BRIEF COMMUNICATION

Potential innovative targets in the treatment of pain: Combined μ and NOP receptor agonists

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ABSTRACT

Opioid analgesics are potent and widely used medications employed to manage moderate-to-severe acute pain; their utility in the management of chronic inflammatory and neuropathic pain is modest and is beset with adverse effects and concerns related to abuse and addiction. The discovery of the nonclassical opioid, ie, the nociception/orphanin receptor (NOP), has sparked interest into another possible analgesic target. Preclinical studies have demonstrated pain mitigating effects associated with NOP receptor activation while simultaneously reducing conventional μ-opioid-related adverse and euphoric effects. Consequently, agents possessing dual agonism of both μ and NOP receptor activations present an innovative and promising potential target for pain management.

INTRODUCTION

Long-term opioid therapy has commonly been prescribed for chronic pain conditions,[1,2] including pain arising from nociceptive origins (such as low-back pain and arthritis) as well as those from neuropathic origins (such as diabetic neuropathy and post-herpetic neuralgia). The efficacy of currently available opioid analgesics has consisted of those agents acting primarily via μ-opioid peptide (MOP) receptor agonism, although some may also exert effects via Δ opioid peptide (DOP) and κ opioid peptide (KOP) receptors.[3] Strong agonists of MOP receptors provide potent analgesia for acute pain, eg, from post-traumatic and post-surgical causes. However, such agents produce very modest improvements in chronic noncancer pain conditions[4]; chronic pain arising from inflammatory and neuropathic origins often respond poorly to μ-opioid analgesics.[5] With chronic use, tolerance and/or hyperalgesia may reduce the effectiveness of opioid analgesics over time.[4] Furthermore, long-term use of such agents is hampered by adverse effects (including respiratory depression, constipation, and sedation) and has been marred by concerns related to abuse and addiction. Although reliance on long-term opioid analgesics for the management of chronic pain conditions had been increasing steadily in recent decades, recent epidemiologic studies suggest that this trend is beginning to reverse,[6] due largely to fears of drug abuse, addiction, and accidental overdose leading to respiratory arrest and death.[7-9]

There is still a considerable need for new analgesics that can effectively modulate moderate-to-severe chronic pain while, at the same time, incurring fewer adverse effects as well as lower abuse potential than opioid analgesics that are currently available. Instead of focusing on powerful analgesics with selective affinity for MOP receptors, efforts are now shifting to medications that bind nonselectively to multiple opioid receptors producing analgesia while, at the same time, mitigating unwanted effects encountered with MOP activation.[3]

THE NOP RECEPTOR

In 1994, another receptor, ie, the nociceptin/orphanin (NOP) receptor (previously referred to as the opioid-like receptor-1), was discovered.[10] The NOP receptor shares approximately 60 percent homology in the structural components of classical opioid (MOP, DOP, and KOP) receptors.[11,12] Unlike

classical opioid receptors, the NOP receptor possesses little or no affinity for opioid peptides, eg, β-endorphin and enkephalin, or morphine-like compounds. One year after the identification of the NOP receptor, the natural ligand for NOP receptor was identified. Referred to as the N/OFQ peptide, this 17-amino acid protein shares structural similarities with dynorphin A and other endogenous opioid ligands.[11] Despite the similarities, the N/OFQ peptide has little or no binding affinity for classic opioid receptors, suggesting that N/OFQ peptide-NOP receptor system is pharmacologically unique from classic opioid receptors.[11] When N/OFQ peptide binds to and activates NOP receptors, a number of cellular processes are activated. The activated NOP receptor couples to Gi/o-proteins to inhibit adenylate cyclase, decreasing Ca^{2+} conductance and increasing K^{+} conductance, among other intracellular processes.[11,12] Once activated, NOP receptors reduce afferent neuronal excitability and thereby modulate neurotransmitter release from axon terminals, including γ-amino butyric acid, glutamate, dopamine, and norepinephrine.

