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The role of the dynorphin- κ opioid system in the reinforcing effects of drugs of abuse

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Abstract

Background—Initial hypotheses regarding the role of the κ opioid system in drug addiction suggested that κ receptor stimulation had anti-addictive effects. However, recent research suggests that κ receptor antagonists may reverse motivational aspects of dependence. In the present review, we revisit the studies that measured the effects of κ receptor ligands on the reinforcing and rewarding effects of drugs and postulate underlying neurobiological mechanisms for these effects to elaborate a more complex view of the role of κ receptor ligands in drug addiction.

Results—The review of studies indicates that κ receptor stimulation generally antagonizes the acute reinforcing/ rewarding effects of drugs whereas κ receptor blockade has no consistent effect. However, in a drug dependent-like state, κ receptor blockade was effective in reducing increased drug intake. In animal models of reinstatement, κ receptor stimulation can induce reinstatement via a stress-like mechanism. Results in conditioned place preference/ aversion and intracranial self-stimulation indicate that κ receptor agonists produce, respectively, aversive-like and dysphoric-like effects. Additionally, preclinical and postmortem studies show that administration or self-administration of cocaine, ethanol, and heroin activate the κ opioid system.

Conclusion— κ receptor agonists antagonize the reinforcing/ rewarding effects of drugs possibly through punishing/ aversive-like effects and reinstate drug seeking through stress-like effects. Evidence suggests that abused drugs activate the κ opioid system, which may play a key role in motivational aspects of dependence. Kappa opioid systems may have an important role in driving compulsive drug intake.

Keywords

Drug addiction; Kappa opioid; Drug abuse

Over two decades, research on the relationship between the dynorphin/ κ opioid system and drug addiction has increased, and extensive reviews on this issue have been made. In the present review, we focus on the effects of the κ opioid system on the reinforcing/rewarding effects of drugs of abuse and postulate underlying neurobiological mechanisms for these effects. We also briefly discuss neuroadaptations in the dynorphin/ κ opioid system during chronic exposure to drugs of abuse.

Physiological function of the dynorphin/ κ opioid system

Dynorphins are opioid peptides derived from the prodynorphin precursor, along with the enkephalins and the endorphins, and contain the leucine (leu)-enkephalin sequence at the *N*-terminal portion of the molecule (Rossier 1982; Rossier and Chapouthier 1982; Schwarzer 2009). Except dynorphin A(2–13), an inactive metabolite of dynorphin A(1–17), dynorphins bind to all three opioid receptors (Schwarzer 2009). However, dynorphins, especially dynorphin A, are considered to show a preference for κ receptors (Chavkin et al. 1982).

Dynorphins have widespread distribution in the central nervous system (Watson et al. 1982) and play a role in a wide variety of physiological systems, including neuroendocrine regulation, pain regulation, motor activity, cardiovascular function, respiration, temperature regulation, feeding behavior, and stress responsivity (Fallon and Leslie 1986). Activation of the dynorphin/ κ receptor system produces actions that are similar to other opioids but also actions that are opposite to those of μ receptors (Table 1). For example, both the μ receptor agonist morphine and κ receptor agonist ketocyclazocine exert antinociceptive effects in rats, but these drugs increase and decrease, respectively, locomotor activity in rats (Iwamoto 1981).

Ketocyclazocine is a κ receptor agonist with a weak affinity for μ receptors (i.e., K_i value, 909 $\mu\text{g/kg}$ compared with 7.1 $\mu\text{g/kg}$ of naloxone or 26 $\mu\text{g/kg}$ of buprenorphine) (Rosenbaum et al. 1985). Based on the data in a three-choice drug discrimination paradigm (White and Holtzman 1983) and the receptor-binding comparison with that of [^3H]-U69593 (Nock et al. 1988), ketocyclazocine appears to mainly act at κ receptors (Leander 1983; Locke et al. 1982), although we cannot completely exclude μ receptor-mediated action of the drug (Ko et al. 1998; Picker 1994). Similarly, μ agonists decrease milk or water drinking behavior in rodents, whereas κ agonists increase these behaviors (Hartig and Opitz 1983; Locke et al. 1982). Because of diuretic actions of κ agonists, the effect of κ agonists on water intake is less clear than that on feeding. It appears that κ agonists initially suppress drinking with increased latency to drinking, whereas morphine decreases drinking without behavioral disturbance. However, after the initial suppression, κ agonists enhance drinking. For example, U50488, a κ agonist, dose-dependently suppressed water drinking (adipsia) during the first hour of treatment, followed by a period of polydipsia likely caused by diuresis in normally hydrated rats (Badiani and Stewart 1992). Similarly, a study by Lee and Clifton (1992) also showed the initial suppression of water drinking by PD117302 and U50488H, which was followed by sustained increase of drinking. In the motivational domain, μ agonists produce rewarding effects, whereas κ agonists produce aversive effects in animals and humans (McLaughlin et al. 2003; Shippenberg et al. 2007; Zimmer et al. 2001). Neurochemically, κ receptor stimulation decreases dopamine release in the brain, whereas activation of μ receptors increases it (Di Chiara and Imperato 1988). Therefore, to a large extent, κ receptors may be hypothesized to act in opposition to activation of μ receptors (Fig. 1).

