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New vistas in opioid control of pain

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The μ-opioid receptors mainly contribute to the control of pain transmission, while a number of splice variants may have different physiological roles. In fact, some μ-opioid receptor agonists show distinct antinociceptive properties probably mediated via splice variants insensitive to traditional μ-opioid receptor agonists. These atypical μ-opioid receptor agonists are extremely effective against morphine-resistant interactive pain and lack the psychological dependence liability. μ-Opioid receptor splice variants specific for these atypical agonists may be the target for better analgesics effective against morphine-resistant interactive pain and lacking psychological dependence liability.

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Introduction

The opioid receptors are Gi/Go-protein-coupled receptors, and have been classified 4 major subtypes, μ-opioid, δ-opioid and κ-opioid receptors and opioid receptor like-1 (ORL-1) receptor [1]. Among the opioid receptor subtypes, the μ-opioid receptors mainly contribute to the control of pain transmission. Narcotic analgesics used in clinic are all agonists for μ-opioid receptors. The μ-opioid receptors are widely distributed in the central nervous system, including legions involved in pain transmission, for example spinal dorsal horn, medulla, periaqueductal grey matter, thalamus or cortex [2]. Based on the distribution of μ-opioid receptor and on functional studies of μ-opioid receptor agonists, two major mechanisms for producing the analgesic effect of μ-opioid receptor agonists have been proposed [3]. One is suppression of pain transmission on the spinal dorsal horn, thalamus and cortex, and the other is the activation of descending pain control system projected to spinal dorsal horn. To suppress pain transmission, μ-opioid receptor agonists stimulate the μ-opioid receptor on the terminal of primary afferent neuron at spinal dorsal horn or on the terminal of 2nd order neuron in the thalamus to cause presynaptic inhibition of neurotransmitter release; these also stimulate the μ-opioid receptor on the cell-body of 2nd order neuron at spinal dorsal horn and on the cell-body of 3rd order neuron in the thalamus to cause postsynaptic hyperpolarization of excitatory neurons. On the contrary, to activate the descending pain control system, μ-opioid receptor agonists stimulate the μ-opioid receptor located on the GABAnergic neurons in the medulla and periaqueductal grey matter to cause disinhibition of noradrenergic and serotonergic neurons projected to spinal dorsal horn. The released noradrenaline and serotonin by disinhibition of their containing neurons stimulate the α_2 receptor and 5-HT_1 receptor, respectively on the terminal of primary afferent neuron and the cell-body of 2nd order neuron in the spinal dorsal horn to suppress pain transmission. With these common mechanisms, the μ-opioid receptor agonists, including morphine, produce their potent analgesic effect. However, there are differences in the analgesic profiles of diverse μ-opioid receptor agonists [4], supporting the existence of multiple μ-opioid receptors endowed with different physiological roles.

Variability of μ-opioid receptor

The existence of multiple μ-opioid receptors had been originally proposed at early 80s by Pasternak and his colleagues. On the basis of biochemical and pharmacological evidence, μ-opioid receptor had been classically divided into putative μ_1-opioid and μ_2-opioid receptors [4–7]. The putative μ_1-opioid receptor shows a high affinity for both opioid peptides and opioid alkaloids, whereas the putative μ_2-opioid receptor has a higher affinity for opioid alkaloids than for opioid peptides [5,6]. The putative μ_1-opioid and μ_2-opioid receptors have been also identified by the sensitivity for μ-opioid receptor antagonist naloxonazine, which irreversibly binds to putative μ_1-opioid receptor, but reversibly binds to putative μ_2-opioid receptor [6,7]. As a putative μ_1-opioid receptor antagonist, naloxonazine can discriminate the antinociceptive effect of putative μ_1-opioid receptor agonist from that of putative μ_2-opioid receptor agonist [7–9]. At present, more selective antagonists for putative μ_1-opioid or μ_2-opioid receptors have been developed. Tyr-D-Pro-Trp-Gly-NH_2 (D-Pro^2-Tyr-W-MIF-1) [10,11] and Tyr-D-Pro-Trp-Phe-NH_2 (D-Pro^2-endomorphin-1)

[11,12] are selective antagonists for putative μ_2-opioid receptors, and Tyr-D-Pro-Phe-Phe-NH_2 (D-Pro^2-endomorphin-2) [11,12] is selective antagonist for putative μ_1-opioid receptors. However, pharmacological evidence accumulated using these new antagonists suggests the existence of multiple μ-opioid receptors [13,14].

