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NEW PHARMACOLOGICAL STRATEGIES FOR ANALGESIC DRUG DEVELOPMENT: FOCUS ON BIASED μ-OPIOID RECEPTOR AGONISTS

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SUMMARY

Chronic pain affects more than 30% of people worldwide and although mortality rates are highest for other pathologies, it is one of the main sources of human suffering and disability that profoundly impacts patients' quality of life. To date, opioids still represent the reference treatment for moderate to severe chronic pain, however their use is strongly limited by a plethora of unwanted side effects including analgesic tolerance and opioid induced hyperalgesia. In the last few years, numerous efforts have been made in order to develop new analgesic drugs characterized by reduced side effects and by a safer pharmacological profile. Molecules capable of modulating different downstream pathways, known as biased agonists, are one proposed strategy for the treatment of chronic pain due to their suggested ability to discriminate between analgesic and adverse effect. In this review, we discuss the pharmacological outcomes of opioid biased ligands by bringing together cellular results and the available data from clinical trials; in particular, we focus on biased μ-opioid receptor agonists given their therapeutic relevance.

Key words

Biased MOR agonists; chronic pain; opioids; analgesia.

Impact statement

The concept of MOR biased agonism has been used to identify new analgesic drugs. Although some criticism has been raised toward this strategy, it represents a useful step for the development of safer opioid analgesics.

INTRODUCTION

Chronic pain is one of the major pathological conditions that affect the general population with a prevalence ranging from 11% through 40% (1). This kind of pain that lacks the acute warning function of physiological nociception, lasts or recurs for more than 3 to 6 months (2). The occurrence of this condition is influenced by a wide range of factors that strongly affect its duration and intensity (3, 4). Thus, pain management, often requires a multidisciplinary and multimodal approach including pharmacological treatment, interventional therapies, and behavioral/physical therapy (5). Despite research advancement and the suggestions of new targets for moderate to severe chronic pain treatment, opioids still represent the gold standard analgesics due to their action on opioid receptors (6). However, prolonged opioid administration is often related to the development of several side effects including tolerance, physical dependence and opioid induced hyperalgesia (OIH) (7, 8). The appearance of these phenomena strongly limits opioid use and

could determine the reduction/cessation of opioid administration or the progressive dose increase in order to achieve adequate analgesia. Furthermore, respiratory depression, constipation, nausea and itching also represent common dose-limiting side effects (6, 9, 10). In addition, opiate effects on mood and reward behaviors highlights another major concern related to their possible misuse, abuse, and addiction state establishment. These latter could represent some of the main causes responsible for the opioid crisis outcome in US (6) and strongly impact their prescription as well as their usefulness for pain relief (11, 12).

Therefore, efforts are made nowadays to develop innovative analgesics characterized by similar potency and efficacy compared to the common opioid agonists (*i.e.*, morphine, oxycodone, fentanyl) and by a safer pharmacological profile (fewer side effects and lower abuse liability).

Given experimental evidence showing that opioid-induced analgesia and side effects could be processed by distinct cell signaling pathways (13, 16), and the attention dedicated to biased agonists, this review will discuss the molecular mechanisms of some biased μ-opioid receptor agonists and their preclinical and clinical relevance.

THE ENDOGENOUS OPIOID SYSTEM SIGNALING

The endogenous opioid system consists of four natural ligands represented by β-endorphins, enkephalins, dynorphins, and nociceptin/orphanin FQ and includes four cognate seven-transmembrane G protein-coupled receptors (GPCRs) which are μ, δ, κ, and the opioid receptor like-1 (MOR, DOR, KOR, NOP receptor, respectively). This system represents one of the main system involved in neurotransmission and neuromodulation and it is widely expressed across the neuraxis, particularly in pain pathways (17). Indeed, the activation of opioid receptors plays a crucial role in the modulation of pain transmission and therefore in analgesia. Following the activation by agonists, such as endogenous peptides or exogenous ligands like morphine and fentanyl, the receptor engages the GDP-bound Gαβγ complex that promotes the GDP dissociation from Gα thus leading to the separation of Gα and Gβγ subunits through conformational changes. In particular, opioid receptors activation reduces neuronal excitability and pronociceptive transmitters release through the modulation of calcium and potassium ion channels. Indeed, receptors activation is able to induce hyperpolarization by activating K^+ channels and by inhibiting Ca^{2+} channels (18). Moreover, agonist stimulation of these receptors inhibits adenylate cyclase (AC) thus reducing cyclic AMP (cAMP) production (17, 19, 20). The maintained G protein activation induced by opioids could lead to the receptors β-arrestin-mediated desensitization and internalization mainly due to the G protein-coupled receptor kinases (GRKs) phosphorylation at the intracellular C-terminus (18). The resulting phosphorylated arrestin-GPCR complex recruits downstream signaling cascades including ERK, JNK, and p38 mitogen-activated protein kinase (MAPK) which, in turn, leads to proliferation, differentiation, and apoptosis (**figure 1**) (17).

