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HOT TOPICS IN PAIN AND HEADACHE (N. ROSEN, SECTION EDITOR)

# The Utilization of Mu-Opioid Receptor Biased Agonists: Oliceridine, an Opioid Analgesic with Reduced Adverse Effects

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## Abstract

**Purpose of Review** The purpose of this review is to summarize the current understanding of opioid pathways in mediating and/or modulating analgesia and adverse effects. Oliceridine is highlighted as a novel mu-opioid receptor agonist with selective activation of G protein and β-arrestin signaling pathways.

**Recent Findings** Oliceridine (TRV130; [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine) is a novel MOR agonist that selectively activates G protein and β-arrestin signaling pathways. A growing body of evidence suggests that compared to existing MOR agonists, Oliceridine and other G protein-selective modulators may produce therapeutic analgesic effects with reduced adverse effects.

**Summary** Oliceridine provides analgesic benefits of a pure opioid agonist while limiting related adverse effects mediated through the β-arrestin pathway. Recent insights into the function and structure of G protein-coupled receptors has led to the development of novel analgesic therapies.

**Keywords** Oliceridine · TRV130 · G protein-coupled receptors (GPCR) · Partial opioid agonists

## Introduction

Prescription opioids are among the most effective analgesics in clinical use and are a mainstay in the treatment of acute and chronic moderate to severe pain. Their use is limited by a preponderance of adverse effects [1]. Addiction is among the most prevalent of these adverse effects and has been a significant driver in an effort to develop novel opioid pharmacotherapies with less adverse side effects. In this review, current understanding of opioid mechanisms in inducing analgesia is described with current understanding of mu-opioid receptor pharmacology and highlights Oliceridine, a novel opioid agonist which may preferentially induce analgesia with limited adverse effects.

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## Utilization of Oliceridine as Biased Ligand at the Mu-Opioid Receptor

Morphine, the archetypal opioid, is still one of the most commonly utilized analgesic therapies. Morphine elicits analgesia by acting on the mu-opioid receptor (MOR), a G protein-coupled receptor (GPCR) that is expressed extensively in the central nervous system [2]. Oliceridine (TRV130; [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro[4.5]decan-9-yl]ethyl})amine) is a novel MOR agonist that selectively activates G protein and β-arrestin signaling pathways, exhibiting approximately a threefold preference for the G pathway over β-arrestin relative to morphine and fentanyl [2, 3••]. As such, TRV130 is referred to as a "biased ligand," a compound that stabilizes a conformation of the

target receptor, causing it to preferentially couple with specific intracellular pathways while not coupling to others. A "biased ligand" has the potential to act as a full agonist for a certain pathway, while simultaneously being inert or displaying inverse efficacy for another [2].

Studies of knockout mice have demonstrated that opioids signal through distinct MOR pathways, which suggest that ligand bias can be used to elicit differential MOR pharmacology. For instance, it has been shown that morphine analgesia is both enhanced and prolonged in β-arrestin-2 knockout mice compared to wildtype controls. Similarly, morphine-induced adverse effects such as constipation and respiratory suppression have been shown to be reduced in β-arrestin-2 knockout mice. These observations indicate that the β-arrestin mechanism serves as a negative modulator of analgesia and a positive modulator of adverse effects at the MOR [2]. Oliceridine causes low β-arrestin recruitment, approximately 14% that of morphine, and thus differs from morphine when it comes to MOR phosphorylation and internalization [2, 4••]. Therefore, Oliceridine may promise to offer the analgesic benefits of pure opioid agonists while limiting related adverse effects mediated through the β-arrestin pathway [2].

