), the delta opioid receptor (δ, DOR), and the kappa opioid receptor (κ, KOR) [8•]. Upon orthosteric binding by a ligand, the heterotrimeric G-protein complex dissociates into G_{α} and $G_{\beta\gamma}$ subunits that hyperpolarize neurons and diminish the release of proinflammatory neuropeptides [5••, 8•, 9, 10]. In particular, G_{α} inhibits adenylyl cyclase, thereby lowering cAMP, while $G_{\beta\gamma}$ more directly inhibits voltage-gated Ca^{++} channels and enhances inward K^{+} channels. This ultimately hyperpolarizes neurons, reduces excitability, and blocks the release of excitatory neurotransmitters, culminating in analgesia.

Opioid receptors are expressed by central and peripheral neurons, neuroendocrine cells (pituitary and adrenals), immune cells, and ectodermal cells [11–13]. In the peripheral nervous system in particular, receptors are present on dorsal root ganglia (DRG) and in the enteric nervous system. PORs are synthesized in nociceptor cell bodies in the trigeminal ganglia and the DRG and transported from there to peripheral nociceptive nerve terminals on the skin, joints, and viscera [5••].

Enhanced POR Activity During Inflammation

Interestingly, PORs undergo upregulation of receptor density and enhanced activation during periods of inflammation not seen with central opioid receptors (COR) [7••, 14]. The enhanced transport, expression, and accessibility of PORs during inflammation increases the potential for analgesia, and leukocytes, the harbingers of inflammation, are an illustrative example in this respect as they are known to release endogenous opioids that can then activate PORs to provide enhanced analgesia [15].

The mechanistic underpinning of enhanced POR activation during inflammation is multifactorial, and in addition to leukocyte activation, candidate explanations include easier passage of opioids across a leaky perineurium during periods of inflammation for unrestricted access to sensory nerve terminals [16], an increased number of PORs in a phenomenon referred to as sprouting [17], and increased axonal transport of PORs to nociceptive nerve terminals during periods of inflammation [9, 18]. More importantly, the enhanced analgesic effects of opioids in peripherally inflamed versus healthy tissue are well established [8•, 19–21], and animal and human studies have shown that tolerance at peripheral MORs in inflamed tissue is mitigated due to a continuous supply of endogenous opioid immune cells and enhanced MOR recycling [22, 23].

The enhanced activation of the POR system during inflamed states thus provides further impetus for the development of POR therapeutics, especially for chronic pain states that are characterized by persistent peripheral inflammation as discussed in the next section.

Motivating the Development of POR Therapeutics

As noted earlier, systemic opioids are associated with a wide range of side effects broadly categorized into visceral and centrally mediated effects. The more serious acute side effects—such as sedation and respiratory depression—arise from opioid action in the CNS as do the long-term problems of tolerance and physical dependence that are rooted in a complex web of reward pathways and euphoric effects leading to cravings, uncontrolled compulsions, and withdrawal avoidance behaviors [24].

POR activation, in contrast to COR, effectively leads to analgesia but is not involved with the potentially fatal and long-term debilitating and dependency effects seen with systemically active opioids [25, 26]. Selective POR activation also mitigates side effects, in frequency and in intensity, stereotypically characterized as visceral effects that in fact stem from a combination of central and peripheral opioid activation including constipation, nausea, vomiting (MOR mediated), and diuresis (KOR mediated) [5••, 27].

In addition to the mitigation of serious centrally mediated side effects, the move to preferentially target PORs is motivated by inhibiting pain and its associated nociceptive activity at the source. Many chronic pain syndromes are associated with chronic inflammation—such as in arthritis, neuropathies, chronic wounds, and visceral disorders—that originates in peripheral tissue [28, 29]. Coupled with what we know about enhanced activation of PORs in inflamed tissue, preferential POR activation is an ideal candidate for the development of therapeutics for many of the chronic pain syndromes especially in light of recent guidelines advising against conventional opioids for chronic non-cancer pain [30].

Lastly, there is growing evidence from clinical, pharmacological, and genetic studies that a significant proportion of the

analgesic effect from systemically active opioids is enacted through POR activation [13, 31–34]. POR therapeutics thus facilitate a significant proportion of the analgesic effect of conventional opioids that is only further enhanced in the presence of inflammation that is characteristic of many of the chronic pain syndromes.