OPIOID BIASED AGONISM

The term "*functional selectivity*" was introduced for the first time in 1998 and was initially referred to dopamine receptors (21). Theoretically, functional selectivity is due to different agonists' interaction with specific residues at the orthosteric binding site of a GPCR, thereby inducing different conformational changes of the intracellular loops that eventually result in different signaling outputs (22). This phenomenon, also known as "biased agonism" defines the capability of a specific ligand to activate different cellular pathways.

Within the opioid receptor subfamily, G protein signaling is accountable for opioid-induced analgesia whereas the β-arrestin pathway determines the occurrence of side effects (16). Thus, the functional selectivity of G-protein pathway

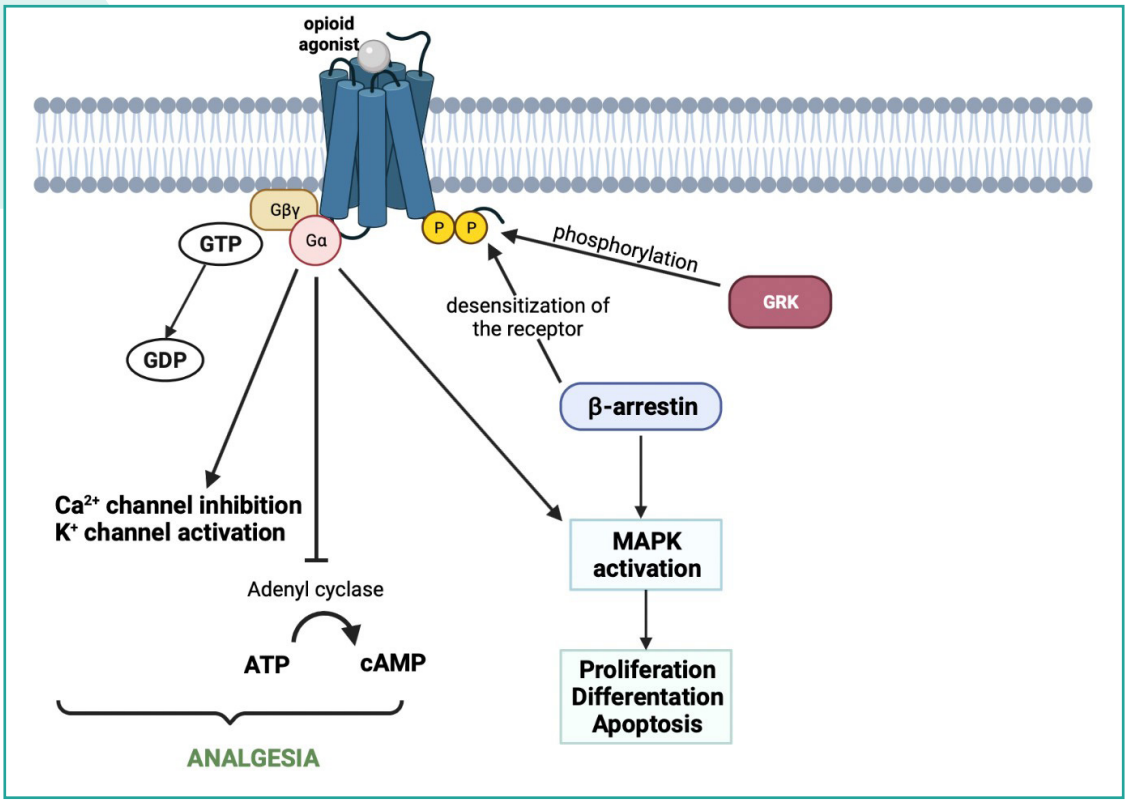

Figure 1. Intracellular pathways following opioid receptors activation.
After the agonist binding to an opioid receptor, conformational changes lead to the activation (via GDP e GTP exchange at the G-protein) of different signaling pathways. G-protein signaling pathways, enabled after the dissociation of G-protein into α and β/γ subunits following agonist binding, are accountable for the inhibition of calcium channels, activation of potassium channels (reducing the excitability of the cell membrane), inhibition of adenylate cyclase and stimulation of mitogen associated protein kinases (MAPKs) cascades. Bias towards G-protein signaling has been associated with analgesia. On the other hand, β-arrestin recruitment and its signaling pathways activation are due to G-protein receptor kinases (GRK) phosphorylation of the active G-protein coupled receptors, thus leading to the internalization/desensitization of opioid receptors and the activation of mitogen associated protein kinases (MAPKs) cascades. Bias towards β-arrestin has been linked to side effect profile.

could be relevant to avoid undesirable opioids effects (**figure 2**). The first suggestion of targeting a specific signaling pathway following MOR-agonist activation came from a study of Bohn and colleagues in 1999 demonstrating that mice lacking of β-arrestin-2 show a more potent and prolonged analgesic effect after morphine administration together with less tolerance, constipation, and ventilatory depression, compared to wild-type mice (13, 23, 24). It is relevant to note that different outcomes regarding tolerance development may