The NOP receptor is abundantly present within the peripheral and central nervous system (CNS). Because of the diverse neuromodulatory effects, N/OFQ binding of the NOP receptor influences an array of physiological functions and behaviors including the hypothalamic-pituitary axis, food intake, motor functioning, as well as cardiovascular and renal functioning.[11] NOP effects in peripheral tissues, eg, lymphocytes, influences the release of cytokines and inflammatory mediators.[11]

The NOP receptor is abundantly present within pain processing pathways such as the dorsal root ganglion; spinal dorsal horn; and periaqueductal gray area, thalamus, and rostro-ventral medulla within the brain.[12] Therefore, the activation of NOP receptors is likely to influence pain transmission.[13] The NOP and classical opioid receptors are not colocalized on the same neurons, but seem to exert their influences in partly distinct neural pathways.[14]

In addition to being present within pain processing pathways, NOP receptors are also highly expressed throughout the mesocorticolimbic reward circuitry. The activation of the NOP receptor with N/OFQ has dopamine antagonist effects (either directly or indirectly via GABA-ergic inhibition).[15] In this way, the activation of NOP receptors would not elicit reinforcing effects encountered with traditional μ-opioid receptor activation.[16]

N/OFQ AND NOP RECEPTOR SYSTEM EFFECTS ON PAIN

Because of the similarity to classic opioid receptors and its extensive presence in pain processing pathways, the identification of the NOP receptor sparked interest into a possible analgesic target to manage pain. Early investigations in preclinical (animal) studies revealed that the N/OFQ–NOP receptor system effects on pain processing are complex and appeared to have species-specific as well as neuroanatomic site-specific differences.[13,17] For example, in rodents, it was unveiled that direct supra-spinal application of endogenous N/OFQ in the brain (intracerebralventricular infusion) produced pain-augmenting, ie, pronociceptive, effects. However, the application of N/OFQ spinally (intrathecal infusion) or in peripheral (systemically administered) sites produced pain mitigating, ie, antinociceptive, effects. By contrast, in nonhuman primates, the N/OFQ–NOP binding consistently produced antinociceptive effects in the periphery, spinal relay, and supra-spinal regions.[17]

The combination of N/OFQ with intrathecal morphine produced a dose-dependent enhancement of morphine-induced antinociception,[18] even when combined with a normally inactive dose of morphine.[19] These findings suggested that analgesic benefit can be achieved by capitalizing on the mechanisms of NOP and classical opioid receptors simultaneously.

In subsequent years, several agonist and antagonist ligands to the NOP were discovered. These agents exerted no influence at MOP receptors and allowed for clarification of the impact of N/OFQ manipulations in experimental paradigms. Synthetic, nonpeptide agonists of the NOP receptor were capable of producing significant analgesia in primate models of pain.[20] In contrast to conventional MOP agonists that lack a robust influence on inflammatory and neuropathic pain conditions, NOP agonists demonstrated efficacy in animal models of inflammatory pain and greater potential for mitigating neuropathic pain.[21] Indeed, NOP agonist effects have demonstrated utility in animal models of peripheral receptor sensitization (carrageenan-induced pain), central sensitization (formalin-induced pain), as well as neuropathic pain (spinal nerve ligation).[20,22,23] The pain mitigating effects of the NOP ligands were reversible with the use of NOP antagonists.

The supraspinal pronociceptive effects of the NOP receptor system led investigators to speculate

that the NOP receptor activation might functionally antagonize other CNS effects of μ-opioid activation, ie, adverse effects such as respiratory depression and even those associated with rewarding effects. Consistent with this hypothesis, it was observed that the combination of N/OFQ and morphine produced analgesia without incurring, or at least ameliorating, adverse effects customarily encountered with morphine use. Furthermore, NOP agonists did not induce side effects encountered with conventional analgesics, including respiratory depression, itching, or motor impairments.[12,17,24] When coadministered with opioid analgesics, NOP agonists ameliorated opioid-related side effects.[20,25,26] In fact, agents acting on NOP and MOP activation demonstrated a limited respiratory depression (or ceiling effect).[22]

The reinforcing euphoric and addictive properties of opiates are considered to be related to influences on the mesocorticolimbic system, ie, a dopaminergic pathway projecting from the ventral tegmental area to the nucleus accumbens.[27] Certain endogenous opioid ligands as well as medication with MOP and DOP receptor agonist influences stimulate dopamine release within the nucleus accumbens and thereby mediate rewarding effects. Experimental evidence has demonstrated that the N/OFQ peptide, in contrast to encephalin and endorphin, suppresses dopamine release in the nucleus accumbens in a dose-dependent manner.[16,28] It is anticipated that NOP ligands, due to their inhibitory influences on dopamine transmission in that system, would fail to elicit rewarding properties, and, in fact, the activation of NOP receptors has been demonstrated to be devoid of reinforcing effects, and inhibited opioid-mediated reward in rodents and non-human primates.[24,25,29-32] Additionally, although naloxone administered to morphine-dependent rats precipitated withdrawal signs, the withdrawal signs were inhibited when the animals were administered intraventricular injections of N/OFQ.[33]

