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REVIEW

Peripheral kappa-opioid agonists for visceral pain

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1 Kappa (κ)-opioid receptor agonists are particularly effective analgesics in experimental models of visceral pain. Their analgesic effects are mediated in the periphery. The molecular targets involved include peripherally located κ-receptors and possibly, at least for some nonpeptidic κ-agonists, additional nonopioid molecular targets such as sodium channels located on primary sensory afferents.

2 Overall, these properties are expected to be of therapeutic interest in various visceral pain conditions, including abdominal surgery associated with postoperative pain and ileus, pancreatitis pain, dysmennorhea, labor pain and functional disorders such as irritable bowel syndrome or dyspepsia.

3 The first κ-agonists to be developed were brain-penetrating organic small molecules. Their development was eventually discontinued due to central side effects such as sedation and dysphoria attributed to κ-receptors located behind the blood–brain barrier.

4 New drug discovery programs are now geared towards the design of peripherally-selective κ-agonists. So far, most of the organic molecule-based peripheral κ-agonists have achieved limited peripheral selectivity and a practically insufficient therapeutic window to justify full development.

5 These compounds have been used in a small number of clinical pilot studies involving visceral pain. Although encouraging, the clinical data available so far with this class of compounds are too limited and fragmented to fully validate the therapeutic utility of κ-agonists in visceral pain. Additional clinical studies with safer κ-agonists (i.e. with higher peripheral selectivity) are still required.

6 The most suitable tools to address this question in the future appear to be the newly discovered class of tetrapeptide-based κ-agonists, which have shown unprecedented levels of peripheral selectivity.

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Abbreviations: CRD, colorectal distension; GPCR, G-protein coupled receptor; IBS, irritable bowel syndrome; KOR1, cloned kappa opioid receptor; TNF, tumor necrosis factor; δ, delta; κ, kappa; κ_1, kappa-1; κ_{1a}, kappa-1a; κ_{1b}, kappa-1b; and κ_2, kappa-2; κ_{2a}, kappa-2a; κ_{2b}, kappa-2b; μ, mu; 7TM, seven transmembrane domains

Introduction

Kappa (κ)-opioid receptors are a subtype of opioid receptors. They are differentiated from mu (μ)- and delta (δ)-opioid receptor subtypes by distinct genes and proteins, tissue expression patterns, functional properties and side effect profiles (Rivière & Junien, 2000). Early on, κ-agonists, like μ- and δ-agonists, were shown to be potent analgesics in a variety of experimental pain models. Unlike μ-agonists, κ-agonists did not induce euphoria/addiction, respiratory depression or gastrointestinal transit inhibition (Rivière & Junien, 2000). Therefore, they were initially viewed as an attractive alternative strategy to design potent and safer analgesics. Unfortunately, brain-penetrating κ-agonists caused side effects such as sedation and dysphoria that resulted in the discontinuation of the development of the first generation of κ-agonists. More recently, numerous studies have established the existence of peripherally mediated opioid analgesia both in somatic and visceral pain models, particularly in conditions involving inflammation (Rivière & Junien, 2000). In visceral pain models, κ-agonists appeared to be the most effective class of opioid agonists. This latter finding has resulted in a renewed interest for peripherally restricted κ-agonists.

κ-*opioid receptors, pharmacological subtypes and cloned receptor*

Pharmacological studies have long established the existence of κ-opioid receptors functionally differentiated from μ- and δ-opioid receptor subtypes (Martin *et al*., 1976). Radioligand binding studies have also evidenced the heterogeneity of κ-binding sites in brain membrane preparations, characterizing two main binding sites termed κ_1 and κ_2, each of them being further subdivided into high (κ_{1a}-, κ_{2a}-) and low affinity (κ_{1b}-, κ_{2b}-) binding sites (Rothman *et al*., 1990). Only one κ-opioid receptor (KOR1) has been cloned in human and rodents so far (Simonin *et al*., 1995). The pharmacology of the cloned receptor is virtually identical to the previously characterized κ_1-receptor. KOR1 is a seven transmembrane domains (7TM) receptor, coupled to G-proteins (G-protein coupled receptors, GPCR) and negatively coupled to adenylate cyclase. Besides

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the κ_1-receptor, none of the other putative κ-receptor subtypes has been cloned and no other ligand selective enough for these κ-receptor binding subtypes was made available, making impossible to explore or convincingly substantiate the existence of additional subtypes of functionally differentiated κ-receptors. For these reasons, this review is limited on purpose to κ_1-receptors and κ_1-selective agonists.

