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Replacement of current opioid drugs focusing on MOR-related strategies

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ABSTRACT

The scarcity and limited risk/benefit ratio of painkillers available on the market, in addition to the opioid crisis, warrant reflection on new innovation strategies. The pharmacopoeia of analgesics is based on products that are often old and derived from clinical empiricism, with limited efficacy or spectrum of action, or resulting in an unsatisfactory tolerability profile. Although they are reference analgesics for nociceptive pain, opioids are subject to the same criticism. The use of opium as an analgesic is historical. Morphine was synthesized at the beginning of the 19th century. The efficacy of opioids is limited in certain painful contexts and these drugs can induce potentially serious and fatal adverse effects. The current North American opioid crisis, with an ever-rising number of deaths by opioid overdose, is a tragic illustration of this. It is therefore legitimate to develop research into molecules likely to maintain or increase opioid efficacy while improving their tolerability. Several avenues are being explored including targeting of the mu opioid receptor (MOR) splice variants, developing biased agonists or targeting of other receptors such as heteromers with MOR. Ion channels acting as MOR effectors, are also targeted in order to offer compounds without MOR-dependent adverse effects. Another route is to develop opioid analgesics with peripheral action or limited central nervous system (CNS) access. Finally, endogenous opioids used as drugs or compounds that modify the metabolism of endogenous opioids (Dual ENKephalinase Inhibitors) are being developed. The aim of the present review is to present these various targets/strategies with reference to current indications for opioids, concerns about their widespread use, particularly in chronic non-cancer pains, and ways of limiting the risk of opioid abuse and misuse.

Contents

Abbreviations: APN, AminoPeptidase N; CNCP, Chronic NonCancer Pain; DENKI, Dual ENKephalinase Inhibitor; GPCR, G Protein-Coupled Receptor; MOR, Mu-Opioid Receptor; NEP, Neutral EndoPeptidase (neprilysin); OR, Opioid Receptor; VDCCs, Voltage-Dependent Calcium Channels; DOR, Delta-Opioid Receptor; KOR, Kappa-Opioid Receptor; Oprm1, OPioid Receptor Mu 1; KO, Knock-Out; PKA, Protein Kinase A; TRPV1, Transient Receptor Potential Vanilloid type 1; TRPM3, Transient Receptor Potential Melastatin type 3; GIRK, G protein-coupled Inwardly-Rectifying potassium.

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1. Introduction

The pharmacopoeia of analgesics is old and has not been improved on for several years. However, the epidemiology of pain is now well-defined and several studies have concluded, for example, that the prevalence of chronic pain in the general adult population is around 30% depending on the country (Bouhassira, Lantéri-Minet, Attal, Laurent, & Touboul, 2008; Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Chenaf et al., 2018; Kuehn, 2018; Macfarlane, 2016) and even higher in elderly subjects. There is therefore a gap between the state of the pharmacopoeia with very limited conceptual innovations and a public health need exacerbated by the fact that there is no effective treatment for several pain syndromes. This worrying situation is aggravated by the increasingly questionable benefit/risk ratio of several classes of analgesics currently on the market. In this regard, the opioid crisis, caused by the propensity of opioids to induce dependence and death and that affects several countries, in particular the United States and Canada, illustrates the very delicate situation we find ourselves in. If, beyond the opioid issue, we: 1) place limitations on the use of certain analgesics (e.g., codeine in children); 2) question the safety and benefit/risk ratio of paracetamol, an issue raised by several studies; 3) take into account the adverse effects induced by nonsteroidal anti-inflammatory drugs due to their action on prostaglandin synthesis; and 4) consider the limited number of alternative analgesics available, we ultimately place the drug management of pain in a very uncomfortable position. Therapists cannot help but be confused given that the therapeutic drug resources at their disposal are unsatisfactory and patients can find themselves in genuine impasses despite the fact that non-drug therapies can be of help to them.

In parallel with this difficult situation, research on the physiology and pathophysiology of pain is prolific. It has provided new knowledge of the molecular mechanisms involved in the detection, transmission and modulation of pain messages and the pathophysiological hypotheses proposed. The ever-increasing number of basic and clinical research publications reflects this dynamic. There is therefore a significant discrepancy between this evolution of knowledge and the more than modest design of new drugs, as exemplified by the opioid family. While basic research has made it possible to identify their site of action, identify endogenous opioid systems and characterize their clinical effects, no substitute has replaced these drugs, whose adverse effects, which limit their benefit/risk ratio, have long been clearly known.

In this context, the first aim of this review article is to provide an analysis of the current use of opioids as analgesics, by focusing on the difficulties revealed by the opioid crisis. We will then give an overview of the different research prospects regarding concepts and/or compounds that could provide substitutes for opioids, with the hope of a better benefit/risk ratio, and strategies to limit abuse and misuse. Among the three mu, delta and kappa opioid receptors (MORs, DORs, KORs) identified (Goldstein & Naidu, 1989), the pharmacological perspectives analyzed in this article will focus on MORs because all the opioids currently in clinical use (with the exception of nalbuphine and pentazocine) activate these receptors, which participate in analgesia but also in opioid-induced adverse effects.

2. Current use of opioid drugs

2.1. Traditional indications for opioid drugs

Opioids have been consumed since 3000 BCE, when opium was already used to reduce pain. Today, opium powder is still available but original molecules that act as MOR agonists are widely used. They include morphine, first synthesized in the 19th century, codeine, pethidine, levorphanol, fentanyl and its derivatives, oxycodone, hydrocodone, hydromorphone, methadone, buprenorphine, tramadol and tapentadol. The usual indications for opioid analgesics were moderate-to-severe nociceptive pains such as per- and postoperative pain, post-traumatic pain, hyperalgesic attacks and cancer pain. The last indication prompted the World Health Organization's proposal in 1987 for a scale (adapted in 1997) to optimize the management of these pain conditions. The clear and circumscribed indications gave opioid drugs a key position as a reference within the pharmacopoeia for nociceptive pains more or less limited to opioids, paracetamol and nonsteroidal anti-inflammatory drugs.

2.2. Opioid drugs in chronic non-cancer pain

Traditionally, the administration of opioids did not include certain types of pain, in particular chronic non-cancer pain (CNCP), whether nociceptive, neuropathic, nociplastic or mixed. The prevalence of chronic pain (overwhelmingly CNCP) ranges from 20 to 46% according to the study, the method used and the country [(Macfarlane, 2016), UK; (Eriksen, Jensen, Sjøgren, Ekholm, & Rasmussen, 2003), Denmark; (Boulanger, Clark, Squire, Cui, & Horbay, 2007), Canada; (Bouhassira et al., 2008; Chenaf et al., 2018), France)]. In 2016, 50 million (20.4%) adults in the United States were living with chronic pain (Dahlhamer et al., 2018). This high prevalence, the desire to reduce pain and the societal pressure of dealing with it have led to an increase in the use of opioids. Their use in CNCP was initially supported by retrospective report of Portenoy and Foley (1986), who considered that opioids could behave like universal analgesics given their efficacy in acute and cancer pain. In the 1990s, Melzack (1990) stated that "what seems less understandable is that many people suffer not because their discomfort is untreatable but because physicians are often reluctant to prescribe morphine", adding, however, in the same article, "I do not suggest that morphine be prescribed indiscriminately". Thus, at that time, some authors called for the long-term use of opioids to be reconsidered, because there was a therapeutic benefit and that the risks were fewer than suggested. This contributed to the liberalization of opioid use and the extension of its prescription for CNCP. A study conducted among members of the Intractable Pain Society in the United Kingdom concluded that 62% of doctors prescribed opioids in CNCP, mainly because of the failure of other treatments (Coniam, 1989). In another study (Turk, Brody, & Okifuji, 1994), 1912 U.S. physicians from seven medical specialties were surveyed on their long-term prescription of opioids. Prescription was relatively infrequent but widespread among specialties, with family practitioners and rheumatologists being the two most likely physicians to prescribe long-term opioids. Most of the respondents expressed relatively little concern about dependence and addiction as impediments to prescribing opioids. Societal pressure was illustrated by press reports such as the front page of the U.S. News and World Report of the March 1, 1997 issue, "No excuse for pain. Doctors have the means at hand to relieve the suffering of millions of Americans. Why aren't they doing it?" This incentive to prescribe opioids has continued and led to the so-called "opioid crisis", which is probably multifactorial. It is the result of: 1) growing consideration for CNCP patients' complaints because of the major impact of pain on their quality of life (Dueñas, Ojeda, Salazar, Mico, & Failde, 2016; Rummans, Burton, & Dawson, 2018), and the lack of innovative therapies in this area, and 2) aggressive pharmaceutical marketing (Dasgupta, Beletsky, & Ciccarone, 2018). Opioids were thus prescribed for chronic pain over the long-term and at high doses, leading to the inflation of prescriptions and associated risks (Chou et al., 2009; Häuser, Schug, & Furlan, 2017; Shipton, Shipton, & Shipton, 2018).

2.3. Concerns about opioid use in chronic non-cancer pain

For many years, the long-term use of opioids in the treatment of CNCP was considered as inappropriate and the literature suggested that it was a controversial practice (see (Turk et al., 1994). This was due to the risks associated with the long-term use of opioids and doubts about their efficacy against CNCP, along with the fact that the management of these patients could not be limited to drug treatment alone

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but required the use of psycho-behavioral and social approaches to help them cope with pain rather than taking it away.

The risks of opioids are pharmacologically predictable as they are linked to their agonist action on MOR, which means that their adverse effects cannot be dissociated from their therapeutic analgesic effect, which is also dependent on MOR activation (Matthes et al., 1996). These adverse effects (constipation, nausea, vomiting and sedation with a high daily incidence, respiratory depression, tolerance, and dependence, whose epidemiology has worsened with the extension of opioid use for CNCP) clearly alter the benefit/risk ratio of currently available opioid analgesics. However, while other adverse effects exist (pruritus, immunosuppression, etc.), it is the issue of tolerance, dependence and prescription opioid use disorder, which can lead to unintentional intoxication (so-called overdose), that is the most problematic today, making the search for alternatives to opioids more pressing. Thus, tolerance to the analgesic effect of opioids implies that the amount of drug required to elicit pain relief must be increased to maintain analgesia. Consequently, patients increase doses (often by self-medication), which in turn leads to an increased risk of the other side effects, including prescription opioid use disorder and overdose (impaired consciousness and respiratory depression).