occur depending on the specific neuronal system. In fact, some evidence shows that β-arrestin-2 knockout (KO) mice do not develop tolerance in the hot plate test, which is related to supraspinal pain responsiveness. Instead, the warm water tail immersion assay, linked to spinal reflexes activated by painful thermal stimuli, highlights the development of morphine tolerance, even if to a lesser degree than the wild-type (WP). Of note, low doses of protein kinase C (PKC) inhibitor (*i.e.*, chelerythrine) is able to completely reverse morphine tolerance in β-arrestin-2 KO mice (25). This evidence suggest that β-arrestin-2 regulates MOR sensitivity to morphine, although other regulatory proteins can also impact receptor function at spinal

cord level. Thus, it is clear that β-arrestins are critical in understanding mechanisms responsible for tolerance development. In this regard, *in vitro* studies show that both β-arrestin-1 and β-arrestin-2 differently regulate MOR signaling and that β-arrestin-2 only can rescue morphine-induced MOR internalization (26).

Over the years, the concept of biased agonism has been extended to the other opioids receptors. Indeed, also DOR activation, known to produce analgesia, anxiolytic- and antidepressant-like effects, is linked to the development of some side effects such as tolerance and convulsions that seems mainly due to arrestin-mediated internalization (15, 19, 27). Moreover, recent evidence also demonstrates that KOR activation in β-arrestin KO mice induces a potent antinociceptive and antipruritic effects, thus suggesting that biased KOR agonists are able to provide analgesia without producing dysphoria, sedation, abuse potential, anxiety, stress, and depression that are common side effects related to the use of KOP agonist (15, 28). To date, only few studies explored biased NOP receptor agonists. Pacifico *et al.* found that lipidation of N/OFQ(1−13)-NH2, a potent NOP receptor agonist, could be a valuable strategy for developing G-protein biased NOP receptor agonists (29). On the other hand, it seems that NOP receptor ligands are capable of fostering the interaction between the receptor and β-arrestin-2 leading to anxiolytic-like effects. At the same time, molecules that inhibit this interaction are responsible for antidepressant-like effects in mice (19, 29, 30).

BIASED MOR AGONIST MOLECULES

The above findings highlight the relevance of functional selectivity in intracellular GPCR sig-

