

Sending out Biased Signals: An Appropriate Proposition for Pain?

Agonistes biaisés pour le traitement de la douleur : Est-ce approprié ?

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Abstract

In the past few years, several biased ligands acting at the mu-opioid receptor were reported in the literature. These agonists are aimed at reducing pain while having fewer side effects than morphine, the gold standard of opioid analgesics. In this mini-review, we describe and discuss the recent advances in mu-biased ligands actually in pre-clinical and clinical development stages, including the latest U.S. Food and Drug Administration review of oliceridine, a biased mu-agonist for moderate to severe acute pain treatment developed by the company Trevena.

Keywords: Morphine, Opioid, Pain, Biased Signaling, G Protein-Coupled Receptor

Résumé en français

Dans les dernières années, plusieurs ligands biaisés agissant sur le récepteur mu-opioïde ont été rapportés dans la littérature. Ces agonistes ont pour but de réduire la douleur tout en ayant moins d'effets secondaires que la morphine, la référence des analgésiques opioïdes. Dans cette mini-revue, nous décrivons et discutons des avancées récentes en matière de ligands biaisés du récepteur mu-opioïde en phase de développement préclinique et clinique, y compris la dernière décision de la U.S. Food and Drug Administration sur l'olicéridine, un agoniste biaisé mu développé pour le traitement des douleurs aiguës modérées à graves par la société Trevena.

Mots-clés : Morphine, opioïde, douleur, signalisation biaisée, récepteur couplé aux protéines G

Introduction

Opioids are the gold standard for the treatment of acute to chronic pain. However, opioid therapy is associated with a wide range of unwanted effects that seriously affect medication adherence in patients dealing with chronic pain [1]. This prompted researchers to intensify their efforts to find new, effective and safe painkillers. In the late nineties, a new paradigm, called biased signaling or functional selectivity [2,3], emerged in the G protein-coupled receptor (GPCR) community, giving rise to new hope for the development of drugs with improved therapeutic profiles [4]. Therefore, the quest for the analgesic holy grail began.

Biased signaling is the ability of a ligand to activate only a subset of the signaling pathways that are usually activated by other GPCR agonists [3]. We could therefore design ligands that engage only signaling pathways that are beneficial and produce the desired effects. However, to apply this concept to drug discovery we have to decipher which signaling pathways are associated with the desired physiological effects [5]. This link between intracellular events and *in vivo* physiology has been made, for the mu-opioid receptor (MOR), with the use of mice lacking β -arrestin 2. Bohn *et al.* [6] showed that morphine's analgesic action was enhanced whereas side effects, such as respiratory depression and constipation, were greatly reduced in these mice. It was evidence that morphine-induced analgesia was dependent on G protein activation and undesirable effects were dependent on β -arrestin 2 recruitment to MOR (**Fig. 1**). This study greatly impacted the development of new MOR ligands in favor of G-protein biased ligands [7].

Olinvo: The promising compound, FDA rejection, and future direction.

Olinvo, also known as TRV130, oliceridine, is a MOR biased ligand developed by the company Trevena Inc. (Chesterbrook, PA). This compound was very promising early in its development as a $G\alpha_i$ -biased MOR agonist [8]. Olinvo was as efficient as morphine to alleviate pain in rodents and showed significantly reduced constipation and respiratory depression, thus increasing its therapeutic window [9]. In January 2018, Trevena submitted a new drug application for Olinvo at the U.S. Food and Drug Administration (FDA) and in October 2018, the FDA voted against its approval. The FDA decision was based on the nonsignificant trend of reduced side effects in patients treated with Olinvo compared with morphine-treated patients. In early 2019, the FDA agreed that Trevena's safety database supports a maximum daily dose of 27 mg of Olinvo and allowed the collection of additional pharmacokinetic parameters on healthy volunteers [10].

The new generation of MOR biased ligands.

In 2016, Manglik *et al.* [11] identified a hit compound after a structure-based virtual screening on the crystallographic structure of MOR. After a structure-activity relationship study, they identified PZM21, a potent $G\alpha_i$ biased compound selective for MOR and structurally unrelated to other MOR ligands, which displayed a strong analgesic action without having the morphine-related side effects [12]. In 2017, a study reported the synthesis of MOR agonists with a large array of bias factors ranging from β -arrestin to $G\alpha_i$ -biased ligands [13]. After extensive testing of these molecules and clinically relevant drugs such as Fentanyl and Morphine in pain and respiratory depression tests, they reported SR-17018 as a highly G-protein biased MOR agonist with a therapeutic window close to 100 (in comparison, fentanyl's is 4). They also showed that the bias factors were correlated with the therapeutic windows of the tested compounds.

Conclusion

The development of biased ligands targeting GPCRs involved in pain modulation is the ongoing work of many research labs and should not be threatened by the recent concerns raised by the failure of Olinvo. Highly biased agonists, such as SR-17018, might be the key to success in order to increase the therapeutic window and safety in humans. Furthermore, many biased agonists targeting other pain-related GPCRs, such as the cannabinoid receptors CB1 and CB2, are under development and could lead to novel potent pain medications in the next few years.

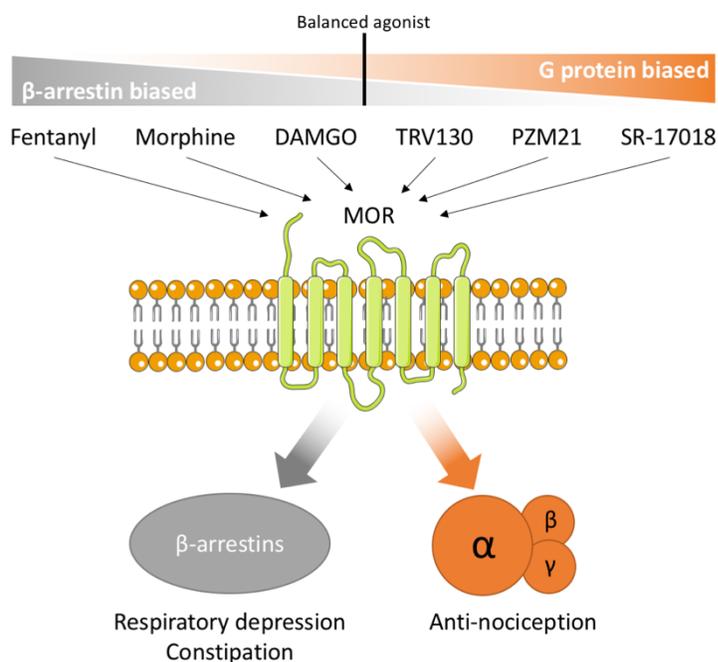


Figure 1. Biased agonism at the mu-opioid receptor.

G protein signaling pathways triggered by MOR are responsible for the antinociceptive effect of opioids whereas the recruitment of β-arrestins at the receptor mediates their adverse effects (respiratory depression and constipation). Consequently, β-arrestin biased MOR agonists, like fentanyl, produce more adverse events than G-protein biased compounds, like PZM21, which could be of great therapeutic interest due to their increased safety profile.

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