New Frontiers in Outstanding POR Therapeutics

The last three decades have seen the development of a myriad of POR therapeutics in various stages of animal, preclinical, and clinical studies. These span across the spectrum of opioid receptors and include (1) predominantly MOR-mediated therapeutics notable for naturally occurring selective peripheral MOR agonists such as herkinorin and mitragynine, novel application of the peripherally limited loperamide, and synthetic peptides such as PZM21, TRV130, and DiPOA; (2) predominantly KOR-mediated therapeutics including the first-generation spiradoline and enadoline that were ultimately abandoned due to neuropsychiatric side effects, the second-generation asimadoline that has become a niche therapeutic for abdominal pain related to IBS, and subsequent drugs such as nalfurafine used for treating pruritus in uremic patients in select markets but not applicable for pain as such [35]; and (3) a relatively limited number of predominantly DOR-mediated therapeutics, often falling under multifunctional ligands with combined MOR and DOR activation profiles as is seen with TY027, RCCHM3, and RCCHM6.

The aforementioned is a limited list from the full gambit of POR therapeutics under past and present development that are discussed in more detail in Vadivelu et al. (2011), Machelska and Celik (2018), Ehrlich et al. (2019), and Martínez and Abalo (2020). However, as only a handful of these therapeutics carry the potential for regulatory approval, the current review will focus on the more promising therapeutics starting with a new look for analgesic effect from loperamide that has historically been used as an antidiarrheal.

Loperamide

Loperamide, traditionally used as an antidiarrheal agent, is an MOR agonist with low blood-brain barrier (BBB) permeability. Interestingly, loperamide is neither big nor hydrophilic, and its low BBB penetration is predominantly due to active extrusion across the brain-to-blood efflux system P-glycoprotein [7••].

Evidence for the analgesic effects of loperamide has been demonstrated in various animal studies including rat models of neuropathic pain [36] and mechanical/heat-induced hypersensitivity [37, 38]. Human studies on the efficacy of loperamide, in contrast, are wanting, and the limited evidence for its use as a topical analgesic for painful oral and skin ulcers in patients with chronic graft versus host disease comes from a small clinical observational study from Japan [39, 40] that remains to be generalized for the treatment of stomatitis, for example, or other painful cutaneous lesions.

In addition to the limited evidence from human trials, the therapeutic effects of loperamide are by no means unequivocally established as illustrated by the counterintuitive results from a recent rat model of polyarthritis where administration of a topical loperamide liposomal gel produced analgesia but exacerbated arthritis and inflammation [41]. Future investigation into the impact of loperamide, topical applications or otherwise, for arthritis and other chronic pain syndromes must proceed with caution to say the least. That said, loperamide deserves closer and continued attention given its analgesic and anti-inflammatory properties [42] and may well find a place as a niche therapeutic in the way that asimadoline, the other P-glycoprotein limited POR agonist, has.

Asimadoline

Asimadoline, formerly EMD 61753, is an amphiphilic molecule with high affinity for KOR and low permeability across the BBB, also secondary to efflux by the system P-glycoprotein. It exhibits a high therapeutic index with central side effects observed at 300–600 times the doses required for analgesic action in rodent models, indicating that its predominant therapeutic action is through peripheral KOR agonism [43, 44].

Asimadoline seems to improve visceral pain more reliably and consistently than it improves somatic pain. In animal models of somatic pain, it produces biphasic effects with pain relief at lower doses or shortly after drug administration versus enhanced pain at higher doses or later time points [43, 45], while enhancing postoperative pain in patients undergoing arthroscopic knee surgery [43] and provoking hyperalgesia in experimental colonic distension models in healthy human volunteers [46].

In contrast to somatic pain, there is more consistent evidence for asimadoline reducing visceral pain; for IBS patients in particular, it decreases pain after barostat-induced colonic distension [47] and, more specifically, in a phase 2b trial produced significant improvement in months free from IBS pain or discomfort, pain scores, pain-free days, and urgency and stool frequency in patients with diarrhea-predominant IBS (IBS-D) [48]. Asimadoline continues under development and under further investigation for the management of patients with IBS-D in particular [5••, 49, 50] and has also been suggested for the management of pain and symptoms associated with functional dyspepsia [7••, 44].