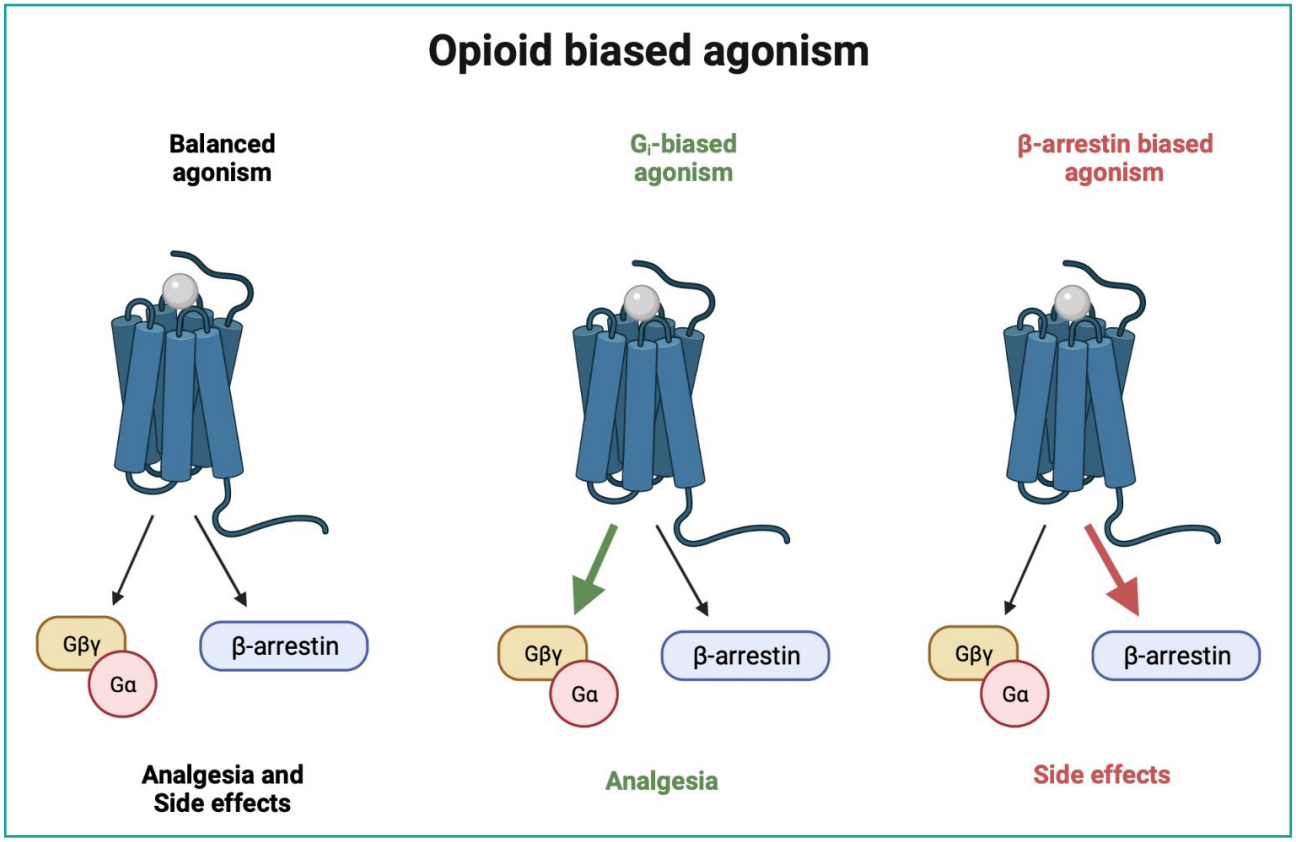

Figure 2. Opioid biased mechanism. In regard to opioid receptor subfamily, ligands that are able to selectively activate G-protein signaling lead to analgesia whereas side effects occurrence is mainly a consequence of the selective β-arrestin-2 recruitment.

naling and suggest that the development of newer MOR agonists able to discriminate antinociception from adverse effects could have an important therapeutic relevance. Although the concept of biased agonist is extended to all four opioid receptors it is important to emphasize that the most satisfactory results have been obtained from the research on μ-opioid receptors. Therefore, by bringing together cellular results and the available data from clinical trials, in this section biased-MOR agonists will be mainly discussed.

Herkinorin

Herkinorin represents the first μ-opioid receptor ligand derived from the selective KOR salvinorin A (31). This molecule acts as an agonist of both MOR and KOR showing high binding selectivity for μ-opioid receptor *in vitro*; a lesser selectivity has been also reported for KOR and DOR (32). Due to its ability to activate G protein coupling and ERK1/2 without inducing receptor-β-arrestin interactions or receptor internalization in MOR-expressing HEK-293 cells (26), herkinorin was initially defined as a biased MOR agonist. However, a more recent study using enzyme complementation assay to assess β-arrestin-2 recruitment, reveals that this molecule seems able to recruit this protein (33). *In vivo* studies demonstrate that herkinorin is able to induce low tolerance development coupled to potent antinociceptive effect at peripheral level only. Although the reduced CNS activity (32) strongly limits its use, herkinorin represents a starting point for the development of analogs.