The efficacy of opioids in CNCP was debated at an early stage by certain authors owing to the lack of evidence from therapeutic trials (Large & Schug, 1995). Since then, a significant number of studies have been conducted on patients with CNCP, with varying results. In addition, numerous guidelines for the use of opioids for these patients have been published regularly (in different countries and languages), reflecting both the desire to manage the treatments and the caution or concern of the medical profession (Chapman et al., 2010; Cheung et al., 2016; Häuser et al., 2014; Ho et al., 2013; Kahan et al., 2011; Kahan et al., 2011; Kalso, 1999; Eija Kalso et al., 2003; Eija Kalso, 2005; Manchikanti et al., 2012b, Manchikanti et al., 2012a; Manchikanti et al., 2017; Petzke, 2015; Reinecke et al., 2009; The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society, 1997; Trescot et al., 2006, 2008). It is not the aim of this review to discuss all the work on the efficacy of opioids for CNCP, rather we prefer to give a summary of findings by referring to two recent meta-analyses (Busse et al., 2018; Reinecke et al., 2015). The study of Reinecke et al. (3647 citations screened, 46 selected randomized clinical trials involving 10,742 patients comparing opioids and non-opioids with placebo, physiotherapy and psychotherapy) concluded that, "Our assessment of maximum efficacy showed no significant differences between opioids and other pharmacological and non-pharmacological treatments […] thus, opioids alone are inappropriate and multimodal treatment programs may be required for CNCP". Busse et al. (2018) performed an extensive meta-analysis (96 randomized clinical trials and 26,169 patients with CNCP: neuropathic or nociceptive pain or with pain present in the absence of tissue damage) comparing opioids and any non-opioid control (drugs or placebo). They concluded that, "Evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo […], comparisons of opioids with non-opioid alternatives suggested that the benefit for pain and functioning may be similar". They also showed that opioids were associated with less pain relief during longer trials (potentially without any difference from placebo at 6 months) and suggested that this could be the result of opioid tolerance or opioid-induced hyperalgesia.

Given these data, the comments of Large and Schug (1995) were particularly relevant and premonitory. They wondered if the use of opioids for CNCP was "caring or crippling" and asked the question: "Will prescribing liberate the patient from pain and extend autonomy, or will it cripple the patient with an additional burden of drug dependence?". Today, in line with the U.S. government's efforts to rein in the use of the narcotics that spawned the drug epidemic, the Food and Drug Administration will require drug companies to study whether prescription opioids are effective in quelling chronic pain, although some consider the available data to be sufficient.

Thus, opioid indications remain primarily for moderate-to-severe acute pain and nociceptive cancer pain. The benefit of their long-term use in CNCP is not convincing. This, in addition to their adverse effects, some of which are potentially serious, warrant the development of research to replace MOR exogenous opioid agonists with innovative compounds that ensure a better benefit/risk ratio.

3. Research to replace current opioid drugs

Many fundamental studies have aimed at proposing new analgesic concepts. Unfortunately, these efforts have not, to date, resulted in the introduction of new drugs that are conceptually different from existing products. The last conceptually original analgesic marketed was ziconotide in the late 1990s. However, research has continued, including work aimed at finding substitutes for opioids with the hope of coming up with compounds that are as effective but better tolerated. We evoked here two key strategies inspired by the endogenous opioid neurotransmission system that have been developed to achieve this objective. They are focused on MOR, a target for both the analgesic and adverse effects of opioid drugs, with the aim of designing products that are free of mu-dependent adverse effects and on endogenous opioids with the aim of strengthening them or using them as drugs.

3.1. Strategies based on MOR and its effectors

Innovation in this context must aim at designing compounds to retain the therapeutic analgesic benefit of opioid drugs while limiting or even eliminating the risk of opioid-like adverse effects. To achieve this end, different strategies have been proposed, such as selective activation of MOR splice variants that are preferentially involved in analgesia, and biased activation of MOR towards analgesia-mediating intracellular pathways. Alternatively, targeting MOR at the periphery or designing compounds with a limited ability to cross the blood brain barrier would make it possible to reduce the adverse effects originating in the central nervous system (CNS). Finally, the identification of several ion channels modulated downstream of MOR and important for the analgesic effect of opioids could open up new pharmacological perspectives for achieving analgesia independently of opioid receptors.

3.1.1. Targeting MOR splice variants

Alternative splicing is a genetic mechanism that allows the production of different proteins from a single gene. Regulated exon skipping during the maturation of pre-messenger RNA results in a set of mature RNAs coding for different protein isoforms. Many MOR splice variants have been identified, and the presence of two different promoters in the associated *Oprm1* gene, located upstream of exons 1 and 11, adds to the complexity and diversity of MOR variants.

In mice, rats and humans at least, the *Oprm1* gene codes for three classes of splice variants (Pasternak & Pan, 2013) (Fig. 1). Transcription driven by exon 1 promoter produces a variety of full-length MOR receptors, sharing the first three *Oprm1* exons which code the seven transmembrane (TM) domains and the receptor's binding pocket. These 7TM variants therefore differ only by their intracellular C-terminal tail. In parallel, transcription from exon 1 also produces a class of short proteins containing only a single TM domain (1TM) with various C-termini. The third class of *Oprm1* variants is produced through exon 11-driven transcription. The resulting proteins are 6TM, which lack the first TM domain coded by exon 1. Both their N- and C-terminals are intracellular with varying sequences.

In mice, the expression of these variants has been detected in the spinal cord and DRG and in the brain, with considerable variations between regions (Xu et al., 2014). Interestingly, variations have been observed between mice strains with different susceptibilities to opioid

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tolerance and dependence, and chronic morphine administration resulted in profound remodeling of *Oprm1* variant expression patterns, affecting both promoters (Xu et al., 2015).

Insight into the physiological relevance of 1TM, 6TM and 7TM variants was first obtained by comparing different *Oprm1* knock-out (KO) mice strains. In exon 2 KO, lacking both 6TM and 7TM variants, the complete loss of morphine-induced analgesia, withdrawal syndrome and reward effect were observed (Matthes et al., 1996). Morphine also loses its analgesic effect in exon 1 KO mice, which lack 1TM and 7TM variants, showing the importance of full-length receptors for morphine-induced analgesia (Schuller et al., 1999). 7TM variants all share the same binding pocket but their C-terminal tails vary, which confers them different biases towards βarrestin 2 recruitment and different susceptibilities to desensitization (Tanowitz, Hislop, & von Zastrow, 2008). As a result, they have been involved to varying degrees in tolerance, reward and physical dependence on morphine (Xu et al., 2017). In parallel, 1TM variants are unlikely able to bind opioids. Yet, their expression contributes to morphine-induced analgesia (Xu et al., 2013). The co-expression of different 1TM variants with the 7TM MOR-1 variant increases protein expression of the latter and decreases its ubiquitination. The two proteins dimerize in the endoplasmic reticulum, and it has been suggested that the shorter variant acts as a chaperone to stabilize MOR-1.

Among the huge contributions of GW Pasternak and his collaborators to our knowledge of MOR splice variants, their most interesting work, at least regarding pharmacological perspectives, is undoubtedly that on 6TM variants. These receptors also play a role in opioid-induced analgesia, since in exon 11 KO mice, which lack only 6TM variants, the analgesic activity of heroin and buprenorphine is lost. Morphine, on the other hand, retains its analgesic potency in these mice (Grinnell et al., 2016; Pan et al., 2009). More insight was provided by the characterization of IBNtxA (3-iodobenzoyl-6β-naltrexamide), a naltrexone derivative with a high analgesic potency in naive, inflamed and neuropathic animals (Majumdar et al., 2011; Wieskopf et al., 2014). This effect, which is additive to that of morphine and blocked by naloxone at high doses only, is dependent on 6TM receptors, as evidenced by the complete loss of IBNtxA binding in the brain and analgesic potency in exon 11 MOR KO. In contrast, IBNtxA remains analgesic in exon 1 MOR/DOR/KOR triple KO mice (in which all opioid receptors are KO except for 6TM MORs). Furthermore, the loss of the analgesic effect of IBNtxA in a complete MOR KO targeting both exon 1 and exon 11 can be restored by lentiviral-driven expression of the mMOR-1G 6TM variant (Lu et al., 2015). 6TM variants are therefore necessary and sufficient for IBNtxA-induced analgesia. IBNtxA does not induce respiratory depression in mice and rats at supra-analgesic doses, and induces less constipation than morphine (Lu et al., 2015; Majumdar et al., 2011). IBNtxA induces a significantly reduced physical dependence compared to morphine, as evidenced by naloxone precipitated withdrawal and a conditioned place preference test showed no reward effect. Animals developed analgesic tolerance to IBNtxA, albeit more slowly than with morphine, and no cross-tolerance with morphine was observed. Although the analgesic effect of 6TM activation by IBNtxA has yet to be understood and confirmed in humans (no clinical study is currently ongoing), pharmacological targeting of these MOR splice variants represents a promising strategy for the development of safer opioids.