The κ opioid system also appears to play a role in stress responses. Stress increases dynorphin in brain regions related to stress responses (Chartoff et al. 2009; Shirayama et al. 2004).

Anatomically, one third of prodynorphin neurons in the central nucleus of the amygdala co-express CRF, implying a close interaction between the κ opioid and CRF systems (Marchant et al. 2007). Additionally, dynorphin neuron project and make direct synaptic contacts with noradrenergic neurons in the locus coeruleus, a brain region related to arousal, attention, and stress responses (Reyes et al. 2007). Endocrinologically, κ agonists can stimulate the hypothalamic-pituitary-adrenal (HPA) axis (Calogero et al. 1996; Nikolarakis et al. 1987). Behaviorally, the κ opioid system participates in stress-induced analgesia. Forced swim stress-induced increases in the latency to withdraw the tail from hot water in mice was blocked by nor-binaltorphimine (nor-BNI), a κ antagonist, or by disruption of the prodynorphin gene in mice (McLaughlin et al. 2006b; McLaughlin et al. 2003). Similarly, inhibition of the dynorphin system, but not the enkephalin and β -endorphin systems, was effective in antagonizing restraint-induced increases in antinociception measured in the tail-flick and tail-pinch methods

in mice (Suh et al. 2000; Takahashi et al. 1990), although all three opioid systems have also been suggested in stress-induced analgesia (Yamada and Nabeshima 1995). Additionally, nor-BNI and prodynorphin deletion inhibited forced swim-induced and CRF-induced place aversion in mice (Land et al. 2008). It is suggested that disruption of the prodynorphin gene produces compensations in the μ opioid system (Clarke et al. 2003). However, the evidence that both prodynorphin gene disruption and nor-BNI blocked forced swim-induced and CRF-induced place aversions (Land et al. 2008) and forced swim stress-induced analgesia (McLaughlin et al. 2003) supports the role of κ receptors in stress responses. The dynorphin/ κ opioid receptors are also suggested to mediate stress-induced deficits in learning and memory (Carey et al. 2009).

Dynorphin activation is also hypothesized to contribute to negative emotional states. For example, κ agonists produce place aversions in rats and mice (Mucha and Herz 1985; Shippenberg and Herz 1986; Zhang et al. 2005) and aversive effects in humans, such as confusion, dizziness, sweating, and dysphoria, (Pfeiffer et al. 1986; Walsh et al. 2001). Moreover, κ agonists produce depression-like behaviors when measured in forced swim and brain reward stimulation tests in rodents (Carlezon et al. 2006; Dinieri et al. 2009; Mague et al. 2003; Todtenkopf et al. 2004; Tomasiewicz et al. 2008), whereas κ antagonists have antidepressant effects (Carr et al. 2009; Mague et al. 2003; Newton et al. 2002; Pliakas et al. 2001; Shirayama et al. 2004). Kappa antagonists also exert anxiolytic effects in rats (Knoll et al. 2007). Similarly, dynorphin depletion or κ antagonists decrease anxiety-like behavior in mice, which is reversed by treatment with U-50488H, a κ agonist (Wittmann et al. 2009). Consistent with these results, dynorphin gene deletion abolished the stress effect on the enhancement of immobility in a tail suspension test and stress-induced hyperthermia, suggesting a clear role of dynorphin in the stress effect. However, Wittmann et al. (2009) also found that dynorphin deletion produced an increase of immobility in a tail suspension test, although the gene deletion produced only a minor difference in immobility at the third trial out of five trials in a forced swim test. The ventral tegmental area and its projection terminals were identified as neuroanatomical sites for the place aversion effects of κ agonists (Bals-Kubik et al. 1993).