In addition to the management of pain and discomfort related to IBS and investigation into related gastrointestinal syndromes, in the pipeline for asimadoline is also its role in atopic dermatitis. An oral formulation, while it did not improve the primary

endpoint of pruritis in a phase 2 trial (NCT02475447), reduced secondary endpoints of redness and scratch marks [51]. The impact and tolerability of topical applications will be investigated in phase 1 clinical trials [51] that will be interesting to follow.

CR845

CR 845, formerly FE 202845, is a tetrapeptide under development for postoperative and osteoarthritic pain by Cara Therapeutics with analgesic effects reported from animal models of abdominal, inflammatory, and neuropathic pain as well as pancreatitis [52].

While encouraging phase 2 clinical trials has been reported for CR845 attenuating postoperative pain after laparoscopic hysterectomy, in some patients after bunionectomy, and a well-tolerated safety profile in patients with osteoarthritis, these results were only presented via abstracts, press releases, and at the ClincalTrials.gov website [53]. Independent, peer-reviewed studies are accordingly wanted and awaited [5••, 7••], and as of now it remains unclear the patient populations that CR845 might hold the most promise for.

Recent Innovations in POR Therapeutics

Recent innovations in POR therapeutics are notable for bottom-up approaches rooted fundamentally in and deriving from pharmacokinetic and pharmacodynamic principles (Table 1). These have reinvigorated the potential for systemically available selective POR therapeutics, and the two major organizing principles can be characterized as (1) reducing CNS entry and (2) tissue-specific peripheral opioid activation.

The former goal of reducing CNS entry can be achieved through the efflux of opioids across the BBB as seen for loperamide and asimadoline or through the development of hydrophilic, polar, and/or bulky compounds with limited penetration across the BBB in the first place as intended in the recent development of a large molecular weight polyglycerol morphine conjugate (PG-M). The latter goal of tissue-specific peripheral opioid activation harkens back to the enhanced activation and activity of PORs in inflamed tissue from earlier in the review and has notably been achieved in the recent design of pH-sensitive opioid ligands that preferentially bind and activate PORs in the inflamed environment of injured tissue compared to the normal environment of (say) an uninflamed brain or the myenteric plexus of a normal intestinal wall.

Table 1 Recent innovations in POR therapeutics

Limited BBB permeability	pH-sensitive opioid ligands
Bulky/hydrophilic compounds *Polyglycerol Morphine (PG-M)* • Hyperbranched dendritic polyglycerol covalently bound to morphine • Produced analgesia without sedation or constipation in a rat model of unilateral hind paw inflammation[1] Addition of polar functional groups *NKTR-181* • Polyethylene glycol side chain attached to a morphinan pharmacophore, leading to 17- to 70-fold lower rate of brain entry in rats compared to oxycodone[2] • MOR agonist with analgesic effect: provided thermal nociception and visceral pain relief comparable to that from oxycodone in a mouse model[2] • Lower abuse potential: diminished drug liking effects in healthy, non-physically dependent recreational opioid users[3] • Phase 3 trials are underway for osteoarthritis (NCT02367820) and chronic low back pain (NCT02362672) Addition of zwitterionic functional groups *Amino acid side chains* • Illustrated by zwitterionic derivatives of 14-O-methyloxymorphone by the substitution of different amino acids and dipeptides at the C6 position[4] • The recently published extensive library of these derivatives by Spetea et al. was notable for potent in vitro MOR/DOR agonism in the majority of these compounds with anti-nociception in a mouse model of visceral pain mediated through POR activation	Fentanyl-based MOR agonists *NFEPP* (pKa 6.82 ± 0.06)[5] • Derivation: fluorination of fentanyl at the piperidine ring two carbon bonds from the tertiary amine • Selective analgesia in rat models of inflammatory insults via hind paw injury, surgical incision, sciatic nerve injury, and abdominal visceral pain without exhibiting side effects of respiratory depression, sedation, constipation, or addiction potential[5,6] *FF3* (pKa 7.22 ± 0.01)[7] • Derivation: fluorination of fentanyl at the phenylethyl side chain two carbon bonds from the tertiary amine • Selective injury-restricted analgesia in rat models of inflammatory, postoperative, abdominal visceral, and neuropathic pain with increasing central activity at higher doses notable for side effects of respiratory depression, sedation, and addiction potential[7,8] *FF6* (pKa 7.94 ± 0.01)[8] • Derivation: Bis-fluorination of fentanyl at the phenethyl ring four carbon bonds from the tertiary amine • Fentanyl-like in vivo profile with nonspecific analgesia in a rat model of pain and side effects of sedation and constipation[8] *RR-49* (pKa 6.60)[9] • Derivation: Bis-fluorination of fentanyl at the phenethyl group with substitution at the ethyl side chain and the phenyl residue two and four carbon bonds, respectively, from the tertiary amine • In vivo animal studies are underway to test the expectation of reduced CNS effects and abuse liabilities[9]