3.1.2. Biased MOR agonists

The simplistic view of ligand-receptor interaction was challenged 15 years ago with the discovery of ligand-directed signaling, also called functional selectivity or biased agonism (Galandrin, Oligny-Longpré, & Bouvier, 2007). After opioid binding and G protein activation, MOR is phosphorylated, primarily by G protein-coupled receptor kinase (Benovic, Strasser, Caron, & Lefkowitz, 1986), which enhances βarrestin binding to the receptor (Fig. 2A). βarrestin was first discovered owing to its role in mediating receptor desensitization (Lohse, Benovic, Codina, Caron, & Lefkowitz, 1990) and internalization (Goodman et al., 1996). The finding that they can mediate G protein-independent cellular signaling downstream of G protein-coupled receptor (GPCR) (Violin & Lefkowitz, 2007) made it possible to identify and design "biased" ligands, i.e. molecules that can preferentially trigger G protein-dependent and not βarrestin-dependent signaling and thus prompt different physiological and pharmacological outcomes (Fig. 2B). This insight has opened up a promising avenue for the design of GPCR-targeted therapeutics with an improved benefit-risk ratio. Regarding opioid receptors, seminal studies performed on naive βarrestin 2 KO animals suggest that the inhibition of βarrestin 2 function could lead to the enhanced analgesic efficacy of morphine with reduced adverse side effects, namely no or delayed analgesic tolerance and less

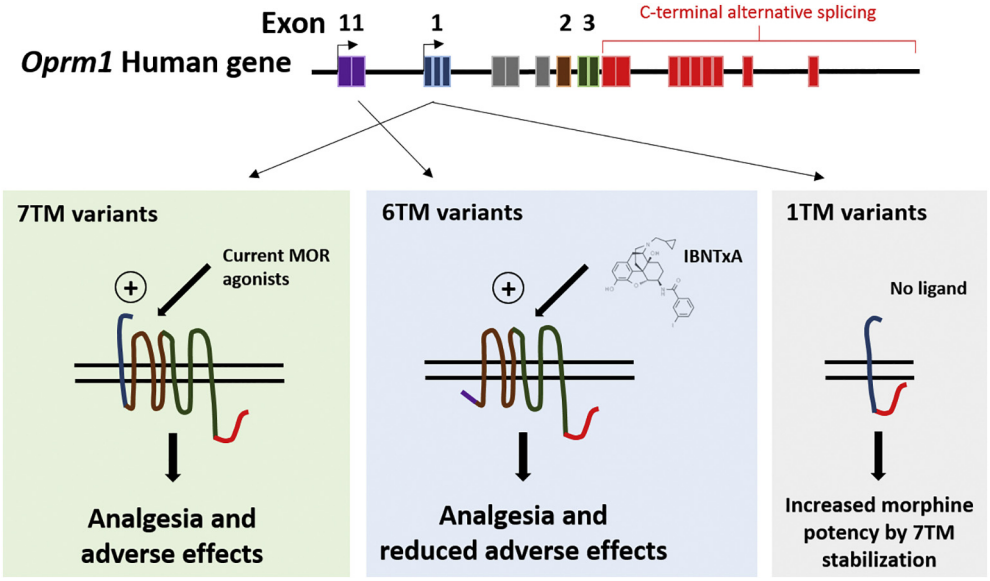

Fig. 1. MOR splice variants. Schematic representation of the human Oprm1 gene. The three classes of splice variants (7-TM, 6-TM and 1-TM) are presented. 1- and 7-TM variants are produced from the promoter associated with exon 1 (blue) and 6-TM variants from the promoter of exon 11 (pink). Selective activation of 6-TM variants by IBNTxA produces analgesia with fewer adverse effects than morphine, who acts preferentially on 7-TM variants.

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constipation and respiratory depression (Bohn et al., 1999; Bohn, Gainetdinov, Lin, Lefkowitz, & Caron, 2000; Bohn, Lefkowitz, & Caron, 2002; Raehal, Walker, & Bohn, 2005). These studies strongly supported the hypothesis that compounds that do not recruit βarrestin 2 may prove to be safer than current clinical opioids. However, it has been observed that morphine-induced hypothermia and conditioned place preference were enhanced in βarrestin 2 KO (Bohn et al., 1999; Bohn et al., 2003).

Molecules promoting signaling through the $G\alpha_i$ protein over βarrestin, such as TRV130 (oliceridine), have shown an analgesic effect in animal studies as potent as that of morphine and with attenuated adverse side effects, such as respiratory depression and gastrointestinal dysfunction (DeWire et al., 2013). It should be noted, however, that oliceridine has abuse-related effects and undesirable constipation in rodents (Altarifi et al., 2017; Austin Zamarripa et al., 2018; Liang, Li, Nwaneshiudu, Irvine, & Clark, 2018). PZM21, a molecule structurally unrelated to prototypical MOR agonists such as morphine, is another potent $G\alpha_i$ activator with high selectivity for MOR and minimal βarrestin2 recruitment. It was initially shown to strengthen the affective component of analgesia versus the reflexive component and to be devoid of both respiratory depression and morphine-like reinforcing activity in mice receiving equianalgesic doses of morphine, while inducing slightly less constipation than that due to morphine (Manglik et al., 2016). A re-examination study of the signaling profile of PZM21 and its ability to depress respiration concluded that PZM21 was a low efficacy agonist for both $G\alpha_i$ activation and βarrestin recruitment and that it significantly depressed respiration in a manner similar to an equi-antinociceptive dose of morphine in mice (Hill et al., 2018). It has also recently been shown that both PZM21 and oliceridine induce other adverse side effects such as opioid-induced hyperalgesia, and hyperalgesic priming, which is a model of transition to chronic pain (Araldi, Ferrari, & Levine, 2018; Kandasamy & Price, 2015).

The initial postulate that molecules exerting preferential coupling and activation of $G\alpha_i$ protein over βarrestin would have an analgesic effect as potent as that of morphine and attenuated adverse side effects, such as respiratory depression and gastrointestinal dysfunction, therefore needs to be refined. It has not been directly demonstrated that βarrestin does in fact mediate the respiratory adverse effects of opioids in mice (Schmid et al., 2017). In addition, there is evidence that respiratory depression also involves MOR coupling to GIRK channels via the activation of $G\alpha_{i/o}$ proteins (Montandon, Liu, & Horner, 2016). The compensatory recruitment of βarrestin 1 observed in βarrestin 2 KO mice could be involved in the modified pharmacological (analgesic or adverse) effects of morphine initially observed in βarrestin 2 KO mice. Recently, enhanced opioid-induced analgesia and diminished analgesic tolerance were observed in knock-in mice with a series of serine- and threonine-to-alanine mutations that render MOR unable to recruit βarrestin. Surprisingly, respiratory depression, constipation, and opioid withdrawal signs were unchanged or exacerbated, indicating that βarrestin recruitment does not contribute to the severity of opioid adverse effects, thus predicting that G-protein-biased μ-agonists are still likely to elicit severe adverse effects (Kliewer et al., 2019). More work is therefore needed to decipher which signaling pathway should be targeted over others in order to improve the benefit-risk ratio of biased MOR agonists. The recent design of a panel of novel MOR ligands whose signaling properties activate to various degrees either G protein or βarrestin (Schmid et al., 2017) and the use of a refined methodology (Ehrlich et al., 2019; Stoeber et al., 2018) should be helpful in this respect.

Oliceridine (TRV130), a biased MOR agonist, was evaluated in several randomized, controlled clinical trials. The first randomized, double-blind and placebo-controlled trial in healthy volunteers showed it had a greater analgesic effect than morphine in relieving cold-induced pain but also induced dose-related adverse effects. However, respiratory drive was lower and nausea less severe (only after the two lowest doses) than with morphine (Soergel et al., 2014). Two phase II randomized, double-blind and controlled trials were performed in patients with post-operative pain following bunionectomy (Viscusi et al., 2016) and abdominoplasty (Singla et al., 2017). The results obtained showed that oliceridine induces significant analgesia compared with placebo, with

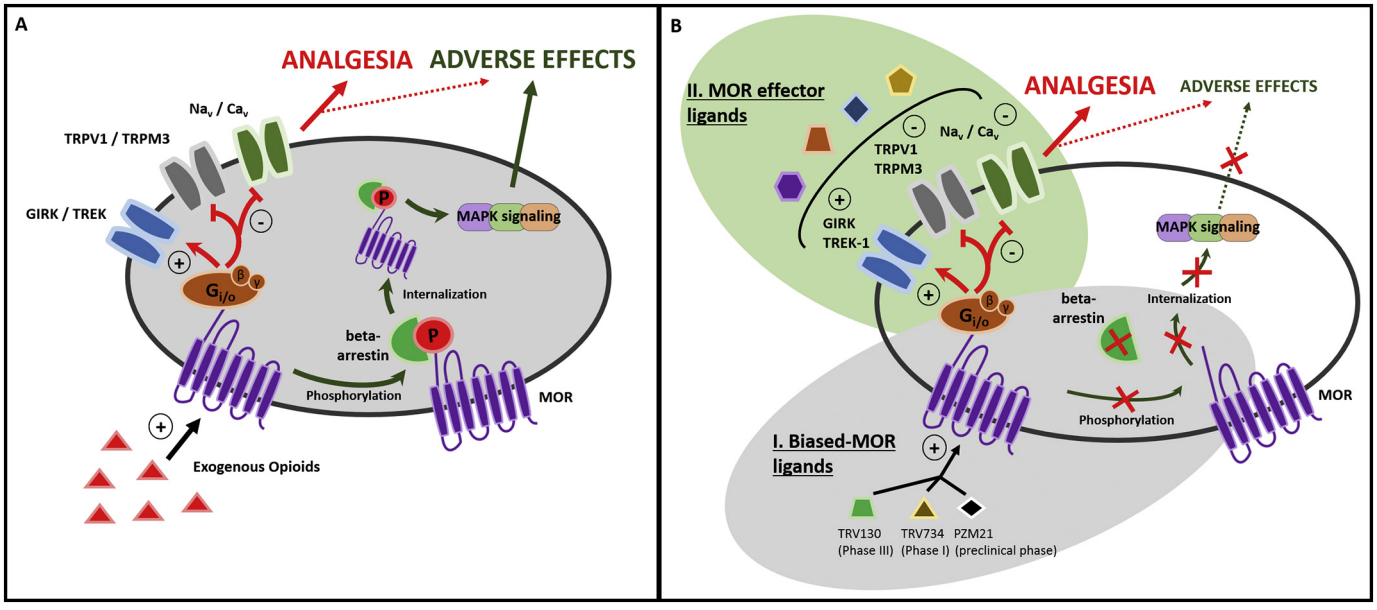

Fig. 2. Panel A) Mechanisms of opioid-induced analgesia / adverse effects. Activation of MORs by opioids induces dissociation of Gi/o proteins into Gαi/o and Gβγ subunits that inhibit and activate various ion channels (TRPV1, HCN, ASIC, Nav, Cav, TRPM3 and GIRK, K2P, respectively). These modulations of ion channels induce a decrease in neuronal excitability and underlie analgesia and adverse effects. In parallel, MOR activation induces its phosphorylation by G protein-coupled receptor kinase (GRK) and internalization after βarrestin binding to the phosphorylated site. Barrestin also activates the MAPK signaling pathway that contributes to opioid-related adverse effects. Panel B) New therapeutic strategies. I. Biased-MOR ligands. This therapeutic strategy is based on MOR agonists that activate the receptor and Gi/o complex with only limited βarrestin recruitment, thus reducing associated adverse events. II. MOR effectors ligands. Direct activation of the MOR-modulated ion channels by specific ligands (colored geometric shapes) is an alternative strategy to reduce G protein activation and βarrestin-dependent adverse effects, while maintaining analgesic efficacy.