κ-*agonists*

Most of the selective κ-agonists available to date have been optimized at the κ_1-binding site or the cloned KOR1. Thus, they are all κ_1-selective, with agonist potencies in the nanomolar range (typically 0.1 to 10 nM). Prototypic representatives of this class of compounds include both organic (i.e., U50,488, enadoline/CI-977, asimadoline/EMD61753, ADL 10-010, ADL 10-0116) and peptidic molecules (i.e., FE 200665 and FE 200666 (Rivière *et al*., 1999; Binder *et al*., 2001)). Enadoline and U50,488 readily penetrate the brain (Rivière *et al*., 1999), whereas the others have various degrees of peripheral selectivity ranging from moderate (i.e., asimadoline (Rivière *et al*., 1999), ADL 10-0101, ADL 10-0116 (Murphy *et al*., 2000)) to high (i.e., FE 200665, FE 200666 (Rivière *et al*., 1999)).

Opioid receptors and pain pathways

Opioid receptors are expressed on nerves involved in pain transmission (ascending sensory pathways) and modulation (descending inhibitory pathways) in the periphery, the spinal cord and the brain (Mansour *et al*., 1994; Ji *et al*., 1995). Opioid receptors are present on peptidergic and nonpeptidergic C-fibers of primary sensory afferents, where they prevent the activation and sensitization of these fibers and inhibit the release of pain transmitters. In addition, during inflammatory processes, opioid receptors in dorsal root ganglia are transported towards the peripheral sensory nerve endings at the site of inflammation (Janson & Stein, 2003). At the same time, immune cells containing endogenous opioid peptides accumulate within the inflamed tissue (Stein *et al*., 1989; 1990; 1993). Upon release, these opioid peptides interact with the neuronal opioid receptors to elicit local analgesia. Opioid receptors, and particularly κ-receptors, are also present on immune cells where they exert an immunomodulatory function and control the release of cytokines (Alicea *et al*., 1996). Overall, peripheral opioid receptors and κ-receptors in particular may produce antinociception and anti-inflammatory responses through a variety of neuroimmune mechanisms. For instance, in rheumatoid arthritis models, κ-receptor expression increases and κ-agonists induce local analgesic and anti-inflammatory effects, partly through the inhibition of tumor necrosis factor (TNF)-alpha release (Walker, 2003).

Analgesic effects of κ-*agonists in visceral pain models*

κ-agonists are particularly potent analgesics after systemic administration in a wide variety of visceral pain models (Riviere *et al*., 1993; 1994; Diop *et al*., 1994a, b; Langlois *et al*., 1994; 1997; Sengupta *et al*., 1996; 1999; Friese *et al*., 1997a, b; Burton & Gebhart, 1998; Joshi *et al*., 2000; Sandner-Kiesling *et al*., 2002; Su *et al*., 1997; 2002; Kamp *et al*., 2003). The antinociceptive effects of κ-agonists in visceral pain are consistent across a multitude of experimental conditions irrespective of species (rats or mice), targeted visceral organs (duodenum, colon, bladder, vagina, uterus or peritoneum), nature of noxious stimuli (distension or chemical irritant), nature of measured endpoint (cardiovascular, visceromotor or electrophysiological responses), anesthetized or conscious animals, basal or inflammatory pain and chemical nature of κ-agonists (organic molecules or peptides). Experimental visceral inflammation decreases pain thresholds, increases pain response and enhances the analgesic potency of κ-agonists (Langlois *et al*., 1994; 1997; Burton & Gebhart, 1998; Sengupta *et al*., 1999). Peritoneal irritation-induced pain is also associated with gastrointestinal transit inhibition (Riviere *et al*., 1993; 1994; Friese *et al*., 1997a). In these conditions, blockade of peritoneal irritation-induced pain by κ-agonists results in a normalization of intestinal transit. The ability of κ-agonists to reverse peritoneal irritation-induced ileus is correlated with antinociceptive potency in this model (Friese *et al*., 1997a). These data suggest that κ-agonists might be appropriate to treat post operative pain associated with ileus.

Involvement of peripheral κ_1*-receptors in* κ-*agonist-induced visceral analgesia in intact animals*

In visceral pain models using intact animals, κ-agonists are active at relatively low doses (typically 0.010–0.5 mg kg^{-1}, given by systemic routes) and the rank order for analgesic potencies is consistent with the potency rank for agonist activity at the cloned KOR1 (Friese *et al*., 1997a; Burton & Gebhart, 1998; Rivière *et al*., 1999). These effects are most likely mediated by the κ_1-receptor, considering the selectivity of the agonists for κ_1-receptors and the fact that the analgesic effects of these compounds are generally blocked by opioid antagonists (Diop *et al*., 1994a, b; Langlois *et al*., 1994; 1997; Friese *et al*., 1997b; Burton & Gebhart, 1998). Furthermore, these models suggest that the κ_1-receptors involved in mediating κ-agonist responses are located in the periphery, as the effects of κ-agonists are generally blocked by peripherally restricted opioid antagonists and/or peripherally restricted κ-agonists are equally effective compared to brain penetrating compounds in these models (Friese *et al*., 1997a; Burton & Gebhart, 1998; Rivière *et al*., 1999; Sandner-Kiesling *et al*., 2002).