[1] González-Rodríguez et al. 2017, [2] Miyazaki et al. 2017, [3] Webster et al. 2018, [4] Spetea et al. 2019, [5] Spahn et al. 2017, Rodriguez-Gaztelumendi et al. 2018, [7] Spahn et al. 2018, [8] Del Vecchio et al. 2019, [9] Rosas et al. 2019

Limited BBB Permeability

Nanocarriers, developed extensively in the field of cancer [54], have recently been proposed and undergoing development for selective pain therapy [7••, 55]. Sustained release formulations of morphine have been engineered through lipid-based nanocarriers [56–58] and esterase-sensitive dendrimers [59] for prolonged analgesia, and dendritic polyglycerol (PG) based carriers are more recently undergoing development for selective analgesia.

In particular, González-Rodríguez et al. covalently bound morphine to such a PG using a pH and leukocyte esterase-sensitive ester linkage [60••] that can then selectively uncouple in and extravasate across leaky blood vessels of inflamed tissue. In the normal environment of a non-inflamed brain, in contrast, the bulky and hydrophilic PG-morphine (PG-M) would not cross the BBB. Indeed, a rat model of unilateral hind paw inflammation has provided early proof of concept for selective POR activation through PG-M: in contrast to morphine, intravenous PG-M produced analgesia without sedation or constipation, and free morphine was only measured in tissue from the inflamed paw while not in the contralateral non-inflamed paw tissue, the blood, or the brain [60••].

Although polyglycerols are biocompatible [61] and the pH-sensitive ester linkage facilitates targeted drug delivery to peripherally inflamed tissue, their potential for organ toxicity and side effects in the form of PG-M and associated compounds remains to be tested, especially across the spectrum of different pain syndromes.

While a more comprehensive safety profile of PG-M is yet to be determined, its foundation of limited BBB permeability can still serve as a motivating principle for other peripherally restricted opioid formulations to provide selective analgesia while minimizing central and visceral side effects [60••]. The MOR agonist NKTR-181 is an interesting such example that has delayed BBB permeability owing to a polyethylene glycol side chain attached to a morphinan pharmacophore [62•]. It provided analgesia in acute heat pain models in naive animals with an improved side effect profile compared to oxycodone, likely due to its 17- to 70-fold lower rate of brain entry in rats. Human studies also suggest a lower abuse potential for NKTR-181 as it induced diminished drug liking effects in healthy, non-physically dependent recreational opioid users [5••, 63]. Company-sponsored phase 3 trials for patients with osteoarthritis (NCT02367820) and chronic low back pain (NCT02362672) are currently underway.

The addition of hydrophilic functional groups to an opioid pharmacophore was also recently employed by Spetea et al. in producing an extensive library of amino acid–based zwitterionic derivatives of 14-O-methyloxymorphone by substitution at the C6 position [64]. The majority of these derivatives provided analgesia in a mouse model of visceral pain and, in addition to potent MOR and DOR agonism in vitro, were selective for PORs given that their co-administration with naloxone methiodide reversed their antinociceptive effects. Further studies need to be pursued to establish a safety profile for these zwitterionic selective POR agonists.