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a faster (and stronger in the case of bunionectomy) effect than morphine. The tolerability of oliceridine, which did not induce severe adverse effects, was similar to that of morphine in patients who underwent bunionectomy while nausea, vomiting, respiratory effects were less frequent in patients treated with oliceridine who underwent abdominoplasty. Three recent phase III studies (Bergese et al., 2019; Singla et al., 2019; Viscusi et al., 2019) of patients with moderate-to-severe pain following surgery or with a painful non-surgical medical condition confirmed the significant dose-dependent analgesic effect of oliceridine versus placebo and showed that it was no less effective than morphine. In these studies adverse effects also increased dose-dependently, with no significant difference from those induced by equianalgesic doses of morphine. However, post-treatment rescue antiemetic use was significantly lower with oliceridine regimens than with morphine.

At the end of 2018, the FDA declined to approve oliceridine (from Trevena, Inc), citing safety concerns, particularly prolongation of the QT interval on the ECG, and depression of the respiratory drive. After carrying out studies, on QT in particular, Trevena looks forward to resubmitting a new drug application in the first quarter of 2020.

3.1.3. Drugs acting on MOR effectors

Biased agonists are still direct activators of MOR, which may explain why they retain some of the adverse effects of opioids. Another hypothesis is that compounds that would not interact with MOR but that would directly modulate MOR effectors specifically involved in the analgesic effect and not in the adverse side effects of opioids, would exert analgesic effects with a higher benefit/risk ratio.

3.1.3.1. MOR downstream cellular signaling. The binding of morphine to MOR results in the activation of a $G\alpha_{i/o}$ protein which inhibits adenylate cyclase, which in turn decreases intracellular cAMP levels (Crain & Shen, 2000; Crain, Shen, & Chalazonitis, 1988; Cruciani, Dvorkin, Morris, Crain, & Makman, 1993). Decrease in cAMP results in decreased PKA activity and subsequently alterations in numerous downstream PKA-dependent signaling cascades. Likewise, the Gβγ complex initiates various second messenger pathways (Emery & Eitan, 2019). The Gβγ subunit actively mediates certain negative effects associated with opioid treatment, including the reduction of acute analgesia (Bonacci et al., 2006) and the promotion of hyperalgesia (Bianchi, Norcini, Smrcka, & Ghelardini, 2009). Blocking Gβγ activity boosts opioid antinociception, blocks hyperalgesia, and attenuates tolerance and the development of dependence. This effect of Gβγ signaling appears to be mediated by the PLC pathway (Bianchi et al., 2009; Mathews, Smrcka, & Bidlack, 2008).

Downstream of these signaling pathways, inhibition of voltage-dependent Ca^{2+} and Na^{+} channels, ASICs and TRP channels has been reported and activation of K^{+} channels (Cai et al., 2014; Williams, Christie, & Manzoni, 2001) observed (Fig. 2B). Among these effectors, we selected ion channels, for which information is available on the impact of their modulation not only on analgesia but also on opioid-like adverse side effects. We carried out the following analysis bearing in mind that ion channels can be targets of interest because of their role as MOR effectors and because of their specific role in transmitting pain messages. Here, particular focus will be placed on their link with MOR.

3.1.3.2. Ion channel effectors of the MOR

3.1.3.2.1. Voltage-dependent calcium channels. Opioids regulate the activity of high-threshold L-(Cav1.x), N-(Cav2.2), P/Q-(Cav2.1), R-(Cav2.3) and low-threshold T-(Cav3.x) type voltage-dependent calcium channels (VDCCs) via the activation of opioid receptors (OR) and nociceptin/orphanin FQ (N/OFQ) opioid receptors (Abdulla & Smith, 1997; Kim, Rhee, & Akaike, 1997). The inhibitory effects of opioids on high-threshold VDCCs are acutely mediated by the activation of $G\alpha_{i/o}$ proteins (Kim et al., 1997) or by the direct interaction of Gβγ with the channel pore formed by the α subunit of the channel (Zamponi & Currie, 2013).

Up-regulation of L-type VDCC function is an important factor in the development of physical dependence on drugs of abuse such as ethanol, morphine, and nicotine (Little, 1991; Shibasaki, Kurokawa, Katsura, & Ohkuma, 2009; Walter & Messing, 1999). Repeated in vivo treatment with morphine induced an increase in Cav1.2 protein level in the mouse frontal cortex and limbic forebrain, and morphine-induced place preference was suppressed by an L-type VDCC antagonist (Shibasaki, Kurokawa, Mizuno, & Ohkuma, 2011).

While Cav2.1 channels play limited roles in afferent pain pathways (Bourinet et al., 2014), and opioid receptor effects are generally presumed to be inhibitory, activation of Cav2.1 is a common mechanism described for both MORs and DORs in several supraspinal structures (Iegorova, Fisyunov, & Krishtal, 2010; Margolis, Fujita, Devi, & Fields, 2017) whose pharmacological consequences need to be clarified.

Cav2.2 channels are almost exclusively expressed in neuronal tissue (Nowycky, Fox, & Tsien, 1985). Interactions have been demonstrated between Cav2.2 channels and all four members of the extended opioid receptor family (Beedle et al., 2004; Evans et al., 2010). Opiate analgesics inhibit presynaptic Cav2.2 channels in the spinal dorsal horn via $G\alpha_{i/o}$ protein coupled MOR (Heinke, Gingl, & Sandkühler, 2011; Khasabova, Harding-Rose, Simone, & Seybold, 2004; Wu, Chen, & Pan, 2004). MVIIA (ziconotide) is a specific inhibitor of the N-type calcium channel, Cav2.2, is currently used for the treatment of severe chronic pains in patients unresponsive to opioid therapy and is non-addictive (Vetter & Lewis, 2012). However, it produces severe side-effects, including dizziness, nystagmus, somnolence, abnormal gait, and ataxia (Sanford, 2013). Interestingly, taking into account that the cytoplasmic β subunits of Ca^{2+} channels increase the surface expression of the pore-forming α subunit of Ca^{2+} channel, Khanna and coworkers discovered a molecule able to bind to Cavβ and inhibit its coupling with Cav2.2 channels. This led to a reduction in Cav2.2 currents in rat dorsal root ganglion sensory neurons, which induced analgesia in both postsurgical and neuropathic pain models. Moreover, unlike ziconotide, this compound failed to induce akinesia after intracerebroventricular injection (Khanna et al., 2019).

Cav2.3 KO mice have been reported to show functional deficits in pain perception (Saegusa et al., 2000), suggesting that Cav2.3 channels contribute to pain transmission. It was also demonstrated that the genetic or pharmacological blockade of Cav2.3 channels (particularly supraspinal ones) resulted in enhanced morphine-induced analgesia and reduced morphine tolerance in mice (Yokoyama et al., 2004).

T-type calcium channels were found to exert a modulatory role in the acute and chronic actions of opioids, and T-type VDCC blockers (i.e., mibefradil) augment the antinociceptive effects of morphine, prevent the development of tolerance to its antinociceptive effects and suppress morphine withdrawal syndrome (Doğrul, Yeşilyurt, Işimer, & Güzeldemir, 2001; Dogrul, Zagli, & Tulunay, 2002; Park et al., 2010). In addition, T-type calcium channel membrane expression is dynamically regulated and increased under chronic pain conditions arising from nerve injury, diabetes, and chemotherapy agents (Bourinet et al., 2014). Thus, counteracting this aberrant upregulation may be an effective means of mediating analgesia (Francois et al., 2013).

3.1.3.2.2. Sodium channels. There is evidence that opioid agonists can inhibit voltage-dependent Na^{+} currents in an opioid receptor independent manner, acting directly on these channels (Joshi, Lamb, Bielefeldt, & Gebhart, 2003; Su, Joshi, Kardos, & Gebhart, 2002; Zou, Chen, Wu, & Zhou, 2000), but very few studies have reported Nav channel control by OR. It has been shown that the MOR agonist DAMGO inhibits PGE2-induced potentiation of tetrodotoxin-resistant sodium currents (TTX-R I_{Na}). It has also been demonstrated that the activation of MOR inhibits the voltage-dependent Na^{+} currents expressed in non-pyramidal neurons of the medial prefrontal cortex (Witkowski & Szulczyk, 2006), suggesting an involvement of this channel in opioid-induced mood regulation and drug dependence (Williams et al., 2001). Of note, Nav1.7

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has recently been identified as a regulator of opioid analgesic activity in mice and humans (Minett et al., 2015). Nav1.7 deletion has profound effects on the expression of several genes, which leads to an upregulation of the enkephalin precursor (Penk) mRNA and met-enkephalin protein in sensory neurons. Application of the opioid antagonist naloxone potentiates noxious peripheral input into the spinal cord and dramatically reduces analgesia in Nav1.7-null mutant mice and in a human Nav1.7-null mutant. A follow-up study demonstrated that both MORs and DORs are required for the opioid component of Nav1.7-null mutant analgesia (Pereira et al., 2018). These results could explain, at least in part, why Nav1.7 channel blockers alone do not replicate the analgesic phenotype of null mutant humans and mice (Deuis et al., 2017; Emery, Luiz, & Wood, 2016) and suggest that the co-administration of low dose opioids and specific Nav1.7 antagonists could have useful adverse-effect free analgesic effects.

3.1.3.2.3. Transient receptor potential channels. The transient receptor potential vanilloid type 1 (TRPV1), a non-selective cation channel activated by heat and involved in the transduction of noxious stimuli by nociceptive peripheral neurons (Caterina et al., 2000), is known as the receptor of the chili pepper alkaloid capsaicin. Capsaicin is used as an analgesic because after activating the channel, it induces its desensitization (O'Neill et al., 2012). In addition, new TRPV1 antagonists with an optimized benefit/risk ratio, avoiding hyperthermia, are currently being developed (Andreev et al., 2013; Lehto et al., 2008; Reilly et al., 2012; Voight et al., 2014).

