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Review

The role of κ-opioid receptor activation in mediating antinociception and addiction

Yu-hua WANG[1, 2], Jian-feng SUN[2], Yi-min TAO[2], Zhi-qiang CHI[2], Jing-gen LIU[2, *]

[1]School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210046, China; [2]State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

The κ-opioid receptor (KOR), a member of the opioid receptor family, is widely expressed in the central nervous system and peripheral tissues. Substantial evidence has shown that activation of KOR by agonists and endogenous opioid peptides *in vivo* may produce a strong analgesic effect that is free from the abuse potential and the adverse side effects of μ-opioid receptor (MOR) agonists, such as morphine. In addition, activation of the KOR has also been shown to exert an inverse effect on morphine-induced adverse actions, such as tolerance, reward, and impairment of learning and memory. Therefore, the KOR has received much attention in the effort to develop alternative analgesics to MOR agonists and agents for the treatment of drug addiction. However, KOR agonists also produce several severe undesirable side effects such as dysphoria, water diuresis, salivation, emesis, and sedation in nonhuman primates, which may limit the clinical utility of KOR agonists for pain and drug abuse treatment. This article will review the role of KOR activation in mediating antinociception and addiction. The possible therapeutic application of κ-agonists in the treatment of pain and drug addiction is also discussed.

Keywords: κ-opioid receptor; dynorphin; desensitization; antinociception; tolerance; addiction; drug withdrawal; cocaine reward; negative mood state

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Introduction

Pharmacological studies have established the existence of two types of κ-opioid receptor (KOR). One subtype of KOR, κ1, binds U69593 with a high affinity, whereas the κ2 subtype binds this drug with a low affinity[1]. A naloxone benzoylhydrazone sensitive KOR subtype (κ3) has also been proposed but not been fully confirmed by sufficient evidence[2–4]. So far only KOR1 has been cloned in human and rodents[4, 5]. KORs are coupled to heterotrimer Gi/o proteins. Activation of KORs leads to an inhibition of adenylyl cyclase through the Gα subunit and induces increased potassium channel conductance and decreased calcium conductance via the Gβγ subunit[6]. Modulation of these ion channels by KORs in neurons results in decreased action potential generation and neurotransmitter release. Stimulation of KORs has also been shown to activate ERK (extracellular regulated kinase), JNK (c-Jun N-terminal kinase), and p38 MAPK (mitogen-activated protein kinase) signal transduction cascades[7–13]. Additionally, there is evidence that activation of KORs stimulates Na-H exchanger-3 activity via Na^+-H^+-exchanger regulatory factor-1/Ezrin-radixin-moesin-binding phosphoprotein-50, independent of pertussis toxin-sensitive G proteins[14]. After repeated or sustained exposure to agonists, KORs are desensitized by receptor phosphorylation and recruitment of β-arrestin and endocytosed via a clathrin-and dynamin-dependent pathway. These internalized receptors either return to the membrane by dephosphorylation and EBP50/NHERF-1-dependent recycling or are degraded via both lysosome and proteasome systems[15, 16]. G-protein receptor kinase 3 (GRK3) and β-arrestin 1/2 play important roles in the modulation of KOR trafficking[12, 17].

KORs are widely expressed throughout the brain, spinal cord, and peripheral tissues[7]. High levels of KOR mRNA have been detected in the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex (PFC), hippocampus, striatum, amygdala, locus coeruleus (LC), substantia nigra (SN), dorsal raphe nucleus (DRN) and hypothalamus of both the rat and human brains[5, 18–20]. These brain areas are implicated in the modulation of reward, mood state and cognitive function. KORs are also expressed at several

* To whom correspondence should be addressed.
E-mail jgliu@mail.shcnc.ac.cn
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levels of pain circuitry, including areas such as the dorsal root ganglia, dorsal spinal cord, rostral ventromedial medulla, periaqueductal gray (PAG), sensory thalamus and the limbic regions [12, 21–23]. Activation of KORs *in vivo* produces many effects including analgesia, dysphoria, water diuresis, corticosteroid elevations, immunomodulation, decreases in pilocarpine-induced seizure and associated mossy fiber sprouting and hilar neuron loss[16]. KOR agonists have attracted considerable attention for their ability to exert potent analgesic effects without high abuse potential[24–27] and antagonize various MOR-mediated actions in the brain, including analgesia, tolerance, reward and memory processes[28].