DEVELOPMENT OF μ AND NOP MIXED AGONISTS

In light of the aforementioned findings, a search has been undertaken for innovative agents possessing concurrent NOP and MOP activating effects that can provide pain relief without the risks associated with conventional opioid analgesics, ie, respiratory depression, dependence, and withdrawal.[3,32] Several agents are in development, including AT-121,[34] a buprenorphine derivative, BU-08028,[35] and a naloxone derivative, BU-10038.[36] These agents have been demonstrated in preclinical animal paradigms to exert pain mitigating effects comparable to morphine without incurring common morphine-related adverse effects.[17]

In 2014, Cebranopadol (GRT6005), another investigational drug, was developed. It is a novel agent that has full agonist activity at MOP and high partial activity at NOP receptors currently in clinical stages of development internationally by Grünenthal, a German pharmaceutical company. Having been investigated in, and based upon the findings of, a number of animal models of acute and chronic pain states, including nociceptive, inflammatory, and neuropathic pain,[13,22,37-39] it has undergone initial Phase 2 and Phase 3 trials.

Cebranopadol is formulated as a small immediate-release tablet for oral use.[40] Its plasma concentration increases gradually after oral administration; peak plasma concentration and effects are appreciable approximately 4-6 hours after ingestion. It has a long half-life of 24 hours, allowing for once-daily dosing.[40] The anticipated dose ranges between 200 and 600 μg daily.

Early clinical trials suggest safety and efficacy of Cebranopadol for a variety of pain conditions[40-46] (Table 1). Many of these investigations were designed to assess the tolerability of Cebranopadol and compare its pain mitigating effects against placebo. Although some studies incorporated conventional agents in some arms of the study,[41,43,45,46] the effectiveness of Cebranopadol was never directly compared with those conventional agents.[41,43,46] Some studies were limited by brief duration of investigation,[42,44] small samples,[40,45] and low retention rates.[40,43] Nonetheless, results of these studies suggest that Cebranopadol may be a promising alternative to traditional opioids.

Common treatment-related adverse effects encountered with Cebranopadol included somnolence, fatigue, dizziness, nausea, vomiting, constipation, headache, and sweating. In the clinical trials summarized in the table, the emergence of treatment-related adverse effects appeared to be dose related[41-44] and contributed to trial discontinuation.[43] Additionally, consistent with findings in animal studies, Cebranopadol demonstrated ceiling in respiratory depression in healthy human volunteers.[47] Although these findings are encouraging, assessment of respiratory effects of Cebranopadol at varying doses, and in nonhealthy clinical populations, has as yet to be determined.