## Mechanism of Action

The four main types of opioid receptors are mu (μ), kappa (κ), delta (δ), and opioid-like-1 (ORL1) receptors. Opioid receptors belong to a family of seven-transmembrane (7 TM) guanine nucleotide binding protein-coupled receptors (GPCRs). Activated opioid GPCRs produce inhibitory G proteins that cause a kinase cascade to prevent the activation of differential pain signaling pathways [5–7]. The analgesic effect of opioids is driven by μ-receptor activation while the β-arrestin recruitment produces the unwanted effects of respiratory depression and constipation. Mu pathway selective opioids have been pursued as ideal replacements for conventional opioid agonists [8]. Oliceridine has been shown to do exactly this during in vivo studies in mice. TRV-130 provides similar analgesic effects with diminished respiratory depression and constipation [8]. Unfortunately, Oliceridine has less overall efficacy than morphine and acts as a partial agonist leaving it susceptible to being outcompeted. In comparison, buprenorphine was designed as a deliberately weak partial agonist of the μ-receptor that binds at an extremely high affinity for an extended period of time allowing it to outcompete a toxic dose of other opioids blocking overdose and withdrawal effects of opioid dependent individuals; its major function differs from that of Oliceridine in the fact that it is not designed for use as a primary analgesic [9]. As such, buprenorphine serves as a functional antagonist related to its very weak agonistic effects at the κ-receptor that can be useful for treating other psychological ailments and a true antagonist at the δ-receptor providing a potential attenuation of the reward-pathway detrimental during drug use [10].

## μ-Receptor G Protein Pathway Selective Modulator (μGPS)—Role in Opioid Therapy

Opioid receptors have been targeted for the treatment of pain and related disorders for thousands of years. Mu, kappa, and delta opioid receptors represent the classic receptor subtypes, but there are others, such as opioid receptor like-1 (ORL1) that are less characterized. All four opioid receptor classes, including ORL1, are expressed throughout the nociceptive neural circuitry in addition to critical regions of the central nervous system that are included in reward and emotion-related brain structures [11]. All four receptors also share the commonality of being G protein-coupled, but it is the MOR that is targeted by most opioids used for pain management and responsible for most, if not all, observed acute and chronic effects of conventional opioid drugs including morphine, hydrocodone, oxycodone, and heroin [11, 12]. The MOR is a seven-transmembrane domain G protein-coupled receptor (GPCR) that interacts with inhibitory heterotrimeric G proteins, which function to transmit agonist-induced changes in the conformation of the MOR to downstream signaling events [12]. These downstream signaling events are responsible for the commonly known effects of opioids that include, but are not limited to, analgesia, euphoria, constipation, and cardiac/respiratory depression. If the MOR and the corresponding downstream signaling cascade are activated on a continual basis, homeostatic changes can take place and result in tolerance and addiction [12].

Heterotrimeric G proteins are made up of three proteins: one Gα subunit, and a heterodimer of β and γ subunits. The MOR normally interacts with the Gαi/o class of adenylate cyclase inhibitory Gα proteins, which in the resting state are in complex with the associated βγ heterodimer that is comprised of one of the five different β, one of the 12 different γ proteins, and GDP [12]. When the MOR is activated by endogenous agonists like the mu-opioid peptide endorphin or exogenous compounds such as morphine or fentanyl, the GDP dissociates from the Gα subunit, is replaced by GTP, and Gα-GTP proceeds to separate from the βγ heterodimer [11, 12]. The newly active Gα-GTP and βγ subunit interact with intracellular signaling proteins to generate physiological responses [12]. The most important aspect of opioid receptor signal transduction relates to the ability of this mechanism to module calcium and potassium ion channels. The Gα-GTP interacts directly with the G protein-gated inward rectifying potassium channel $K_{ir}3$. Channel deactivation occurs simultaneously with hydrolysis of GTP to GDP, causing cellular hyperpolarization and inhibition of tonic neural activity. Several studies have shown that the inhibitory effects of opioids on

neural excitability are mediated specifically by interactions of opioid receptors with the $K_{ir}3$ channel.

All four opioid receptors, when activated, cause a reduction in the $Ca^{2+}$ currents sensitive to P/Q-type, N-type, and L-type channel blockers. The inhibition of calcium conductance is mediated directly by the binding of the dissociated Gβγ subunit directly to the channel. It is this binding that is believed to reduce voltage activation of channel pore opening, and many studies have shown that opioid receptors interact with and modulate $Ca^{2+}$ channels. It has also been shown that acute administration of opioid agonists reduces $Ca^{2+}$ content in synaptic vesicles and synaptosomes with compensatory upregulation of vesicular $Ca^{2+}$ content during the development of opiate tolerance. Activation of mu, delta, and kappa opioid receptors also inhibits adenylyl cyclase activity, simultaneously reducing cAMP-dependent $Ca^{2+}$ influx. Newer data suggest that while opioid receptors may have powerful effects on ion channels, they have slower paced, yet potentially equally as potent effects on other signal transduction pathways [11].