Effect of the κ opioid system on the reinforcing/ rewarding effects of drugs

Numerous studies have been performed on the effects of κ agonists and antagonists on various actions of drugs of abuse, especially cocaine. These studies have led to the hypothesis that κ receptor stimulation may have anti-addictive effects (Prisinzano et al. 2005; Shippenberg et al. 2001, 2007). However, the potential of κ antagonists in drug addiction treatment has also been recently proposed (Bruchas et al. 2009; Shippenberg 2009). In the section below, we revisit the studies that measured the effects of κ receptor ligands on the reinforcing actions of abused drugs.

Opioids

Unlike μ agonists, κ agonists do not produce reinforcing effects. U50488H, a κ agonist, failed to substitute for heroin self-administration in rats (Koob et al. 1986; Xi et al. 1998). Rather, κ agonists dose-dependently decreased morphine self-administration in rats and mice (Glick et al. 1995; Kuzmin et al. 1997), whereas nor-BNI, a κ antagonist, had no effect on morphine and heroin self-administration in rats and monkeys (Glick et al. 1995; Negus et al. 1993; Xi et al. 1998). Very low doses of U50488H [0.1, 0.5 mg/kg compared with 2.5–10 mg/kg in Glick et al. (1995) and Kuzmin et al. (1997)] increased (0.1 mg/kg) and then decreased (0.5 mg/kg) heroin self-administration in mice (Xi et al. 1998). The very low dose effect of U50488H is similar to those of dopamine receptor antagonists on psychostimulant self-administration. Increased psychostimulant self-administration by dopamine receptor antagonists is viewed as initial compensatory increase of drug intake by animals to the antagonizing effect of the treatment. Thus, the data may suggest an antagonistic effect of U50488H at a very low dose

on heroin self-administration reflected as a possible shift to the right of the dose–response function. Regarding the effect of κ agonists on μ agonist-induced conditioned place preference (CPP), it is well established that κ agonists themselves produces conditioned place aversion. Therefore, the decreased morphine-associated CPP by κ agonists (Tsuji et al. 2001) is likely to result from the addition of the aversive effects of κ agonists to the rewarding effect of μ agonists via a separate circuit, rather than the direct involvement of the κ agonists in mediating the reward activity of μ agonists. Additionally, co-administration of U69593, a κ agonist, failed to alter morphine pretreatment-induced potentiation of morphine-induced CPP in rats (Shippenberg et al. 1998). Thus, although the stimulation of κ receptors can decrease the self-administration and CPP of μ agonists, κ receptor activation may have more of a punishment action than a key role in the acute reinforcing/rewarding mechanism of μ agonists.

Early studies showed that rats physically dependent on morphine self-administered dynorphins in a stable manner under a fixed ratio schedule of reinforcement and showed no morphine-like withdrawal signs during self-administration (Khazan et al. 1983). Similarly, rats dependent on morphine also self-administered ketocyclazocine and ethylketocyclazocine, κ agonists, for 15 days without morphine-like withdrawal signs (Young and Khazan 1983). Blockade of κ receptors by nor-BNI potentiated naloxone-precipitated morphine withdrawal symptoms in rats (Spanagel et al. 1994). However, gene disruption of κ receptors reduced naltrexone-precipitated morphine withdrawal in mice (Simonin et al. 1998), and 5'-guanidinonaltrindole, a κ antagonist, had no effect on the withdrawal-induced increase in heroin choice over food in a choice self-administration paradigm in rhesus monkeys (Negus and Rice 2009). In humans, prodynorphin and κ receptor polymorphisms were reported to be associated with opioid dependence (Clarke et al. 2009; Gerra et al. 2007). Collectively, the data suggest that the κ opioid system may modulate morphine dependence, but unclear is how the κ opioid system interacts with motivational aspects of opioid dependence.