Mitragynine and 7-hydroxymitragynine (7-HMG)

Mitragynine has been isolated from *Mitragyna speciosa* (traditionally known as kratom), a medicinal plant used for its analgesic properties. This molecule demonstrates mixed MOR agonist and DOR/KOR antagonist activity (34). In murine models, mitragynine does not recruit β-arrestin-2 and induces a lower tolerance as well as physical dependence than MOR opioid agonists (15). It is also capable to produce a lower respiratory depression compared to codeine (35). The second most plentiful alkaloid with a bias towards G-protein signaling extracted from kratom is 7-hydroxymitragynine, a full MOR agonist showing a binding affinity 5-fold higher than mitragynine (34, 36). However, both these molecules are able to induce opioid-like adverse effects (*e.g.*, withdrawal, constipation) even if to a lesser extent than morphine (19).

Although mitragynine and its derivatives seem to show an interesting pharmacological profile, the concerns related to their toxicity mainly due to their ability to interact with different cellular pathways, strongly limited their use. However, these compounds could be useful for the development of new effective molecules characterized by lower side effect (37).

Oliceridine

Oliceridine (TRV130) is a novel intravenous G protein-selective MOR agonist developed by Trevena, Inc. and it is the first biased agonist approved by US FDA in 2020 (Olinvyk™). It has been authorized for moderate-to-severe acute pain management and for whom alternative treatments are inadequate and it is currently tested for clinical use in Europe and Asia (**figure 3**). Oliceridine exhibits nearly a 3-fold preference for G-protein signaling over β-arrestin, thus providing potent analgesia with reduced adverse events generally related to opioids (38-40).

Although there are no structure similarities between oliceridine and morphine, the former has higher selectivity for MOR than the latter (41). In particular, this molecule is able to preferentially activate MOR, leading to a decreased cAMP activity which, in turn, generates analgesia. At the same time, oliceridine reduces MOR activation of β-arrestin which is related to respiratory depression, opioid tolerance, OIH, and feedback inhibition of the G-protein

pathway (38). Nonetheless, Araldi and coworkers reported that peripheral injection in the dorsum of rats' hind paw of both oliceridine and PZM-21 elicit OIH and hyperalgesic priming; this latter procedure represents a model commonly used to investigate the transition to chronic pain induced by the administration of potent MOR agonists (*e.g.*, DAMGO, fentanyl) (42). Overall, results show that after continuous infusion of oliceridine in rats (28 days) and in monkeys (14 days) there are no peculiar noxious effects compared with those associated with chronic opioid administration and that oliceridine shows an advantageous risk-benefit profile when compared to equianalgesic doses of morphine (43, 44). Indeed, a randomized phase II study suggests that oliceridine may enhance the analgesic efficacy with acceptable tolerability when compared to that of classical opioids (45).

Different clinical trials on oliceridine are in agreement on its improved pharmacological profile. ATHENA was a phase III, open-label, multicentric trial conducted from 2015 to 2017 in order to assess the safety and tolerability of oliceridine in a wide setting of patients with moderate-to-severe acute pain and painful conditions for which intravenous opioid would be warranted. In this study, among patients that experienced adverse events (64%) nausea, vomiting, and constipation were the most frequent "probably" or "possibly" related to oliceridine that were reported in 33% of patients although with lower incidence (46, 47).

When compared to morphine, oliceridine displays several differences including β-arrestin recruitment, receptor phosphorylation, and receptor internalization. In addition, DeWire and coworkers demonstrated that oliceridine administration in mice results in less gastrointestinal dysfunction as well as in an increased therapeutic index for analgesia versus respiratory suppression and sedation in rats, compared to morphine. The enhanced respiratory safety profile has been confirmed also by ATHENA (47, 48). Likewise, APOLLO-1 (a phase III, multicenter, randomized, double-blind, placebo- and active-controlled study for the management of moderate-to-severe acute pain following bunionectomy) and then APOLLO-2 (a phase III, multicenter, randomized, placebo- and active-controlled study for the management of moderate-to-severe acute pain following abdominoplasty) have demonstrated the reduced incidence of adverse events regarding the gastrointestinal and respiratory functions, confirming previous phase Ib and phase II studies (41, 49-51).