Although this topic bears further study, it has been observed that among the different opioid receptor subtypes, receptor trafficking and regulation are agonist-dependent. At present, there are a number of research entities working to establish the various mechanisms for the differences in ligand-dependent MOR regulation. Some groups argue that MOR internalization does not uncouple the receptor from its signal transduction pathways, but rather induces recycling of uncoupled receptors to the plasma membrane. Others are convinced that the morphine-bound receptor, while not internalized, is still able to signal at the cell membrane. Since signaling is never attenuated, the cellular machinery adapts to produce tolerance. There also exists the possibility that morphine acts like a "collateral agonist" to promote receptor G protein uncoupling and activation of JNK. Despite this controversy, it seems likely that a number of different processes work together to govern MOR regulation and opioid tolerance [11].

Opioid-induced anti-nociception is mediated by MOR signaling to pertussis toxin sensitive Gαi. Additionally, spinal cord expression of Gβγ is required for MOR coupling to analgesic responses, which likely occurs through modulation of calcium and potassium channels in the dorsal horn and dorsal root ganglion. Interactions with various adenylyl cyclases, including AC1, AC5, and AC8, have also been shown to contribute to morphine-induced analgesia and tolerance. This signaling, via protein kinases (e.g., PKC, PKA, JNK) and various other protein-protein interactions, may be capable of modulating pathways of reward and analgesia. However, while components like PKC1 may be necessary for the function of morphine reward mechanisms, it is clear that there is not enough evidence to date to make firm conclusions regarding which substrates for MOR-dependent transcription factors and kinase signaling pathways are required for behaviors like tolerance, analgesia, and reward [11].

There has been a recent surge in the literature looking at the link between MOR signaling and behavior. It first evidenced that ERK 1/2 phosphorylation is upregulated by chronic treatment with morphine and in opioid withdrawal. It was subsequently shown that MOR-induced ERK 1/2 activity in the periaqueductal gray region can counteract morphine tolerance. The same mechanism of ERK 1/2 signal transduction has also been implicated in morphine reward and plasticity, including place preference and psychomotor sensitization, while ERK 1/2 activity in the amygdala can quiet anxiety experienced during morphine withdrawal. These observations suggest that ERK 1/2 signaling may play a role in MOR plasticity in the central nervous system.

## The G Protein Pathway of Pain Nociception and Analgesia

Upwards of 30% of drugs on the market function as modulators of G protein-coupled receptors (GPCRs), but surprisingly, only a small fraction of the nearly 400 GPCRs encoded by the human genome actually serve as drug targets. The function of GPCRs is largely to transduce extracellular stimuli into intracellular responses. In doing so, GPCRs mediate nearly all physiologic processes, including acute and chronic pain [13].

Nociception refers to the transduction of noxious stimuli, irrespective of cognitive awareness, with "nociceptor" describing a sensory neuron that is sensitive to noxious stimuli. Normal nociceptive transmission begins when a noxious stimulus activates nociceptive axons innervating a target organ. This signal is transmitted by primary sensory neurons to the spinal cord dorsal horn, where it is subject to modulatory control [13]. Certain postsynaptic spinal neurons, including secondary sensory neurons, send ascending axons to the thalamus, where information is relayed to higher cortical regions. Ascending fibers also simultaneously send collateral branches into the brainstem and midbrain regions that are involved in pain modulation, attention, and emotion. In turn, the supraspinal centers send descending projections to the spinal cord that can serve to either inhibit or facilitate nociception. It is these descending pathways that contain the GPCRs that are currently targeted by analgesic medications [13]. It is important to note that drug classes such as opioids exert their effects by acting directly or indirectly at GPCRs. Since regulators of G protein signaling (RGS) proteins negatively regulate GPCR signaling by accelerating the rate of hydrolysis of GTP back to GDP and the inactivation of Gα-GTP, these proteins have also been implicated in the actions of opioids [12].