Involvement of nonopioid blockade of sodium currents in direct effects of κ-*agonists on visceral sensory input*

κ-agonists have a direct inhibitory effect on visceral sensory input in the periphery. They inhibit the firing of decentralized pelvic afferents activated by colorectal distension (CRD) (Sengupta *et al*., 1996; 1999; Su *et al*., 1997; 2002; Joshi *et al*., 2000). These effects require higher doses than those needed in visceral pain models using intact animals (about 10-fold higher doses, typically 5–10 mg kg^{-1}, arterial administration) (Sengupta *et al*., 1996; 1999; Su *et al*., 1997; 2002; Joshi *et al*., 2000). The inhibitory activity on pelvic afferents is not correlated with the potency rank at the cloned KOR1. This response to κ-agonists cannot be completely antagonized by high doses of nonselective opioid antagonists or selective κ-antagonists (Sengupta *et al*., 1996; Su *et al*., 1997). KOR1 oligoantisense pretreatment does not alter the response to κ-agonists (Joshi *et al*., 2000); likewise, different enantiomers

of U50,488 are all equally potent and effective in inhibiting the firing of pelvic afferents, despite marked differences in agonist activity at κ_1-receptors (Su *et al*., 2002). Taken together, these data indicate the involvement of a nonopioid mechanism in the response to κ-agonists in decentralized pelvic afferents. Whole-cell patch-clamp experiments performed on rat colon sensory neurons have established that organic, but not peptidic, κ-agonists have nonopioid sodium channel blocking properties when used at micromolar concentrations (i.e. about a 1000-fold higher concentrations than those for κ-agonist activity) (Joshi *et al*., 2003).

Clinical data on κ*-agonists in visceral pain*

Very limited clinical information is available regarding κ-agonists in visceral pain. Fedotozine was the first compound with κ-agonist activity to be evaluated for visceral pain in a clinical setting. The compound was superior to placebo in reducing abdominal pain and bloating in nonulcer dyspepsia (Fraitag *et al*., 1994) and irritable bowel syndrome (IBS) (Dapoigny *et al*., 1995). It also increased pain perception thresholds to colonic distension in IBS patients (Delvaux *et al*., 1999). Fedotozine is an atypical κ-agonist with mixed κ/μ-opioid activity (Allescher *et al*., 1991), with high affinity for the κ_{1a}-binding site (Lai *et al*., 1994), and relatively low affinity for the cloned KOR1 (Lai *et al*., 1994).

More recently, a pilot study reported that the κ-agonist, ADL 10-0101, was effective in reducing pain in patients suffering from chronic pancreatitis (Eisenach *et al*., 2003). ADL 10-0101 is a classical κ_1/KOR1-selective agonist with peripheral selectivity. The analgesic response appeared to be robust and was not associated with the central side effects of brain penetrating κ-agonists, suggesting that the compound did not reach the brain, which therefore supported that the effects were mediated in the periphery. The onset of analgesia was immediate, reaching a plateau within 60 min, and remaining at maximal levels for the duration of the monitoring period (4 h). During this time interval, the plasma levels of the compound are estimated to have ranged from high nanomolar (first hour, during and after administration) to intermediate/low nanomolar levels ($\sim$100 nM or less, 3rd and 4th hours). The plasma levels were perfectly suitable to activate κ_1-receptors but were probably too low to elicit a nonspecific sodium channel blockade, at least during the last 2 h of the study, when visceral analgesia was still maximal. Despite these preliminary and encouraging results, more definitive clinical proof of concept for the therapeutic relevance of peripheral κ_1-receptors in visceral pain is still needed.

Conclusion

κ-agonists exert potent analgesic activity in a wide variety of visceral pain models. These effects are mediated at peripherally located κ-receptors and possibly through additional nonopioid action at sodium channels located on peripheral nerve endings of primary sensory afferents. The analgesic potency of κ-agonists in visceral pain is enhanced in the presence of inflammation, as previously reported for somatic pain models involving inflammation. The possibility of multiple neuroimmune sites and mechanisms of action for κ-agonists in visceral pain is likely, but not as well established as in somatic pain models. Overall, the pharmacological profile of κ-agonists in visceral pain models suggest that peripherally selective κ-agonists might be useful to treat a variety of visceral pain conditions including abdominal surgery associated with postoperative pain and ileus, pancreatitis pain, dysmennorhea, labor pain and functional disorders such as IBS or dyspepsia.

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