Several investigations show that oliceridine could have reduced analgesic tolerance (52-55). However, other investigations reported that oliceridine, despite biased agonism on MOR, maintains an abuse potential similar to that of conventional opioids. In fact, a study from Altarifi *et al.* shows that repeated administration of oliceridine in rodents leads to effects comparable with morphine intracranial self-stimulation (ICSS), while Austin Zamarripa and coworkers find that oliceridine and oxycodone exhibit equipotent reinforcement effects in rats. Nevertheless, when compared to morphine, oliceridine displays less tolerance, which occurs after 4 days of treatment, and OIH event though there are evidence for physical dependence development and conditioned place preference (CPP) (55-57).

PZM-21

Despite the poor structure analogy between PZM-21 and opioids, computational docking and structure-based optimization led to the identification of this molecule as a non-prototypical G_i activator of MOR with minimal β-arrestin-2 recruitment (19, 58). Some evidence showed that systemically administration of PZM-21 is able to produce hyperalgesia at low doses and analgesia at high doses as well as hyperalgesic priming at both tested doses (42). Moreover, it has been recently demonstrated that PZM-21 causes long-lasting potent antinociception in the hot plate and formalin tests in rodents and in non-human primates (NHPs). However, its potency is lower than that of oth-

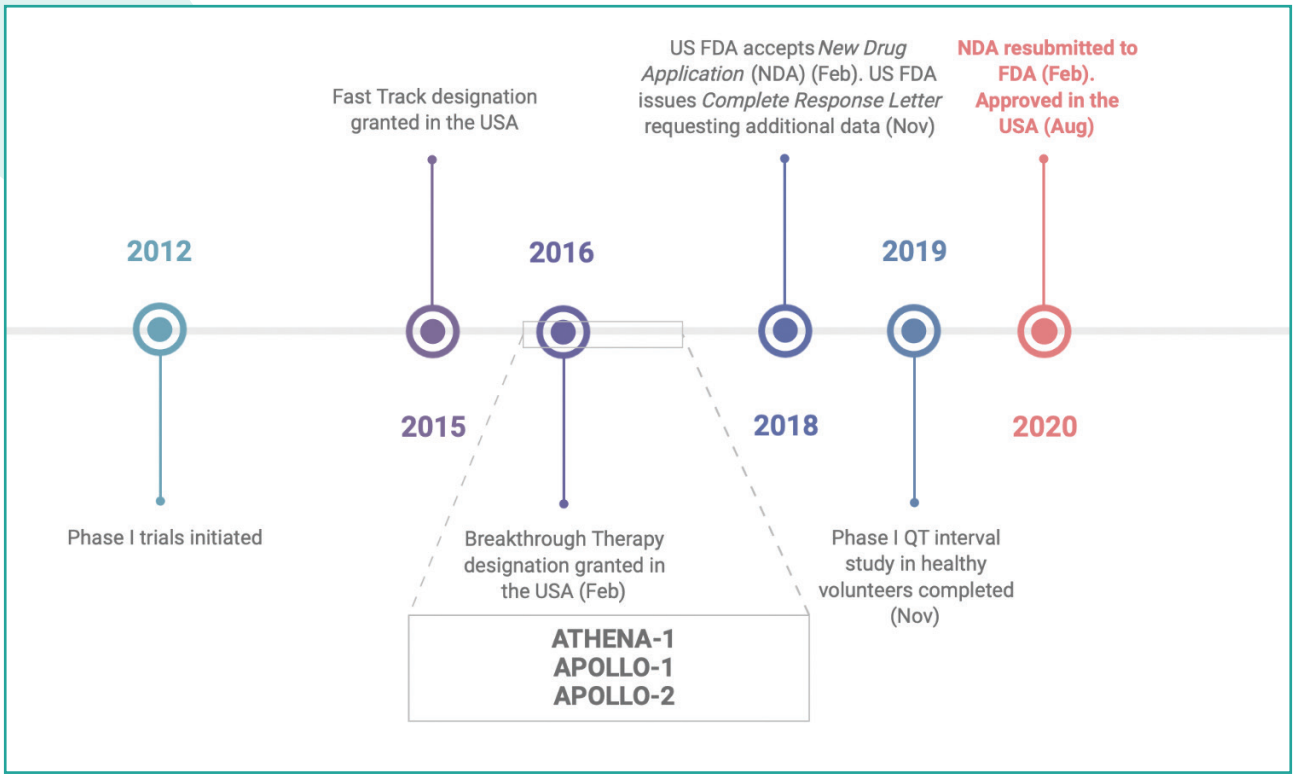

Figure 3. Key milestones in clinical investigation for the development of oliceridine.