Chronic pain conditions can cause normal regulation of nociceptive signaling to become altered. For instance, inflammatory mediators released by peripheral tissues and immune cells in response to injury act at GPCRs to sensitize peripheral nociceptors, causing them to become more responsive to

noxious and innocuous stimuli. This, in turn, makes the receptors unnecessarily sensitive and prone to activation. The combination of a newly expanded human GPCR repertoire and recent insights into the function and structure of the receptors paves the way toward the development of novel analgesic therapies [13].

## Pharmacology

Structurally, Oliceridine shows no similarities to morphine, fentanyl, or other previously described MOR agents. The agent has also been shown to be remarkably selective for the MOR, exhibiting an approximately 400-fold preference over the KOR, DOR, and NOP receptors (for reference, morphine is only tenfold selective for the MOR versus the KOR and DOR). When compared to morphine, Oliceridine has similar G protein-coupling efficacy (71% versus 92%, compared to full agonist, DAMGO) and greater potency (8 nM versus 50 nM). In further comparisons with morphine, Oliceridine seems to cause fewer adverse symptoms, resulting in less reduction in respiratory drive and less severe nausea [4••, 14••]. It has also been repeatedly shown to have the capacity to create equal or greater analgesia (measured by cold-pain test) and faster onset of action than morphine [4••, 14••]. Oliceridine is hepatically metabolized, mediated via both CYP3A4 and CYP2D6 enzymes [4••]. The drug has no known active metabolites, so its activity is tightly linked to its plasma concentrations, with a short delay between concentration and effect. This attribute is important for an opioid intended to treat acute pain, since opioids are traditionally dosed based on an individual's need and level of discomfort. Despite this, studies have suggested that the drug does exhibit a degree of dose nonlinearity when given to healthy volunteers [4••].

## Safety and Efficacy

A growing body of evidence suggests that compared to existing MOR agonists, Oliceridine and other G protein-selective modulators may produce therapeutic analgesic effects with reduced adverse effects. Based solely on the bias of Oliceridine for the G protein signaling, it would be expected that Oliceridine treatment produces robust and sustained anti-nociception with low potential for abuse-related effects with repeated treatment. Although acute treatment may be associated with negative side effects such as inhibition of gastrointestinal function, inhibition should be expected to subside with repeated use since MOR agonist-induced constipation is relatively resistant to tolerance [3••].

Studies that have tested the analgesic properties of Oliceridine have consistently shown that the drug produces robust anti-nociception that is, in fact, sustained during repeated dosing regimens that are typically sufficient to produce tolerance to morphine anti-nociception. This evidence underscores the idea that it is, in fact, MOR-mediated β-arrestin signaling that contributes to tolerance in assays of acute pain-simulated behavior. This notion implies that preferential G protein signaling produces anti-nocipetion with reduced tolerance. The apparent resistance of Oliceridine to tolerance is consistent with that of other G protein-biased MOR agonists such as herkinorin [3••].

Despite the promising and predictable anti-nociceptive capabilities of Oliceridine, considerations of the drug's abuse-related effects have not been as consistent. Several studies have shown that the abuse liability for Oliceridine may be similar to that of morphine and other unbiased MOR agonists [3••]. This evidence contrasts with that of a recent report that demonstrated how a single dose of Oliceridine failed to produce a conditioned place preference in mice, but is consistent with clinical studies showing that MOR agonist rewarding effects are retained and even enhanced in β-arrestin 2 knockout mice [15, 16]. The evidence is also in line with data demonstrating that Oliceridine produces a morphine-like increase in abuse-related subjective effects such as scores of "Liking" and "High." [14••] Overall, these results point to the potential safety concern that G protein-biased MOR agonists like Oliceridine retain opioid-like abuse potential.