TRPV1 activity can be regulated by MOR (Endres-Becker et al., 2007; Vetter, Wyse, Monteith, Roberts-Thomson, & Cabot, 2006). This channel has been involved, at least in part, in morphine-induced acute antinociception and the development of morphine tolerance and dependence (Rowan et al., 2014; Viola Spahn et al., 2013; Vardanyan et al., 2009). Indeed, increased TRPV1 expression has been observed in both the peripheral and central nervous systems of rodents following chronic morphine administration (Chen, Geis, & Sommer, 2008; Vardanyan et al., 2009) and also in peripheral neurons in a murine bone cancer pain model (Niiyama, Kawamata, Yamamoto, Omote, & Namiki, 2007), which is substantially resistant to morphine analgesia. TRPV1 antagonists also attenuated morphine tolerance and associated thermal hyperalgesia (Chen et al., 2008; Nguyen, Nam, Lee, Kim, & Jang, 2010) and withdrawal symptoms in morphine-dependent mice (Nguyen et al., 2010).

Transient receptor potential melastatin 3 (TRPM3) channels are thermosensitive nociceptor channels involved in the detection of noxious heat (Vriens et al., 2011), and inhibitors of TRPM3 channels have strong anti-nociceptive properties (Chen, Chen, Qian, Fang, & Zhu, 2014; Krügel, Straub, Beckmann, & Schaefer, 2017; Straub et al., 2013; Suzuki et al., 2016). It was recently observed that local activation of peripheral MORs causes strong analgesia by inhibiting TRPM3 channels via a short signaling cascade involving Gβγ proteins (Dembla et al., 2017). The same mechanism of action has been seen with other GPCR-mediated pain killing drugs (Badheka, Borbiro, & Rohacs, 2015; Quallo, Alkhatib, Gentry, Andersson, & Bevan, 2017). These results support TRPM3 as a major target of an intracellular signaling cascade initiated by activated MORs at the peripheral level. Direct pharmacological inhibition of TRPM3 channels could therefore be a feasible alternative to MOR agonists.

3.1.3.2.4. Potassium channels. G protein activated inwardly rectifying K^+ (GIRK) channels, particularly GIRK2 subunit expressing channels, are involved in pain perception (for a review see (Lüscher & Slesinger, 2010) and are involved in the acute analgesic effect of morphine (Ikeda, Kobayashi, Kumanishi, Niki, & Yano, 2000; Marker, Stoffel, & Wickman, 2004; Mitrovic et al., 2003). However, studies using the GIRK-channel inhibitor tertiapine (Devilliers et al., 2013; Marker et al., 2004) or GIRK KO mice (Cruz et al., 2008; Marker et al., 2004) demonstrated that these channels play only a partial role in the antinociceptive effect mediated by high doses of morphine. Also, another study observed that morphine analgesia was mostly preserved in mice lacking both GIRK2 and GIRK3. However, the morphine withdrawal syndrome induced by naloxone was strongly attenuated in these animals (Cruz et al., 2008). On the basis of a combination of biochemical, histological, and electrophysiological approaches, it has also been suggested that GIRK signaling could be a pathway involved in the abusive effects of morphine (Nassirpour et al., 2010). Of note, GIRK channels have been shown to be involved in opioid-induced respiratory depression (Montandon et al., 2016) and impairment of the upper airways (Levitt, Abdala, Paton, Bissonnette, & Williams, 2015). Despite years of GIRK research, very few tools exist to selectively modulate the activity of GIRK channels. To our knowledge, only one GIRK activator has been shown to exert an analgesic effect in the formalin test after injection of a single dose (Abney et al., 2019). More work is needed to ascertain the analgesic potential of GIRK activators and to assess their safety profile.

The TWIK-related potassium channel 1 (TREK-1) is another downstream effector of MOR (Devilliers et al., 2013). TREK-1 is a member of the K2P channel family (Bayliss & Barrett, 2008; Enyedi & Czirják, 2010; Lesage & Lazdunski, 2000; Lesage, 2003; Maingret et al., 2000; Mathie & Veale, 2007; Patel et al., 1998) involved in polymodal pain perception (Alloui et al., 2006; Noël et al., 2009) and in pain pathophysiology (Descoeur et al., 2011). It is noteworthy that although the TREK-1 K^+ channel is a crucial contributor of morphine-induced analgesia in naive mice and in several pathological contexts, it is not involved in several morphine-induced adverse effects such as constipation, respiratory depression, dependence (Devilliers et al., 2013) and abuse liability, as measured by the conditioned place preference (CPP) test (Mirkovic, Palmersheim, Lesage, & Wickman, 2012). These observations suggest that direct activation of the TREK-1 K^+ channel, acting downstream from MOR, could have strong analgesic effects without opioid-like adverse effects. A number of pharmacologically active compounds enhance the activity of TREK-1 channels (Mathie & Veale, 2007; Vivier, Bennis, Lesage, & Ducki, 2016) but most, if not all, of these compounds are non-selective for TREK-1 channels. At least one of them, riluzole, has demonstrated analgesic effects in several pathological contexts in rodents and it has recently been shown that its analgesic effect is lost in TREK-1 KO mice (Poupon et al., 2018). A series of novel molecules able to activate TREK-1 and displaying potent anti-nociceptive activity has recently been synthesized (Rodrigues et al., 2014; Vivier et al., 2017). The furyl analogue 36 is the most promising of these series since it exerts antinociceptive activity in naive mice, and is effective in relieving inflammatory and neuropathic hypersensitivity in rodents. This effect is strongly reduced in TREK-1 KO mice and in mice treated with the TREK-1 blocker spadin. In parallel, it failed to induce respiratory depression, constipation, dependence or sedation (personal unpublished data).

3.1.4. Peripherally acting MOR agonists

Another strategy of replacing current opioid drugs while ensuring a better benefit/risk ratio and reducing, in particular their main CNS adverse effects is to develop compounds with only peripheral opioid action (Fig. 3). The prerequisite for the success of this strategy is the existence of a peripheral endogenous opioid system. In addition to their neuronal expression, endogenous opioids are expressed in neuroendocrine tissues and granulocytes, monocytes/macrophages and lymphocytes (Stein & Machelska, 2011). Released from immune cells in painful tissues, they activate the opioid receptors present on nociceptors, including MORs that are up-regulated in these (inflammatory or peripheral neuropathic) situations, and thus constitute an endogenous pain control system at the source of pain generation. Several changes observed in inflamed/injured tissues facilitate this role: the sprouting of opioid receptor-bearing peripheral sensory nerve terminals; a disrupted perineural barrier facilitating the access of opioid agonists to their receptors and a decrease in tissue pH (Stein, 2018), which increases opioid agonist efficacy (Stein & Machelska, 2011).

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Several animal studies have demonstrated an analgesic effect of peripherally administered exogenous opioids (Jagla, Martus, & Stein, 2014; Stein & Machelska, 2011). Interestingly, a recent study (Spahn et al., 2017) led to the synthesis of a fentanyl derivative (NFEPP) designed to selectively activate MOR only at low pH. NFEPP, with a low PKa close to the pH of injured tissue, produced peripheral, injury-restricted analgesia in rat models of inflammatory and postoperative pain (i.e. in tissue with low pH), with no accompanying respiratory depression, sedation, constipation, or addiction potential. This was confirmed by the same team in models of neuropathic (CCI model) and abdominal pain (writhes due to acetic acid administration) with damaged tissue (Rodriguez-Gaztelumendi, Spahn, Labuz, Machelska, & Stein, 2018). However, another fentanyl derivative (FF3) with a PKa not low enough to restrict its activity to injured/acidic tissue induced analgesia but with opioid-like adverse effects at high doses, similar to well-tolerated doses of NFEPP (Spahn et al., 2018). Thus, it was suggested that "the pKa of a [opioid] ligand should be close to the pH of the injured tissue (as shown for NFEPP) to obtain selective peripheral analgesia without side effects".

Another strategy has recently been developed that uses the attachment of morphine to hyperbranched polyglycerol. This conjugate of high-molecular weight and hydrophilicity, administered intravenously, selectively induced analgesia on the inflamed paw in a naloxone methiodide-dependent manner, without inducing constipation or sedation (González-Rodríguez et al., 2017). All these results justify proposing the pain tissue-specific activation of opioid receptors as a new pharmacological pathway. Clinical studies should be carried out as soon as the various compounds are available for human testing.

In humans, the local administration of opioids has been shown to induce analgesia, as demonstrated with intra-articular morphine (whose effect was reversed by naloxone) in the princeps paper of Stein et al., (Stein et al., 1991) and in a meta-analysis of 15 randomized clinical trials comparing the effect of an intra-articular single dose of morphine administered at the end of arthroscopic knee surgery with that of bupivacaine (Wei et al., 2014). The M6G metabolite of morphine administered intravenously was found to be as active as morphine over the first 24 h postoperatively (Hanna, Elliott, & Fung, 2005) and its analgesic efficacy was similar to that of morphine at later time points albeit less during the first four post-operative hours (Binning et al., 2011). An analgesic effect of M6G was also observed in experimental pain models (Tegeder et al., 2003). The limited diffusion capacity of M6G through the blood brain barrier led some authors to consider it to act peripherally, confirming the ability of mu opioid receptor agonists to induce peripheral opioid analgesia. However, an earlier animal study showed that naloxone inhibited the analgesic effect of the subcutaneous administration of M6G whereas naloxone methiodide, which does not diffuse through the blood brain barrier, failed to modify it (Wu, Kang, Bickel, & Pardridge, 1997). In addition, the hypothesis of an analgesic action of opioid receptor agonists, administered peripherally, was contradicted by the work published by Picard, Tramèr, McQuay, & Moore, 1997 (Picard et al., 1997). They performed a meta-analysis of 22 clinical trials conducted on patients with acute surgical pain to assess the efficacy of opioids administered peripherally at various sites (except the joints) and concluded that the trials provided no evidence of clinically relevant analgesic efficacy. Stein and Machelska (Stein & Machelska, 2011) considered this negative result to be due to the perineural administration of opioids along non-injured nerves. However, in two negative studies included in the meta-analysis, opioids were administered in a tooth socket or in a surgical wound. Another study (Aykaç, Erolćay, Dikmen, Oz, & Yillar, 1995) reported positive results after the intrapleural