Whether it is through bulky/hydrophilic compounds, the addition of hydrophilic functional groups to opioid pharmacophores, or nanocarrier-based opioid formulations, each drug will have to undergo individualized testing across the spectrum of chronic pain syndromes to establish not only efficacy but also a comprehensive side effect profile. That said, the development of bulky and/or hydrophilic conjugates with opioid pharmacophores for selective analgesia and precluding central sedative effects is a promising new field of development in POR therapeutics.

pH-Sensitive Opioid Ligands

Novel computer simulation-based—in silico—methods have recently been used by Stein and collaborators to take advantage of the presence of acidosis in inflamed tissue in light of their hypothesis that opioid receptors and ligands exhibit enhanced conformation dynamics in inflamed compared to non-inflamed tissue [8•, 65]. Based on the assumption that protonation of a tertiary amino group of opioid ligands is essential for the activation of opioid receptors [66], they reverse engineered the new agonist NFEPP to selectively function in acidotic environments, characteristic of inflamed and injured tissue, while being relatively inactive in non-inflamed tissue with physiologic pH around 7.4 [67••].

The fluorination of fentanyl (pKa 8.44 ± 0.05) at the piperidine ring leads to the novel NFEPP (pKa 6.82 ± 0.06) that significantly protonates only at lower than physiologic pH to then more effectively bind PORs in inflamed tissue. NFEPP has been shown to provide selective analgesia in various rat models of pain including for unilateral hind paw inflammation, surgical incision, sciatic nerve injury-induced neuropathy, and abdominal pain [68] and did not have the typical central and peripheral side effects—including no respiratory depression, sedation, motor impairment, reward pursuit, or constipation—even at doses ten times higher than those providing analgesia [67••]. While mechanistically precluded for patients with CNS inflammation, NFEPP is a promising candidate for trials on patients with peripheral tissue damage across the spectrum of chronic pain syndromes.

Subsequent to the development of NFEPP, other fentanyl-derived pH-sensitive opioid ligands have entered the POR therapeutics pipeline (Fig. 1). The approach with these fentanyl-based compounds thus far has been to replace single hydrogen atoms with fluorine atoms in one or two places resulting in a lower pKa that can then facilitate selective analgesia at peripherally inflamed tissue [7••].