Findings of studies that have considered gastrointestinal inhibition brought on by the action of MOR agonists have been discordant. Several findings have suggested that reductions in MOR-mediated β-arrestin signaling may reduce or eliminate the constipating effects of MOR agonists. Studies have found that morphine-induced constipation is reduced in β-arrestin 2 knockout mice relative to their wildtype controls and that β-arrestin 2 knockout mice develop tolerance to the gastrointestinal effects of morphine [17, 18]. However, while there is some evidence that may suggest that the potency of Oliceridine to produce gastrointestinal inhibition is lower than that of morphine, a recent study found that β-arrestin signaling does not seem to play a role in initial expression or tolerance of the constipating effects of MOR agonists. In fact, the effects of acute and repeated administration of Oliceridine on gastrointestinal function were shown not to differ from those of morphine. One of the explanations for the discrepancy in findings is that Oliceridine may lack sufficient bias for G protein vs. β-arrestin signaling to produce reliable decreases in gastrointestinal inhibition [3••].

Research models have shown that Oliceridine causes fewer gastrointestinal adverse effects than morphine at equivalent analgesic doses. This difference is reflected well by the lack of gastrointestinal dysfunction at the subanalgesic dose of 0.3 mg/kg s.c. of Oliceridine compared to definitive dysfunction caused by morphine at a similarly subanalgesic dose of 1 mg/kg s.c. In comparing maximal doses of Oliceridine and

morphine, colonic motility was still evident at maximal doses of Oliceridine whereas morphine at equivalent analgesic doses completely blocked gastrointestinal function. The same kind of improvement was seen in comparing the fecal boli accumulation assay and charcoal meal gastrointestinal transit tests between the two agents. These observations point to the fact that Oliceridine may cause less opioid-induced constipation than morphine [2]. At present, it appears that further study is required to more clearly assess the effects of Oliceridine and other G protein-biased MOR agonists on gastrointestinal function.

In further comparing the adverse effects of Oliceridine and morphine, it has been shown that Oliceridine does not cause respiratory suppression as severe as that of morphine even at eightfold over the equianalgesic dose. It has also been demonstrated that the sedative capacity of Oliceridine is nowhere near that of morphine. These results suggest that Oliceridine may have an increased therapeutic index for analgesia versus respiratory suppression and sedation. In mice, it has been shown that analgesia induced by Oliceridine is reversible after administration of 3 mg/kg naloxone 15 min after drug dosing. This observation, along with evidence showing that naloxone shifts the EC50 of Oliceridine-evoked G protein coupling in a concentration-dependent manner consistent with a competitive mechanism of action, not only indicates that Oliceridine-induced analgesia is MOR mediated but also that Oliceridine exhibits a short residence time on the receptor [2]. These naloxone-related findings also reveal that Oliceridine is similar enough to other opioids that in the event of overdose, there is an existing antidote that could successfully serve a rescue function.

## Further Development

Although evidence is not always consistent, the use of pathway selective opioids to activate the μ-pathway and decrease β-arrestin recruitment is a generally accepted method to decrease adverse side effects. This is shown through the negative response of an oliceridine analogue, TRV-0109101, failing to promote mechanical allodynia and further decrease allodynia induced by a non-selective opioid [1]. As such, it can be concluded that the β-arrestin pathway at least partially mediates adverse opioid effects. Additionally, surveillance of these novel μ-selective opioids is suggested through phase 4 trials in order to identify long-term side effects and ensure that the benefits of decreasing immediate side effects is not detrimental to long-term health. Also, the addictive nature of opioids, including the limited evidence on Oliceridine, should not be ignored and the current treatment options for withdrawal symptoms can be improved.

## Conclusion

Oliceridine is a novel MOR agonist which functions as a biased ligand that selectively activates G protein and β-arrestin signaling pathways. Recent advances in the understanding of MOR-mediated pathways and GPCR function paves the way toward the development of novel analgesic therapies. A growing body of evidence suggests that compared to existing MOR agonists, Oliceridine and other G protein-selective modulators may produce therapeutic analgesic effects with reduced adverse effects. At present, further study is required to more clearly assess the safety and efficacy of Oliceridine and other G protein-biased MOR agonists in providing analgesia while potentially reducing rates of adverse opioid related effects.

## Compliance with Ethical Standards

**Conflict of Interest** Ivan Urits, Omar Viswanath, Vwaire Orhurhu, Kyle Gress, Karina Charipova, and Anh Ngo declare no conflict of interest. Alan D. Kaye serves on the Speakers Bureau of Depomed and Merck.

**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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