The role of the κ-opioid system in the modulation of antinociception and drug addiction

The κ-opioid system consists of the dynorphin family of neuropeptides and KORs[29, 30]. Dynorphins (Dyns) are composed of seven peptides of varying lengths that are formed from the precursor prodynorphin (PDyn; see Schwarzer, 2009[31]). They are released from the presynaptic terminal of depolarized PDyn-containing neurons following sequential enzymatic cleavage, mainly by proprotein convertase-2[32, 33]. The Dyn/KOR system can mediate antinociception and drug reward through presynaptic and postsynaptic modulation of the levels of several neurotransmitters such as dopamine (DA), γ-Aminobutyric acid (GABA) and glutamate[19, 34]. It has been well established that the Dyn/KOR system exerts an inhibitory effect on brain reward function by suppressing DA release from the mesolimbic reward pathway and the nigrostriatal pathway[4, 35–38]. These brain regions are intimately associated with the development of drug dependence. Numerous studies in both nonhuman primates and rats have demonstrated that κ-agonists functionally attenuate many behavioral effects of cocaine, including behavioral sensitization[39, 40] place preference[40–42], and self-administration[43–46]. Administration of κ-agonists also attenuates the reinstatement of extinguished drug-taking behavior in an animal model of relapse[46, 47]. These inhibitory effects of κ-agonists on cocaine-induced abuse-related behaviors are possibly achieved by inhibiting the release of DA from dopaminergic neurons[37, 48].

A role for KORs in pain circuits has been widely described in both the central and peripheral nervous systems. Although it has been reported that KOR activation antagonizes MOR-mediated analgesia, numerous studies have documented potent antinociceptive effects after intrathecal and systemic administration of selective κ-agonists[49–52]. Moreover, κ-opioid agonists are free from the abuse potential and adverse side effects of μ-agonists such as morphine[24–27]. Additionally, pharmacologic studies in KOR and PDyn knockout mice indicate important roles for KORs in mediating inhibition of visceral, chemical, inflammatory and thermal pain[12, 53, 54]. Peripherally selective κ-agonists (including the peptide κ-agonists[55]) act as particularly potent analgesics after systemic administration in a wide variety of visceral-pain and inflammatory-pain models as well as in thermal hyperalgesia induced by capsaicin. Moreover, the analgesic potency of κ-agonists is enhanced under inflammatory conditions[56–61]. Both central and peripheral sites of action may contribute to these endpoints[62–64].

The role of the κ-opioid system in modulation of the aversive effects of stress and drug relapse

Although accumulating evidence demonstrates that KOR agonists produce potent analgesic effects and suppress drug reward, these agonists have also been shown to produce aversive mood and facilitate drug relapse[7]. For example, KOR activation produces dysphoria (defined here as an unpleasant or aversive state) in humans[65, 66] and pro-depression-like behaviors (*eg*, anhedonia, dysphoria, and anxiety) in rodents[67–70]. Moreover, the aversive effects of KOR agonists have also been characterized extensively in rodents using place conditioning paradigms, where they establish conditioned place aversions (CPAs) after systemic administration[30, 41, 71–73] or microinfusion into the mesocorticolimbic DA system[67, 74]. In addition, stimulation of KORs with selective agonist can cause a Dyn/KOR-dependent reinstatement of extinguished cocaine CPP (conditioned place preference) or drug self-administration[75–78]. These reports suggest that activation of the Dyn/KOR system is likely to play a major role in stress-induced reinstatement and that blockade of KOR receptors with selective antagonists may be a useful and powerful therapeutic strategy for protecting individuals from relapse to drug abuse. Furthermore, the fact that KOR function appears to have a profound influence on behaviors that are thought to reflect motivational and emotional states in animal models suggests that KORs might represent a viable target for psychiatric medications. An application of KOR antagonists is in the treatment of depressive and anxiety-related disorders, both of which are triggered or exacerbated by stress[12].

Potential therapeutic applications of κ-opioid agonists in pain relief and drug addiction treatment

Potential therapeutic applications in pain relief

Although MOR agonists are still regarded as the gold standard to relieve severe pain, their therapeutic utility is limited by the tendency to cause addiction following repeated or prolonged administration. Because KOR agonists can exert potent analgesic effects and suppress the drug reward response, they were initially expected to be used as non-addictive analgesics. However, in clinical trials[51, 56], selective κ-agonists that freely enter the central nervous system (*eg*, ICI199441, enadoline, and spiradoline) have been shown to produce unpleasant central side effects, such as dysphoria, sedation and diuresis. As a result, there has been an attempt to develop peripherally selective κ-agonists[51] and mixed κ/μ-agonists[79–81] in the hopes of developing strong analgesics devoid of central side effects. Synthetic κ-agonists, as well as Dyn A, have been reported to reduce morphine tolerance in a variety of antinociceptive tests[80, 82, 83]. Although the endogenous Dyns, Dyn A analogs (*eg*, E2078) and other peptide κ-agonists (*eg*, CR665 and CR845) have several advantages such as high activity, high specificity and low toxicity, the delivery of peptides as therapeutic agents remains a challenge due to their metabolic