Table 1. Table of Cebranopadol Phase II and Phase III investigations

Type of pain	Phase	Participants	Design/comparators	Primary outcome/results
Acute post-bunionectomy pain[41]	IIa	Enrolled = 684 N = 258	Double-blind, RCT	Summed pain intensity scores 2-10 hours were significantly reduced with Cebranopadol compared to placebo
		M = 33; W = 225 Age range: 18-75 years	Cebranopadol 200, 400, and 600 µg vs. placebo; morphine 60 mg	Percentage of reported adverse effects: morphine (92 percent); Cebranopadol 200 µg (67.3 percent), 400 µg (77.6 percent), and 600 µg (84.2 percent)
Osteoarthritis of knee*,[42]	IIa	Enrolled = 207 N = 127	Double-blind, randomized, parallel group	Cebranopadol 400 µg produced statistically significant reduction in pain ratings compared to placebo Percentage of reported adverse effects: placebo (40.6 percent); Cebranopadol 75 µg (46.9 percent), 200 µg (50 percent), and 400 µg (83.9 percent)
		M = 36; W = 91 Age range: 40-75 years	Cebranopadol 75, 200, and 400 µg vs. placebo	Treatment discontinuation due to adverse effects: Cebranopadol 75 µg (9.4 percent), 200 µg (6.3 percent), and 400 µg (41.9 percent)
Chronic low back pain[43]	II	N = 635 M = 223; W = 412	Double-blind, RCT	Cebranopadol 200, 400, and 600 µg and tapentadol were significantly better than placebo
		Age range: 18-80 years Mean age: 57.5 years	Cebranopadol 200, 400, and 600 µg vs. placebo; tapentadol PR 200 mg BID	56.2 percent completed trial; treatment discontinuation rates due to adverse effects: Cebranopadol 200 µg (32.1 percent), 400 µg (40.6 percent), and 600 µg (47.7 percent), tapentadol (26.2 percent)
Diabetic polyneuropathy*,[44]	IIa	Enrolled = 189 N = 122	Double-blind, randomized, parallel group	Cebranopadol 200 µg was numerically but not statistically better than placebo; Cebranopadol 25 and 75 µg did not differ from placebo; a greater percentage of Cebranopadol-treated patients reported > 30 percent reduction of pain from baseline as compared to placebo
		M = 84; W = 38 Age range: 18-75 years	Cebranopadol 25, 75, and 200 µg vs. placebo	Discontinuation rates were highest for Cebranopadol 200 µg (13.3 percent), due to adverse effects
Diabetic polyneuropathy*,[45]	IIa	Enrolled = 91 N = 89	Double-blind, randomized, cross-over	Cebranopadol 80, 100, and 120 µg and morphine CR demonstrated clinically meaningful reductions in baseline pain
		M = 55; W = 34 Age range: 32-76 years	Cebranopadol 40, 80, 120, and 200 µg; morphine CR 60 mg; placebo	Cebranopadol 120 µg condition had the highest rates of >30 and >50 percent reduction of pain from baseline Three subjects discontinued morphine CR but 0 subjects discontinued Cebranopadol due to adverse effects

Table 1. Table of Cebranopadol Phase II and Phase III investigations (continued)				
Type of pain	**Phase**	**Participants**	**Design/comparators**	**Primary outcome/results**
Chronic cancer pain[46]	III	Enrolled N = 200	Randomized, parallel group	Cebranopadol was superior to morphine PR in terms of amount of daily rescue medication required over 2 weeks of maintenance
		N = 125	Cebranopadol 200-1,000 µg/day vs. morphine prolonged release 30-150 mg/day	Both conditions resulted in significant pain reductions; Cebranopadol produced > 3 point reduction in baseline pain severity ratings
		M = 76; W = 49		
		Age range: 18 + years		
		Mean age = 62.3 years		Percentage of reported adverse effects: Cebranopadol (83.1 percent); morphine (82 percent)
Chronic cancer pain—open label extension[40]	III	N = 76	Open-label study	50 percent completed trial
		M = 44; W = 32	Cebranopadol 200-1,000 µg	Average pain level remained in mild ranges with Cebranopadol, ie, 3-out-of-possible-10
		Mean age: 61.7 years		
*Results are unpublished but are accessible through European Union Clinical Trials Register.				

The abuse potential of Cebranopadol was assessed in a double-blinded, active, and placebo controlled phase 1 trial, involving 48 healthy recreational opioid users.[48] In this study, Cebranopadol of 200, 400, and 800 µg was compared against placebo, as well as hydromorphone immediate-release 8 and 16 mg. As expected, hydromorphone was found to elicit greater rates of drug liking, ie, appeal, as compared with placebo. However, Cebranopadol of 200 µg did not differ from placebo. Both Cebranopadol 200 and 400 µg elicited less drug liking as compared with both hydromorphone doses. The appeal of Cebranopadol 800 µg was comparable to hydromorphone 16 mg. Similarly, sedative effects were significantly lower for Cebranopadol 200 and 400 µg doses as compared with hydromorphone; 800 µg did not differ from hydromorphone 8 mg but was significantly less than that associated with hydromorphone 16 mg.

CONCLUSION

There is currently no optimal analgesic agent that provides effective pain relief, particularly among patients afflicted with chronic inflammatory and/or neuropathic pain. The use of conventional analgesics, which primarily influence µ-opioid receptors, is marred by a number of adverse effects and the risks of tolerance, abuse/misuse, and dependence. Consequently, the quest for an ideal, or at least better, pain reliever continues. The development of NOP receptor ligands has sparked excitement in the field of pain management. It has opened the possibility of a new vista in the treatment of pain that may become the next promising candidate for analgesic intervention.

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