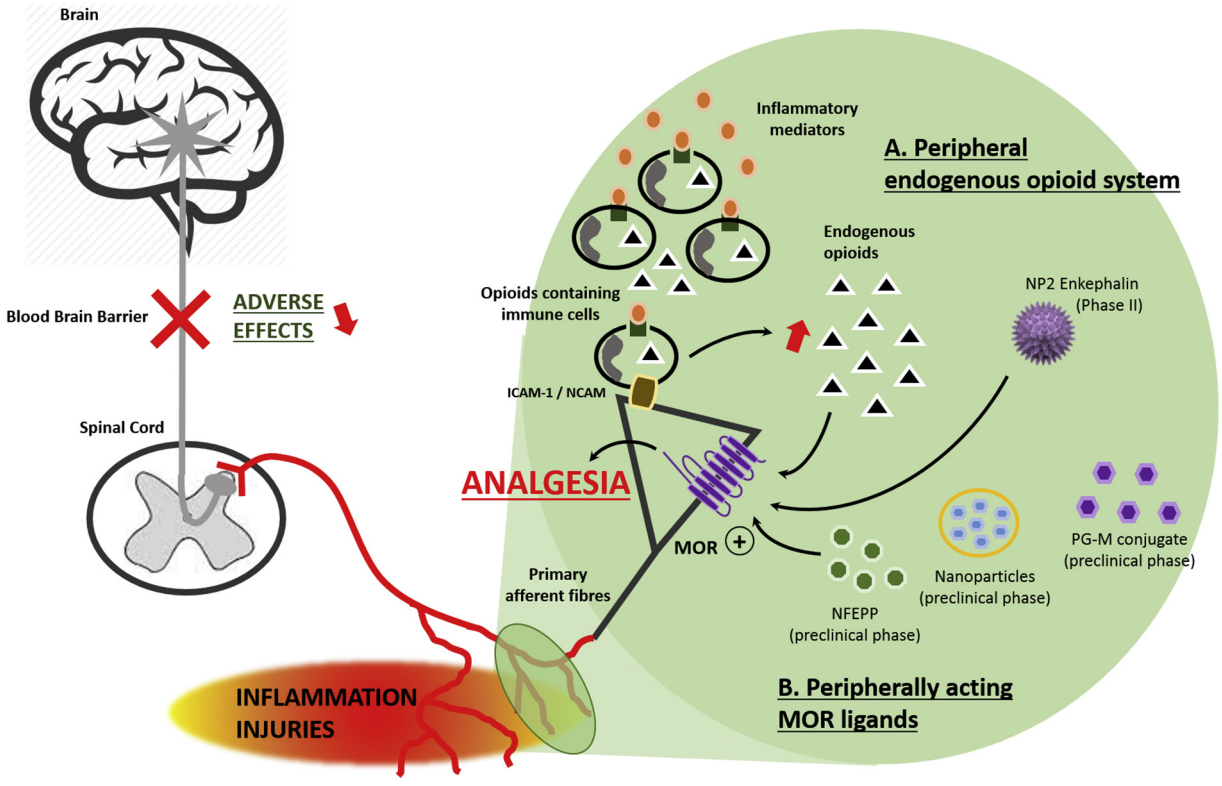

Fig. 3. Therapeutic strategies involving peripheral MORs. A. Peripheral endogenous opioid system. In a context of inflammation and/or tissue injury, inflammatory mediators activate opioids-containing immune cells, present in the tissue and blood stream, inducing the release of endogenous opioids. Activated immune cells are also able to bind nerve fibers via ICAM-1 / NCAM receptors, which increases the opioids release in the vicinity of peripheral nerve fibers terminals, providing analgesia. B. Peripherally acting MOR ligands. The vast majority of opioid-related adverse effects are due to central effects. A promising therapeutic strategy is to use MOR ligands acting only in peripheral tissues in order to limit central adverse effects while maintaining some analgesic effects. PG-M: polyglycerol-morphine.

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administration (for thoracotomy) of a high dose of morphine (20 mg). But Picard et al., (1997) considered the outcome of this study to be of little clinical relevance because of the unconventional (high) dose of morphine used.

To conclude, despite the divergence of certain data, it seems legitimate to consider that opioids administered or distributed locally in acidic/inflammatory painful tissue could have an analgesic effect and could be a good strategy for providing significant analgesia while avoiding the adverse effects of conventional opioids. However, clinical studies are needed to assess the efficacy of compounds designed to target injured tissues with lowered pH.

3.1.5. Other strategies

Two different strategies, still aiming at improving the benefit/risk ratio of current MOR agonists, remain to be discussed. The first is based on the assumption that the more rapidly a drug reaches efficacious levels in the brain to relieve pain the more rapid is the onset of additional CNS effects. Limiting the entry speed could reduce the risk without affecting analgesic activity, which could even be prolonged (Fig. 4A). Accordingly, NKTR-181 was designed from the oxycodone molecule with a polyethylene glycol side chain grafted onto it. This new compound has a penetration rate in the brain of rats 17 to 71 times lower than that of oxycodone. Orally administered, it has an analgesic effect in mice 30 times less powerful than that of oxycodone but with a longer duration (about 4 times) (Miyazaki et al., 2017). In addition, NKTR-181 has an improved therapeutic ratio for CNS adverse effects compared with oxycodone, with reduced abuse potential and behavioral effects.

In humans, a study performed in randomized healthy, adult, non-physically dependent recreational opioid users showed that while oxycodone produced rapid and strong drug-liking effects indicative of high abuse potential, NKTR-181, at the highest dose, had only a slightly different effect from that of placebo (Webster et al., 2018). Moreover, scores for nausea and somnolence for all doses of NKTR-181 were not statistically different from those of placebo and lower than those for oxycodone.

Another study (SUMMIT-07) performed in randomized adults with moderate-to-severe chronic low-back pain refractory to nonopioid analgesics, showed a significant and maintained (12 weeks) analgesic efficacy of NKTR-181 vs placebo (Markman et al., 2019). The most common adverse effects were nausea, constipation and vomiting with a higher incidence than in the placebo group. An open-label phase III study evaluated the 52-week, long-term safety of NKTR-181 in subjects (opioid-naive and opioid-experienced) with moderate-to-severe chronic low back pain or CNCP (Gudin et al., 2019). The safety profile was generally consistent with results obtained in the SUMMIT-07 phase III clinical trial (Markman et al., 2019). The abuse potential of NKTR-181 was assessed in two phase III clinical trials with a newly developed reporting system, the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS®)(Gudin et al., 2019; Lanier et al., 2019) that discerns potentially abuse-related events. In the two trials it identified low rates of withdrawal and a low risk of abuse potential, diversion or addiction associated with NKTR-181.

The other strategy we would like to highlight is the development of ligands targeting MORs and the other opioid receptors individually and/or as heteromers (Fig. 4B). Given the focus of this article on MORs alone, we will just mention a few examples. Eluxadoline, a novel MOR agonist / DOR antagonist, (and KOR agonist), has been developed for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D). In phase III studies, it reduced abdominal pain, significantly vs placebo (Brenner et al., 2019; Lacy et al., 2019; Lembo et al., 2016). A subgroup analysis of phase III trials (Lacy et al., 2019) suggests that eluxadoline is effective in treating IBS-D across a range of commonly encountered patient types and that patients aged ⩾65 years had a greater proportion of responders at the lower, approved, 75 mg eluxadoline dose. CYM51010, a MOR-DOR heteromer-biased agonist induced, in animals, an antinociceptive effect similar to that of morphine but lesser antinociceptive tolerance and less severe signs of naloxone-

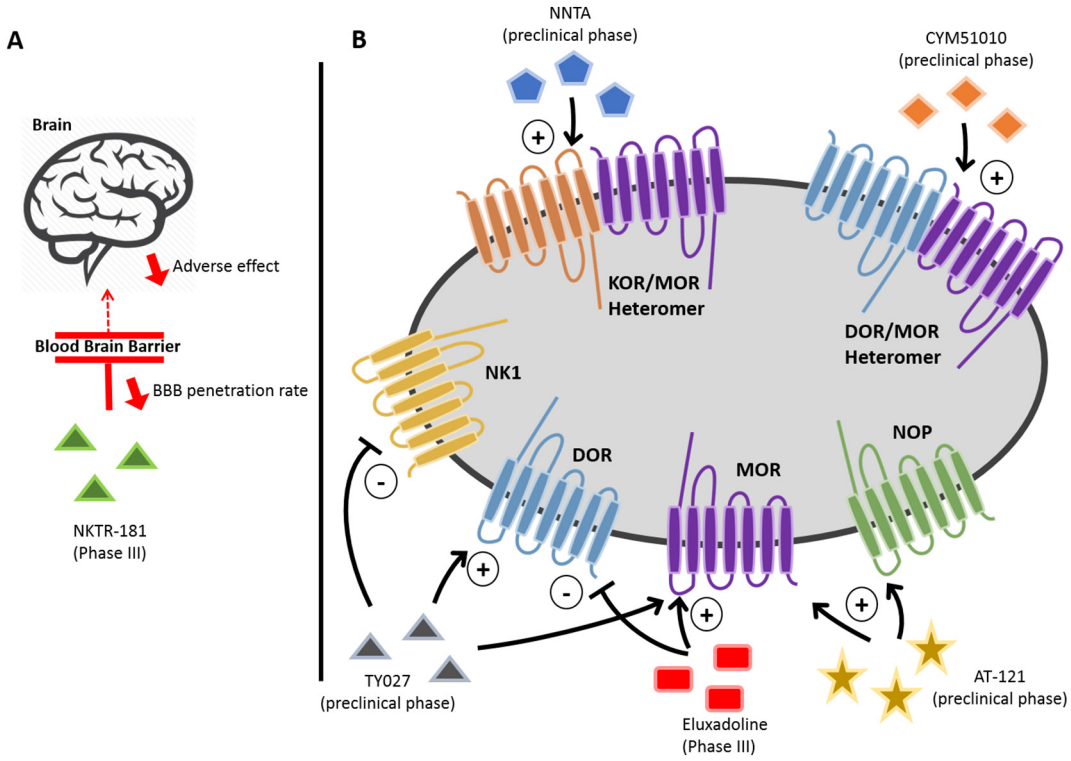

Fig. 4. Other strategies. Panel A: Limiting the rate at which effective levels are reached in the brain to relieve pain, in order to reduce adverse effects and prolong the analgesic effect. Panel B: Targeting heteromers or using multifunctional ligands to potentiate analgesic effect.