instability[55]. Currently, peripherally selective κ-agonists (including the peptide κ-agonists[55]) are under development as new analgesics due to their lack of central side effects such as respiratory depression, nausea, sedation, dysphoria, addiction and analgesic tolerance[51, 56]. Nevertheless, none have thus far been approved for use as analgesics. The popular analgesics available today are still classical compounds with mixed κ- and μ-activity such as pentazocine, butorphanol and nalbuphine[81]. Cyclazocine and morphinan derivatives are novel κ-agonists with additional μ-activity, which have attracted much recent attention for their ability to inhibit antinociceptive tolerance and cocaine-reinforced responding with fewer undesirable side effects[79, 80].

Potential therapeutic applications in the treatment of drug addiction

Drug addiction is a disorder characterized by chronic relapse, which is accompanied by the compulsion to seek and take the drug, loss of control in limiting intake and emergence of a negative emotional state (*eg*, dysphoria, anxiety, irritability) when access to the drug is prevented[84]. The addiction cycle is composed of three stages: binge/intoxication, withdrawal/negative affect and preoccupation/anticipation. Additionally, the withdrawal symptoms after removal of chronic drug administration include signs of physical dependence and negative emotional state (dysphoria, anxiety and irritability)[84]. It has been demonstrated that κ-agonists can attenuate opiate withdrawal symptoms both in opiate-dependent animals and in humans[28, 53, 55, 82, 85–87]. This attenuation may be due to κ-agonists possibly preventing drug withdrawal by inhibiting glutamatergic, GABAergic, or noradrenergic transmission in brain sites that mediate negative mood states such as the central nucleus of the amygdala (CeA) or bed nucleus of the stria terminalis (BNST)[4].

A wealth of studies indicates that κ-agonists can antagonize cocaine-induced alterations in behavior and brain chemistry[34, 88]. Several studies have demonstrated that κ-agonists are effective at decreasing the rate of cocaine self-administration both in humans and in animal models[43, 46, 47, 89, 90]. Also, κ-agonists attenuate the development and long-term expression of cocaine-induced behavioral sensitization following their repeated, intermittent administration[91]. These effects most likely result from the inhibition of limbic DA release after acute administration of κ-agonists[34, 88, 92, 93]. However, there is paradoxical evidence that continuous or prior exposure to κ-agonists can potentiate the rewarding effects of cocaine under stress conditions and stress-induced reinstatement[36, 94, 95]. This evidence suggests that selective antagonists of KOR may represent useful and powerful therapeutic treatments for protecting individuals from relapse to drug abuse.

A growing number of preclinical studies have demonstrated that nonselective κ-agonists with additional activity at MORs can decrease cocaine self-administration with fewer side effects than highly selective κ-agonists[44, 79, 80, 96–98], indicating that mixed-action κ/μ-agonists may have particular utility for the treatment of drug abuse. Taken together, the majority of these findings indicate that κ-agonists antagonize both the behavioral and neurochemical effects of cocaine. The administration of κ-agonists can functionally attenuate behavioral effects of cocaine, including CPP, self-administration and behavioral sensitization. These inhibitory effects of κ-agonists on abuse-related behaviors are possibly achieved by suppressing DA release. Additionally, compounds with mixed κ- and μ-activity may be more promising candidate pharmacotherapies for drug abuse than selective κ-agonists. However, there is evidence that KOR agonists produce aversive mood and facilitate drug relapse. Therefore, further studies are needed to confirm the utility of κ-agonists in the treatment of substance abuse.

Conclusions and therapeutic perspectives

Data from cell culture, experimental animals and humans have provided cellular, neurochemical, and behavioral evidence that KOR activity plays a key role in mediating antinociception, drug withdrawal symptoms and cocaine reward responses. Thus, κ-agonists are likely to become analgesics or even anti-addiction drugs without tolerance and dependence development following chronic drug exposure. Moreover, for the peripherally selective κ-agonists, their ability to exert potent analgesic effects in a variety of visceral pain conditions without presenting central side effects suggest a bright drug development future. Additionally, mixed-action κ-/μ-agonists may have promising uses for the treatment of pain or drug abuse with few side effects. However, all these predicted therapeutic applications require further study.

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