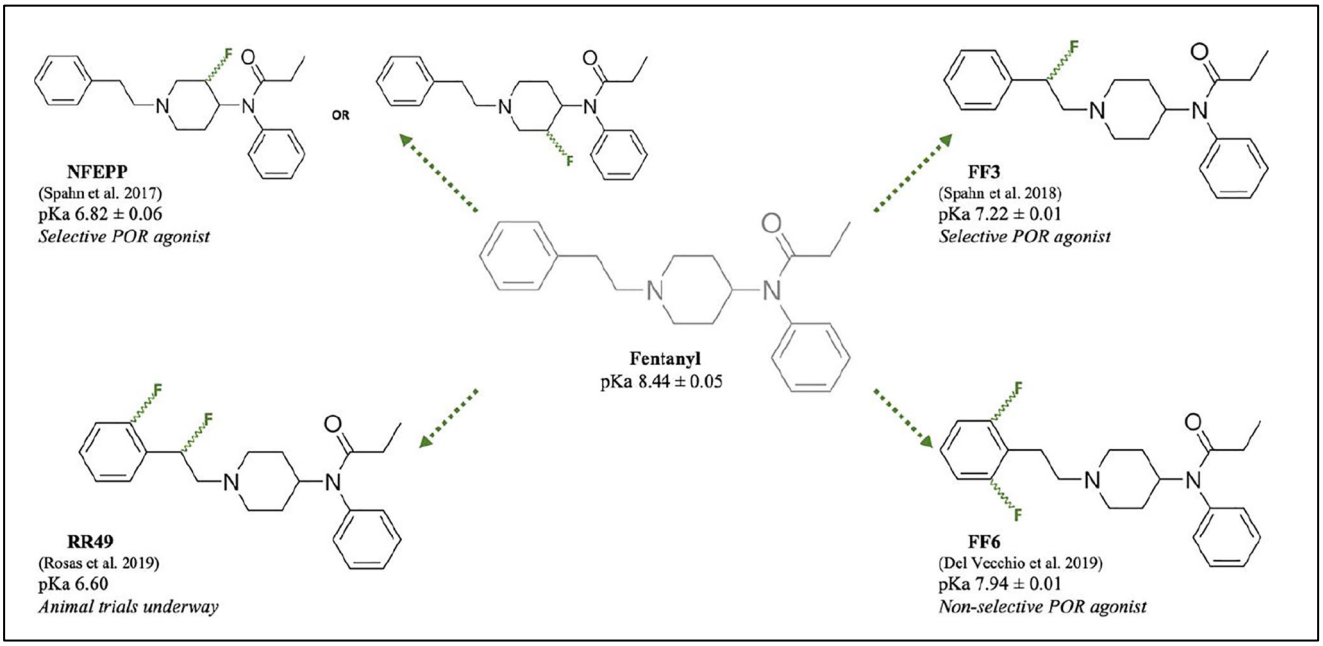

Fig. 1 Fentanyl-derived pH-sensitive opioid ligands have been obtained by replacing single hydrogen atoms with fluorine atoms in one or two places at either the piperidine ring (NFEPP), the phenylethyl side chain (FF3; RR49), or at the phenylethyl ring (FF6; RR49). The fluorination decreases the pKa of these compounds that then significantly protonate and activate only at lower than physiologic pH to facilitate selective analgesia at peripherally inflamed tissue

The Stein et al. research group has published on two other fentanyl-derived compounds identified as FF3 [69•, 70] and FF6 [70]; the former FF3 is derived by replacing hydrogen with a fluorine atom at the phenylethyl side chain of fentanyl and the latter derived by replacing two hydrogen atoms with fluorine atoms at the phenylethyl ring of fentanyl. While FF6 provided analgesia in a rat model of pain, it was not selective between inflamed and non-inflamed tissue: it did not exhibit selective protonation or MOR activation in inflamed tissue and caused sedation and constipation at doses comparable to that of fentanyl, consistent with FF6's higher than physiologic pKa at 7.94 ± 0.01 [70].

Results for FF3 have been more encouraging but not unequivocally so. While FF3 produced injury-restricted analgesia in rat models of inflammatory, postoperative, abdominal, and neuropathic pain, it induced central side effects including sedation, respiratory depression, motor disturbance, and reward behaviors at higher doses [69•]. This transition from peripherally restricted to increasingly systemic action of FF3 could be from its pKa value of 7.22 ± 0.01 not being low enough to restrict its activity to inflamed tissue at higher doses. A relatively lower pKa, as is the case with NFEPP at 6.82, thus might be crucial to minimizing central side effects, and the bis-fluorinated RR-49 reported by Dockendorff and collaborators is a promising new candidate with an estimated pKa of 6.60 [71•].

Conclusion

Systemically active opioids currently form the cornerstone of treating both acute and chronic pain. However, given the extensive serious side effects associated with conventional opioids and the ongoing opioid epidemic, there is an urgent need for the development of alternative therapies especially for the management of chronic pain syndromes. POR therapeutics comprise a major advance in this respect with the goal of peripheral action targeting pain at the source while also mitigating undesirable central side effects.

Recent developments in POR therapeutics have broadly included both a renewed look at previously known therapies as well as the innovation of novel therapies. The former category is notable in particular for loperamide, a well-established antidiarrheal agent, that happens to be a MOR agonist with limited BBB penetration and the similarly centrally limited KOR agonist asimadoline that is finding a place as a niche therapy for the management of patients with IBS-D.

New innovations comprise an especially promising group of POR therapeutics notable for bottom-up approaches of limited CNS entry and tissue-specific pH-sensitive opioid ligand activation. Limited CNS entry in these recent therapies hinges on limiting BBB permeability, whether through linkage with bulky and hydrophilic hyperbranched dendritic polyglycerols as seen with PG-M or the addition of hydrophilic functional groups to opioid pharmacophores as seen with NKTR-181.

Alternatively, the pH-sensitive opioid ligands are designed to be centrally inactive and given their lower pKa values, significantly protonate and activate only at lower than physiologic pH to facilitate POR agonism and analgesia at peripherally inflamed tissue that additionally is characteristic of many chronic pain syndromes.

While these recent advances in POR therapeutics are motivated by sound mechanistic underpinnings, each drug must undergo individualized testing for specific chronic pain syndromes to establish not only the nuances of each drug's therapeutic effect but also a comprehensive safety profile. Basic research in the area of POR therapeutics continues rapidly progressing, and recent findings of positive therapeutic effect in animal models hold promise for clinical trials and clinical impact that remains to be established.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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