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precipitated withdrawal (Gomes et al., 2013). N-naphthoyl-β-naltrexamine (NNTA), designed to act as an activator of MOR-KOR heteromer, produced analgesia in mice but neither significant physical dependence nor place preference in the ED50 dose range (Yekkirala et al., 2011). However, it was only evaluated after central (intrathecal or intracerebroventricular) administration. Among the several compounds that are MOR and DOR agonists and NK1 receptor antagonists, TY027 reduces hyperalgesia in mice and rats without producing analgesic tolerance, reward, naloxone-precipitated withdrawal, vomiting or inhibition of the gastrointestinal transit (Largent-Milnes et al., 2013). Finally, bifunctional agonists of MOR and nociceptin/orphanin FQ peptide (NOP) receptors have been developed (Fig. 4B), which increase the pain-relieving properties and decrease the addictive properties of MOR agonists. A novel partial MOR-NOP receptor agonist has been designed to obtain an analgesic compound devoid of the rewarding effect observed with previously designed bifunctional agonists. It induced antinociceptive and anti-allodynic effects in monkeys, as determined by thermal and capsaicin tests, respectively, and failed to induce opioid-like adverse effects such as respiratory depression, abuse potential, opioid-induced hyperalgesia and physical dependence (Ding et al., 2018).

3.2. Strengthening endogenous opioid mediators

The endogenous opioid system, first discovered in 1975 with Met- and Leu-enkephalin (Hughes, Smith, Morgan, & Fothergill, 1975), consists of several families of peptides (endorphins, enkephalins, dynorphins, endomorphins 1 and 2, nociceptin) whose genes encoding the precursors of the first three peptides, which are ligands for MORs, DORs and KORs, were discovered in humans in the 1980s (Chang, Hazum, & Cuatrecasas, 1980; Horikawa et al., 1983; Noda et al., 1982). Endogenous mediators and their receptors are present along the entire pathway of the nociceptive message: at the periphery on the nociceptor, in the spinal cord and in the brain. Enkephalins (Met- and Leu-enkephalin) are specifically endowed with antinociceptive activity: they activate MORs and DORs (Takei, Ando, & Tsutsui, 2015). This effect was demonstrated by Belluzzi et al. (1976) shortly after the discovery of Met- and Leu-enkephalin in the pig brain and their ability to activate opioid receptors (Hughes et al., 1975). These studies were followed by others using enkephalin (Brady & Holtzman, 1982) and preproenkephalin-deficient mice (Noble, Benturquia, Bilkei-Gorzo, Zimmer, & Roques, 2008) that confirmed their antinociceptive effect. For example, endogenous opioids that are upregulated in the spinal cord following peripheral injury (Lai, Luo, Chen, & Porreca, 2008; Podvin, Yaksh, & Hook, 2016; Xu et al., 2004) or released in the anterior cingulate cortex during sustained pain experiences (Borras et al., 2004; Zubieta et al., 2005) provide inhibitory regulation of pain in its somatosensory and emotional dimensions. This endogenous analgesic activity was seen in post-operative pain conditions in patients in whom a hyperalgesic effect of naloxone had been observed (Levine, Gordon, Jones, & Fields, 1978; Pereira et al., 2015).

It was therefore legitimate to aim to strengthen this endogenous system, at one site or another of the pain pathways/centers, in order to achieve an analgesic effect either by acting on the mediators' metabolism or by administering the endogenous mediator itself, ideally in a targeted way.

3.2.1. Reducing enkephalin degradation

Enkephalins are catabolized by two major enzymes, the neutral endopeptidase neprilysin (NEP) and the aminopeptidase N (APN), into inactive metabolites. The inhibition of these enzymes induces an antinociceptive effect, as initially shown by Roques and co-workers (Roques et al., 1980), who demonstrated the ability of thiorphan, an NEP inhibitor, to significantly increase the antinociceptive effect of D-Ala2 -Met5-enkephalin and to induce a naloxone-reversible antinociceptive effect in the hot plate test.

Work on these inhibitors has intensified and led to molecules known as DENKIs (Dual ENKephalinase Inhibitors), which target both enzymes, (Raffa et al., 2018; Roques, Fournié-Zaluski, & Wurm, 2012) (Fig. 5). The various inhibitors designed (kelatorphan, PC12, RB 101, RB 120, RB3007, PL37, PL265) had an analgesic effect in mice and rats (healthy animals and models of inflammatory or neuropathic pain) subjected to nociceptive stimuli (Bonnard et al., 2015; Chen, Noble, Roques, & Fournié-Zaluski, 2001; Roques et al., 2012). This effect was related to their ability to reduce the degradation of enkephalins (Daugé, Mauborgne, Cesselin, Fournié-Zaluski, & Roques, 1996; Le Guen et al., 2003), a mechanism confirmed by the loss of their analgesic effect in preproenkephalin KO mice (Noble et al., 2008) and after the co-administration of naloxone with kelatorphan (Kayser, Fournie-Zaluski, Guilbaud, & Roques, 1989) or naloxone methiodide with PL265 (Bonnard et al., 2015). In addition to their shared ability to inhibit NEP and APN, DENKIs have different capabilities of crossing the blood-brain barrier (RB101, RB120, PL37 at high doses) or not (Kelatorphan, PL265). Some DENKIs (PL37, PL265) are active after oral administration. In addition, in accordance with the induction of analgesia through the activation of peripheral opioid receptors (Stein, 2018), it has been shown that DENKIs such as PL37 or PL265 have a peripheral effect inhibited by naloxone methiodide (Bonnard et al., 2015; Menéndez et al., 2008).

The discovery of opiorphine occupies a special place in the context of "natural" pharmacology. Opiorphine is a DENKI found in human saliva (Wisner et al., 2006) whose prolonged, naloxone-reversible analgesic effects were demonstrated by various tests after systemic (Popik, Kamysz, Kreczko, & Wróbel, 2010; Rougeot, Robert, Menz, Bisson, & Messaoudi, 2010; Wisner et al., 2006) and intra-cerebroventricular (Tian, Chen, Xiong, He, & Chen, 2009) administration and in a post-surgical animal model of pain (Sitbon et al., 2016) with no occurrence of opioid-like adverse events (Popik et al., 2010; Rougeot et al., 2010; Sitbon et al., 2016). A chemically stable opiorphin analog, STR-324, which crosses the blood-brain barrier, had similar effects in a post-operative pain model (Sitbon et al., 2016) and a neuropathic pain model (Van Elstraete et al., 2018). To conclude, there is preclinical evidence of the analgesic action of DENKIs that has the advantage of strengthening an endogenous analgesic system. It should not be forgotten, however, that NEP induces the metabolism of pain-producing inflammatory peptides such as bradykinin and substance P (Campbell, 2017).

From a clinical point of view, two pharmaceutical companies are developing these two types of DENKIs and have carried out or are planning clinical studies of neuropathic (a phase II study has been performed) and post-operative pain. Previous work showed that, when jointly administered by the intrathecal route, thiorphan, an enkephalinase inhibitor, and bestatin, an aminopeptidase inhibitor, elicited potent, reproducible, and long-lasting analgesia in terminally ill cancer patients who were unresponsive to morphine (Meynadier, Dalmas, Lecomte, Gros, et al., 1988).

Regarding the potential adverse effects of this strategy, although DENKIs do not seem to induce opioid-like adverse effects (in particular because of their action, which is considered to be localized at the sole site of increased enkephalin secretion), the risks of other types of adverse effects due to chronic inhibition of NEP should be taken into account because of the role of NEP in the degradation of many bioactive peptides (Campbell, 2017). It would be useful to analyze results in humans of the first dual-acting angiotensin-receptor–NEP inhibitor following its approval by the FDA in 2015 for the treatment of heart failure.

3.2.2. Using endogenous opioids as drugs

Another way to strengthen the effects of endogenous opioids would be by direct administration. As these peptides degrade rapidly, protection strategies must be found to make them viable as a therapeutic solution (Fig. 3).

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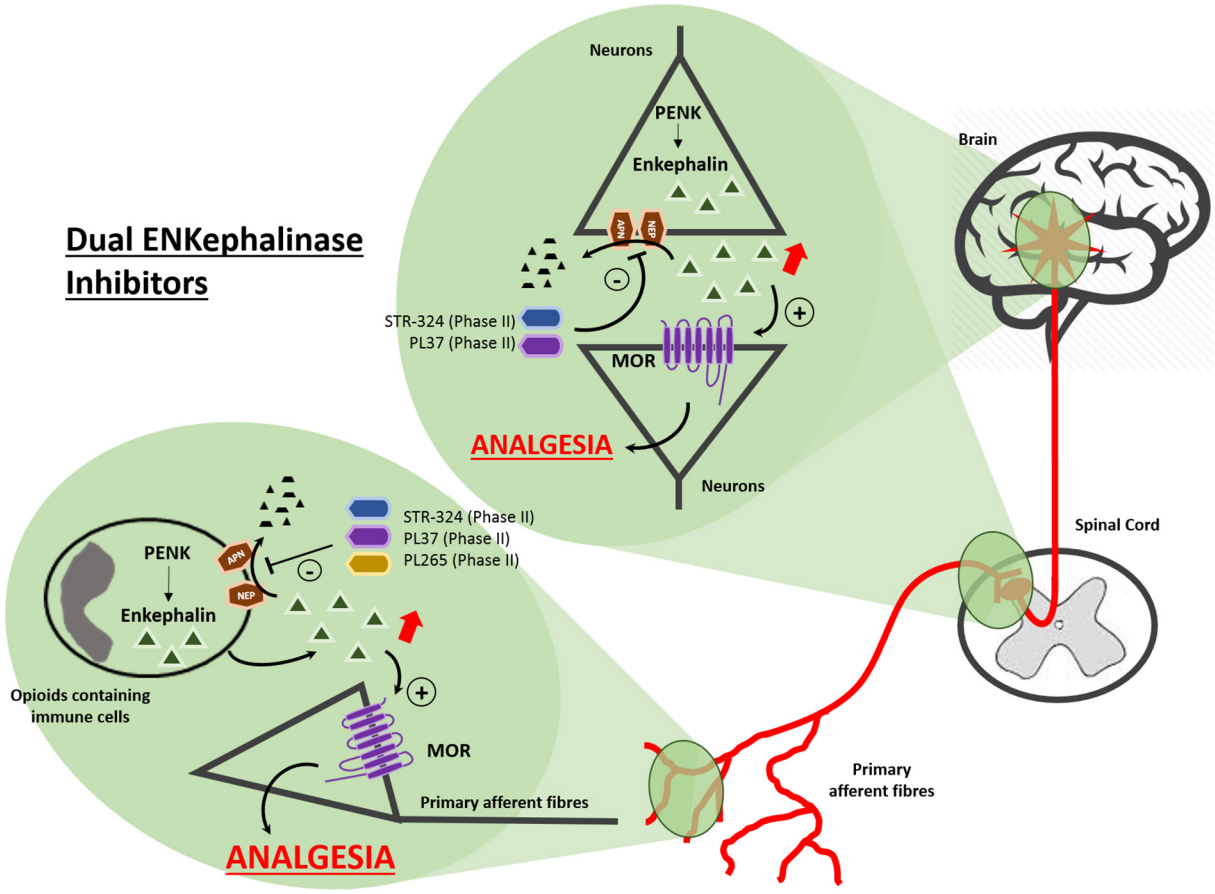