ers commonly used MOR agonists; indeed, PZM-21 is about 10-fold less potent than oxycodone (16, 19, 59). Furthermore, Kudla and colleagues have also shown that the pretreatment with PZM-21 is able to enhance morphine-induced analgesia and to attenuate the expression of morphine reward (16, 60). However, even though PZM-21 does not induce conditioned place preference (CPP) in rodents, in a NHPs model of intravenous drug-self administration, it seems to induce reinforcing and pruritic effects similar to clinically used MOR receptor agonists (59). In addition, repeated administration of PZM-21 leads to the development of antinociceptive tolerance (61).

In regard to respiratory depression, there are controversial data. Manglik *et al.* (2016) reported that PZM-21 causes a reduced development of respiratory depression but, from a study of Hill and colleagues, it seems that this drug is able to depress respiratory function in mice with a profile comparable to that of morphine. These data could be partially explained by evidence highlighting that this side effect results also from G_i/G_o signaling (33, 61).

Piperidine benzimidazoles

SR-17018, SR-15098, and SR-15099 are some of substituted piperidine benzimidazoles with high affinity for MOR. Structure-activity studies have identified halogens and a central piperidine as important structural features for bias (19, 62). In particular, SR-17018, SR-15098, and SR-15099 are partial agonists with a G-protein signaling preference as well as the full agonist SR-14968 whereas SR-11501 is a biased partial agonist for the β-arrestin recruitment (63). These drugs have a long-lasting effect and seem to promote potent antinociception similar to morphine and fentanyl in hot plate and warm water tail withdrawal tests (19). Moreover, SR-17018, SR-15099, and SR-14968 produce in mice a lower respiratory depression than morphine (14, 64).

SR-17018, is able to suppress signs induced by morphine withdrawal but like, but differently

from buprenorphine, substitution of SR-17018 in morphine-tolerant mice is also able to restore morphine sensitivity (14). In addition, it has been showed that SR-17018 induces a higher allodynia suppression in comparison with morphine or oxycodone, in a paclitaxel-induced neuropathic pain model (65); finally, its chronic administration in mice produces less tolerance to the analgesic effect than morphine in the hot plate test (14). However, it is interesting to note that SR-17018 produces antinociceptive tolerance in the warm water tail immersion test, in the same animal species (65). The ability of SR-14968 and SR-17018 to produce antinociceptive effect and limited respiratory suppression (66) has bee also demonstrated in NHPs, thus corroborating their interesting pharmacological profile. However, additional studies are needed to evaluate the future development and potential application of these molecules in humans.

CONCLUSIONS AND FUTURE PERSPECTIVE

This review focused its attention mainly on biased μ-opioid receptor agonists. However, as above mentioned, it is important to underline that the functional selectivity concept involves also the other opioid receptors and it seems to be relevant for developing new pharmacological strategies for the management of chronic pain and for preventing the common side effects related to opioids (*i.e.*, tolerance, itching). Some criticism has been raised concerning biased agonism (67, 68) and it has also been suggested that the peculiar pharmacological profile of selected ligands could be mostly related to their low efficacy/partial agonism rather than to G-protein bias (69, 70). However, given pre-clinical and clinical results, biased agonists can represent a useful step in research strategy for the development of safer opioid analgesics. In this context, also dual agonism shown by selected molecules acting as MOR/NOP receptor agonists (*e.g.*, BU08028, BU10038, and AT-121) as well as MOR/KOR agonists, KOR/DOR agonists, and MOR agonists/KOR antagonists could be considered a promising approach in this field (71).

ETHICS

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Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

LR, LML and CM wrote the draft. All authors revised the final manuscript.

Availability of data and materials

The data underlying this manuscript are available in the article.

Ethical approval

N/A

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