In 1993, the gene for μ-opioid receptor was first cloned and its sequence structure has been identified [15,16]. Identified gene for μ-opioid receptor contains multiple exons and splice variants for its mRNA has been reported soon after cloning of the gene. At present, 19 exons and 33 splice variants have been identified in mouse μ-opioid receptor gene and mRNA, respectively [17–21]. The splice variants have been proposed to be multiple μ-opioid receptors that have been putatively suggested on the basis of pharmacological studies in which antagonists have been used. Although the distributions of most of the splice variants in the rodent central nervous system have been described [17,19–23], the selectivity and intrinsic activity of μ-opioid receptor agonists for each splice variant and the physiological roles of each splice variant are still unknown. However, it has been recently reported that the MOR-1J, MOR-1K and MOR-1L are μ-opioid receptor splice variants insensitive to traditional μ-opioid receptor agonists [D-Ala^2,NMePhe^4,Gly-ol^5]enkephalin (DAMGO) and morphine in the mouse spinal cord [24••,25]. These splice variants are sensitive to μ-opioid receptor agonist $H_2NC(=NH)$-Tyr-D-Arg-Phe-β-Ala-OH (amidino-TAPA), dermorphin tetrapeptide analog containing D-Arg^2, and spinal antinociceptive effect of amidino-TAPA is partially mediated through the activation of these splice variants. This evidence proves the existence of multiple μ-opioid receptors, insensitive to traditional μ-opioid receptor agonists.

Distinct antinociceptive profiles mediated by μ-opioid receptors

The endogenous μ-opioid peptide endomorphin-2 discovered in 1997 [26] displays antinociceptive profiles that are distinct from traditional μ-opioid receptor agonists. The antinociceptive effects of i.t.-injected or i.c.v.-injected endomorphin-2 are potently suppressed by the κ-opioid receptor antagonist nor-binaltorphimine or δ-opioid receptor antagonist naltrindole [14,27–30], although endomorphin-2 is very selective for μ-opioid receptors and does not have significant affinity for κ-opioid or δ-opioid receptors [26]. Activation of μ-opioid receptor by endomorphin-2 leads to the release of the endogenous κ-opioid peptide dynorphin A or the endogenous δ-opioid peptide [Met^5]enkephalin in the supraspinal and spinal sites, which subsequently stimulate κ-opioid or δ-opioid receptor, respectively [27–29]. Traditional μ-opioid receptor agonists, such as morphine, DAMGO or even endomorphin-1, the latter having only one difference in amino acid residue from endomorphin-2 at position 3, do not cause the release of endogenous opioid peptides through the activation of μ-opioid receptors [27–29,31–33]. This phenomenon is also observed with some μ-opioid receptor agonists, especially dermorphin tetrapeptide analogs containing D-Arg^2. The antinociceptive effects of i.t.-administered $(CH_3)_2$Tyr-D-Arg-Phe-Lys-NH_2 ([Dmt^1]DALDA) [31], Tyr-D-Arg-Phe-Sar-OH (TAPS) [32] and amidino-TAPA [33] are potently suppressed by the κ-opioid receptor antagonist nor-binaltorphimine, although those peptides are very selective for μ-opioid receptors and do not have significant affinity for κ-opioid receptors. Like endomorphin-2, these peptides also evoke the spinal release of dynorphins through the activation of μ-opioid receptors; released dynorphins subsequently stimulate κ-opioid receptors. Intriguingly, released dynorphins are variable with these peptides. TAPS causes the release of dynorphin B, whereas [Dmt^1]DALDA, similarly to endomorphin-2, causes the release of dynorphin A [31,32]. Amidino-TAPA causes the release of all three endogenous κ-opioid peptides: dynorphin A, dynorphin B and α-neo-endorphin [33]. In addition, [Dmt^1]DALDA and amidino-TAPA evoke the spinal release of [Met^5]enkephalin and [Leu^5]enkephalin, respectively [31,33]. In fact, their spinal antinociceptive effects are also attenuated by the δ-opioid receptor antagonists naltriben and naltrindole. With a synergistic activation to μ-opioid receptor and κ-opioid or δ-opioid receptors, these μ-opioid receptor agonists show extremely potent and longer-lasting antinociceptive effect than morphine following subcutaneous and intrathecal injections. The distinct antinociceptive profiles of these opioid peptides, which include the release of endogenous opioid peptides, may be mediated by the activation of distinct μ-opioid receptors that are insensitive to traditional μ-opioid receptor agonists, supporting the existence of multiple μ-opioid receptors, probably splice variants endowed with distinct physiological roles.