Alcohol

Kappa agonists decreased free-access ethanol drinking in rats when injected once per day for 4 or 5 days (Lindholm et al. 2001; Nestby et al. 1999). In mice, the acute stimulation of brain-derived neurotrophic factor receptor, which increased prodynorphin, also decreased free ethanol drinking, an effect that was attenuated by nor-BNI, a selective κ antagonist (Logrip et al. 2008). Similarly, acute injections of enadolin (CI-977, a κ receptor agonist) dose-dependently decreased operant responding for both ethanol and water, whereas continuous infusion of enadolin for 4 days increased free-access ethanol drinking and preference, especially a high concentration of ethanol, in chronically (>16 months) ethanol-drinking rats (Holter et al. 2000). Bremazocine also reduced responding for ethanol, saccharin, and food under a fixed ratio schedule in rhesus monkeys (Cosgrove and Carroll 2002). Bremazocine has similar affinities for both μ and κ receptors in vitro (Lahti et al. 1982), while it has weak δ opioid actions (Richards and Sadee 1985). However, behaviorally, U50488H was cross-tolerant with bremazocine but not with morphine (Lahti et al. 1982). Similarly, an in vivo comparison study (Vonvoigtlander et al. 1983) shows that, while chronic morphine produced tolerance to the analgesic effect of itself by the 5.9-fold increase of an ED₅₀ dose in mice, it did not produce cross-tolerance with U50488 and bremazocine. In contrast, chronic U50488 produced tolerance with itself and bremazocine by the 26-fold and over 12.5-fold increases of ED₅₀ doses, respectively, whereas it did not produce cross-tolerance with morphine. This finding suggests that, despite similar affinities of bremazocine at μ and κ receptors in vitro, in vivo actions of bremazocine is similar to those of U50488, a selective κ agonist but not to those of morphine.

Collectively, acute treatment with κ agonists appears to decrease ethanol drinking and non-selectively decrease operant responding, although continuous infusion of a κ agonist might

enhance the rewarding effect of ethanol based on one study (Holter et al. 2000). Note that the κ opioid system has been associated with feeding and drinking (see above). Therefore, the results with κ agonists using a free-access drinking paradigm may involve more general appetitive actions. Additionally, it is suggested that the κ opioid system may affect ingestive behaviors by mediating palatability, especially sweet taste (Beczowska et al. 1993; Lynch et al. 1985; Woolley et al. 2007), although the effect of κ agonists on bitter taste like alcohol hasn't yet been studied. Using conditioned place preference (CPP), it was shown that the dose of U50488 (1 mg/kg), that produced place aversion, decreased stress (foot shock or fear stress)-induced ethanol place preference, while nor-BNI had no effect or enhanced it in rats (Matsuzawa et al. 1998, 1999). These results suggest again that the κ opioid system may antagonize the rewarding effect of ethanol by producing an aversive effect rather than by directly modulating the rewarding mechanism of ethanol. However, Logrip et al. (2009) has recently demonstrated that U50488, a κ agonist (1, 3 mg/kg), inhibited ethanol-induced CPP under the condition in which the drug did not produce place aversion, suggesting actual modulation of the rewarding effects of ethanol.

Under conditions of dependence, the role of κ receptors on the reinforcing effect of ethanol may shift. In a nondependent state, nor-BNI had no effect on operant responding for ethanol in rats and monkeys (Doyon et al. 2006; Williams and Woods 1998). In a free-drinking paradigm, nor-BNI increased unlimited access ethanol drinking in high-drinking rats (approx. 1.5 g/kg ethanol intake) (Mitchell et al. 2005), whereas it decreased 18 h ethanol drinking in mice (Logrip et al. 2008). To induce ethanol dependence especially within a short period (in 2 weeks), it is necessary to maintain blood alcohol level (BAL) at 150–200 mg% (Gilpin et al. 2008; O'Dell et al. 2004), which is difficult to be achieved by voluntary ethanol intake (binge-like drinking, approx. 1.5 g/kg, 80 mg% BAL) (Ji et al. 2008). However, a prolonged exposure to ethanol intake might also induce a dependence-like state. In chronically (>16 months) ethanol-drinking rats, nor-BNI clearly decreased the 24-h withdrawal-induced increase in first-hour ethanol intake under a fixed ratio schedule but not free-access ethanol drinking (Holter et al. 2000). Similarly, nor-BNI significantly attenuated the withdrawal-induced increase in ethanol intake under a fixed ratio schedule in ethanol-dependent rats but not in nondependent rats (Walker and Koob 2008).