Fig. 5. Therapeutic strategies involving Dual-enkephalinase inhibitors (DENKIs). Endogenous opioids are cleaved and inactivated by APN / NEP enkephalinases mainly expressed on immune cells at the periphery and presynaptic neurons in the central nervous system. In painful situations, DENKIs reduce the cleavage of endogenous opioids and increase their local concentration inducing analgesia. This action occurs at the central and/or peripheral level depending on the biodistribution of the compounds.

The design of nanoparticles combined with squalene, whose effects were recently documented (Feng et al., 2019), is one possible solution. It has been shown that the integration of Leu-enkephalin into nanoparticles can have an anti-hyperalgesic effect in an inflammatory pain model after intravenous administration. The effect of two of the preparations used was of a duration comparable to that of morphine (around 70 min) and more prolonged (around 130 min) for one other, nanoparticles being still present 24 h after injection. In all cases, the effect was inhibited by naloxone methiodide, suggesting a peripheral opioidergic action consistent with the much higher distribution of nanoparticles at the inflammatory area. This interesting and novel result needs to be confirmed under other experimental conditions, by testing with other doses. The dose of Leu-enkephalin used was 10 times higher than that of morphine (11.48 mg/kg vs 1 mg/kg) and was also high with regard to the nanomolar affinity of the peptide for opioid receptors (Kosterlitz, Lord, Paterson, & Waterfield, 1980). However, the limited distribution of the nanoparticle outside the inflammatory zone could help to obtain a good adverse reaction profile, although this remains to be confirmed. Of course, this interest in the targeting capabilities of nanoparticles can be applied to exogenous opioids, the key point being probably more the specific targeting than the nature of the ligand (Hua & Cabot, 2013; Li, Qiao, Lu, & Liu, 2014).

No clinical trial has yet been performed with enkephalin integrated into nanoparticles. However, a study of a small patient sample ($n = 10$) suffering from cancer-related chronic pain (Fink et al., 2011) showed that intradermal injection of NP2 Enkephalin (NP2 is a gene transfer vector engineered to express human preproenkephalin) induced analgesia at the two highest doses used with good tolerability. Such a strategy based on gene therapy was positively assessed in animals (for a review see (Guedon et al., 2015).

Pending the possible availability to the patient of all the compounds mentioned above and given the scale of the opioid crisis, it would be useful to consider ways of reducing the risks of abuse and misuse resulting from the dependence that they can cause. Possible initiatives are suggested in the following paragraph.

4. Can we limit abuse and misuse as factors contributing to opioid use disorder?

The considerable increase in the prescription of opioids over the past few decades has been accompanied by an increase in misuse and abuse behaviors that have led to unintentional intoxication and death (Shipton et al., 2018). This trend began, as mentioned above, in the United States, before gradually spreading to most industrialized countries (Chenaf et al., 2016; Gallagher & Galvin, 2018; Manchikanti et al., 2012) and to several developing countries in Africa and Asia (UNDOC, 2018). Although European countries are not currently facing a crisis of the same magnitude as in North America or Australia (Häuser et al., 2017; Van Amsterdam & Van den Brink, 2015), various pharmacovigilance signals have emerged, particularly in Northern Europe, and are attracting the attention of health authorities (*État des lieux de la consommation des antalgiques opioïdes et leurs usages problématiques*, 2019; *European Drug Report 2018: Trends and Developments*, 2018).

The magnitude of the opioid crisis requires us to consider what improvements must be made to limit the phenomenon, its progressive spread and its consequences, particularly abuse and misuse. Two main

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non-pharmacological strategies must be discussed: first, the quality of the doctor-patient relationship and second, the issue of galenic innovation. At the same time, there should be discussion of the relevance of the development and prescription of abuse-deterrent formulations.

Regarding the doctor-patient relationship, the role of practitioners raises questions about their training in the management of opioid analgesics and the lack of information provided to the patient regarding the treatment prescribed to them. Due to their high risk of serious adverse effects and their addictive potential, these treatments should only be prescribed with full knowledge of and compliance with their indications. Even in these conditions, the efficacy, tolerance, and relevance of the therapies should be regularly assessed, without which their deprescription should be considered. However, de-prescription is not innocuous since it implies withdrawing treatment that is insufficiently effective or poorly tolerated without the prescriber being necessarily able to offer other therapeutic options to the patient. In addition, deprescribing an opioid analgesic sometimes requires the use of withdrawal strategies, which potentially involves substitution treatments. This could be difficult to manage for practitioners unused to dealing with addiction, whose task would be eased by improved accessibility of care provided in specialized addiction centers.

Another area of reflection concerns the quality of the interview before prescription of an opioid analgesic. Psychiatric and/or addictive comorbidities are well-known factors of vulnerability to the onset of substance use disorders. These comorbidities, which are frequently associated with chronic pain, need to be identified and require the prescriber's attention. A quality medical history would allow patients to be stratified according to their misuse and abuse risk level so as to assess the relevance of prescriptions and to adapt monitoring of the proper use of opioids. From the first prescription, the patient must be informed of the treatment risks and the measures to be taken to avoid them. This particularly concerns the risk of dependence and progressive tolerance that occurs with long-term opioid exposure. These events can potentially lead to an increase in the doses taken, with the resulting risk of overdoses and death. These elements have been reaffirmed in many guidelines, including recently updated ones, on the use of opioid analgesics in chronic pain outlined above.

The psychological suffering frequently induced by chronic pain is another factor that can be involved in the onset of prescription opioid use disorder. The psychotropic effect induced by opioids can lead to a perception of partial relief of mental suffering, which in turn can sometimes lead to diversion and overuse of the opioid prescribed in order to increase relief (Volkow & McLellan, 2016). This gradual increase in dosage, combined with the tolerance phenomenon, can induce negative (by reducing the pain stimulus) and positive (by a psychotropic effect) reinforcement, if opioids are given repeatedly (Ewan & Martin, 2013). This operant conditioning could be the cause of the craving described by users of opioid analgesics, which can be defined as an emergency to consume the substance in order to feel its analgesic and psychotropic effects (Miguez, Laborda, & Miller, 2014; Volkow & McLellan, 2016).

The second strategy designed to reduce the risk of abuse and misuse is galenic innovations in the development of abuse-deterrent formulations. However, their relevance is not always apparent. They remain poorly prescribed, allow only a partial limitation of diversion, and involve a now confirmed risk of transfer to other non-abuse-deterrent formulations or illegal opioids such as heroin, which have dropped in price (Cicero & Ellis, 2015; Litman, Pagán, & Cicero, 2018).

5. Conclusion

This focus on the replacement of MOR agonists, the vast majority of opioid drugs currently available on the market, raises hope for the commercialization of new compounds in the more or less long term. Pharmacological targeting of MOR splice variants is a promising strategy for the development of safer opioids but for the moment biased agonists are the most advanced products under development with a phase III study of post-operative pain with oliceridine currently in progress. However, the FDA considered that the benefit/risk ratio of oliceridine was not optimal and its re-evaluation is pending. DENKIs were developed some time ago and were evaluated in a Phase II study, whose results have not yet been published and so it is not possible to assess their actual contribution to the pharmacopoeia, particularly for neuropathic pain. The use of (exogenous or endogenous) opioid ligands having peripheral action could be of interest, particularly molecules targeting tissues damaged by acidic substances, thanks to their low PKA, and nanoparticles including exogenous or endogenous opioids. Clinical studies are expected to be made. Ligands of ion channels such as TRPM3 and TREK-1, which contribute to the analgesic activity of opioids downstream of MOR activation, are also targets of potential interest. Hence, direct modulation of these effectors, thus bypassing MOR activation, should result in analgesic effects but devoid of opioid-like adverse effects, as demonstrated for TREK1 activators. Finally, a better benefit/risk ratio can also be achieved by agonists of several opioid or non-opioid receptors or by mu agonists with a slower entry to the CNS. Thus, eluxadoline (a MOR agonist and DOR antagonist, Fig. 4B) and NKTR-181 (a MOR agonist with a slow rate of CNS entry, Fig. 4A) have shown their efficacy in patients with IBS (eluxadoline is approved by both the FDA and EMA) and chronic low back pain, respectively.

The interest of having multiple targets at our disposal is that they could together open up the pharmacopoeia to new concepts, as would agonists of delta and kappa opioid receptors, not mentioned here but some of which are currently under development. This broadening of the spectrum is desired to ensure effective analgesia that can (probably through conceptually different molecules) help in the management of different pain syndromes while providing a good benefit/risk ratio. The renewal of the pharmacopoeia of painkillers is an urgent necessity that should allow the most personalized prescriptions as possible without inducing serious adverse reactions or public health situations such as the crisis we are currently experiencing.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest. We affirm that the manuscript has not been published and is not under consideration for publication elsewhere.

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