Analgesics lacking the dependence liability

The psychological dependence is one of the major side effects resulting from chronic treatment with morphine. It is caused by the rewarding effect of morphine revealed by the increased release of dopamine in the nucleus accumbens through the activation of μ-opioid receptor in the ventral tegmental area [34,35]. All narcotic analgesics used in clinic are μ-opioid receptor agonists and therefore they have rewarding effect and develop psychological dependence. In contrast to μ-opioid receptor agonists, κ-opioid receptor agonists suppress the release of dopamine in the nucleus accumbens [35,36]. Therefore, co-administration of κ-opioid receptor agonists with μ-opioid receptor agonists theoretically suppresses the rewarding effect of the latter agonists [37]. Unfortunately, there is no potent μ-opioid receptor agonist with the agonistic property for κ-opioid receptor. However, as described above the selective μ-opioid receptor agonist endomorphin-2 indirectly stimulates κ-opioid receptor by

released dynorphin A via activation of μ-opioid receptor, and, therefore, shows lack of the psychological dependence liability [38,39]. Similarly to endomorphin-2, amidino-TAPA also lacks the psychological dependence liability [40••]. The released dynorphins via activation of μ-opioid receptors by amidino-TAPA activate the κ-opioid receptors and eliminate the psychological dependence liability of amidino-TAPA [33,40••]. In fact, amidino-TAPA shows a remarkable rewarding effect in prodynorphin-deficient mice.

Management of morphine-resistant interactive pain

Traumatic, inflammatory, ischemic, metabolic and neoplastic insults to the peripheral or central nervous system, usually related to direct nerve injury, stroke, chronic inflammation of tissue, cancer, diabetes, or other nerve diseases, leads to abnormal pain, which is characterized by continuous or intermittent spontaneous pain and abnormal sensitivity of the painful site to a variety of noxious (hyperalgesia) or innocuous (allodynia) stimuli [41]. Since morphine treatment is ineffective or extremely less effective against these abnormal forms of pain in the normal therapeutic dose range, they are usually called as the morphine-resistant interactive pain [42–44]. Like morphine, most narcotic analgesics, except oxycodone, are ineffective against the morphine-resistant interactive pain. Oxycodone is the only narcotic analgesic reported to be effective against morphine-resistant interactive pain [45,46]. Although oxycodone is extremely selective to μ-opioid receptor and does not have remarkable affinity to κ-opioid receptor [47], its antinociceptive effect has been suggested to be partially mediated through the activation of κ-opioid receptor, especially under condition of morphine-resistant interactive pain [48,49]. At present, the mechanism underlying the stimulation of the κ-opioid receptor by oxycodone is unclear. However, the morphine-insensitive mechanism (probably indirect stimulation of κ-opioid receptor) for oxycodone may be involved in the anti-allodynic and anti-hyperalgesic effects of oxycodone against morphine-resistant interactive pain.

As described above the endogenous μ-opioid peptide endomorphin-2 indirectly stimulated κ-opioid receptor by releasing dynorphin A [14,27–30]. Endomorphin-2 was also reported to show potent anti-allodynic effect against neuropathic pain, one of the morphine-resistant interactive pains [50,51]. In addition, the gene transfer for endomorphin-2 reverses allodynia in neuropathic pain state [52,53••]. It is more noteworthy that amidino-TAPA, which induces the release of endogenous κ-opioid peptides dynorphin A, dynorphin B and α-neo-endorphin via activation of μ-opioid receptor to produce antinociception [33], is extremely effective against the morphine-resistant interactive pain [54••]. The anti-allodynic effect of amidino-TAPA is not altered at all in the nerve-injured neuropathic pain. Similarly to oxycodone, the indirect stimulation of κ-opioid receptor via released endogenous κ-opioid peptides by amidino-TAPA and endomorphin-2 may be involved in their potent anti-allodynic and anti-hyperalgesic effects against morphine-resistant interactive pain.

Conclusion

Among the 3 major opioid receptor subtypes, μ-opioid receptor is still a dominant receptor for controlling pain transmission. However, traditional μ-opioid receptor agonists used in clinic all develop dependence and are ineffective against morphine-resistant interactive pain. Fortunately, μ-opioid receptor agonists oxycodone, endomorphin-2 and amidino-TAPA, which cause indirect stimulation of κ-opioid receptor via the morphine-insensitive mechanism to produce antinociception, show excellent effectiveness against morphine-resistant interactive pain. Moreover, releasing the endogenous κ-opioid peptides, endomorphin-2 and amidino-TAPA lack the psychological dependence liability. The μ-opioid receptors (probably μ-opioid receptor splice variants) sensitive to oxycodone, endomorphin-2 or amidino-TAPA but insensitive to morphine, may be the target molecule to produce better analgesics effective against morphine-resistant interactive pain devoid psychological dependence liability.

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