Time course of the action of nor-BNI can be critical for interpretation of results. Nor-BNI can act on both μ and κ receptors, but the μ action of a single injection of nor-BNI is short-lived (<1 day, Spanagel et al. 1994; <1 h after an icv injection, Horan et al. 1992), while κ actions last long. For example, the antagonism of κ opioid antinociceptive effects by a single injection of nor-BNI is reported to last more than 21 days in mice, rats, and rhesus monkeys (Butelman et al. 1993; Horan et al. 1992; Jones and Holtzman 1992). Moreover, it is shown that up to 20 mg/kg of nor-BNI (s.c.) selectively antagonized the κ antinociceptive effect of U50488 in mice without influencing the antinociceptive effects of μ and δ receptor agonists (Takemori et al. 1988). Regarding repeated injections, Spanagel et al. (1994) reported that chronic nor-BNI was able to block the μ and δ receptor-mediated antinociception only 1 and 2 days after the last injection while it was able to do so at κ receptors over 20 days, which again suggests a short μ action of repeated nor-BNI. Therefore, under conditions of the cited studies (one injection with a long pretreatment), nor-BNI may have acted as a selective κ antagonist.

Collectively, while activation of the κ opioid system may have a general suppressant effect on ethanol reinforcement in nondependent animals, the endogenous κ opioid system may contribute to the motivation to seek ethanol in a dependent state (Fig. 1).

Psychostimulants

Extensive studies on the effects of the κ opioid system on cocaine actions have been performed. In studies of psychostimulant self-administration, acute and continuous activation of κ

receptors decreased cocaine self-administration under a fixed ratio schedule, respectively, in rats (Glick et al. 1995; Schenk et al. 1999) and monkeys (Mello and Negus 1998; Negus et al. 1997). However, decreased cocaine self-administration was observed only with low cocaine doses and was associated with a concomitant decrease in responding for food (Mello and Negus 1998; Negus et al. 1997; Schenk et al. 1999). U69593, a κ agonist, decreased cocaine self-administration that was presented with a cue light in rats (Schenk et al. 2001), but failed to do so consistently in rats that were trained to self-administer cocaine without a cue light (Schenk et al. 2001). Specifically, the κ agonist initially decreased responding for cocaine for an hour after the injection in both groups with and without a cue light. However, the suppressed responding for cocaine gradually recovered to the baseline within 4 h in rats without a cue light, which suggests that κ agonist initially exerted nonspecific effect on responding. However, the κ agonist consistently reduced cocaine intake in rats trained with a cue light, which may suggest the specific effect of the κ agonist on the conditioned reinforcement of cue rather than unconditioned drug reinforcement. The finding that daily treatment with U69593 had no effect on the acquisition of cocaine self-administration in rats (Schenk et al. 2001) further supports the lack of a major effect of κ agonists on the acute reinforcing mechanism of cocaine. In contrast, U50488, a κ agonist, produced the leftward-shifted dose–response function of cocaine self-administration (7–60 μ g/infusion) in naïve rats (Kuzmin et al. 1997). Specifically, the leftward shift was observed when U50488 at the highest dose tested enhanced the sensitivity of the animals to the reinforcing effect of very low doses of cocaine while the drug decreased self-administration of 30 μ g/infusion of cocaine in a dose-dependent manner. Similarly, pseudo-continuous intravenous administration of U50488 dose-dependently shifted the choice dose–response function of cocaine to the left under a concurrent choice paradigm with food pellets in monkeys, an effect that was attenuated by nor-BNI (Negus 2004), suggesting the increased sensitivity of the animals to the reinforcing effects of cocaine. Overall, the data suggest that κ agonists decreased cocaine intake not by playing a specific role in the reinforcing mechanisms of cocaine, but perhaps by producing a non-specific effect on responding and that κ agonists can also enhance the sensitivity of animals to the reinforcing effect of cocaine under certain conditions. Salvinorin A, a κ agonist, did not decrease responding for 10% sucrose (Morani et al. 2009), which might argue against the general non-specific effect of κ agonists on responding. However, salvinorin A is a psychomimetic and hallucinogenic κ agonist with abuse potential, which is quite different from other κ agonists. Moreover, it is shown that salvinorin A is reinforcing and rewarding (Braida et al. 2008; Braida et al. 2007), ruling out the generalization of salvinorin A to κ agonists.

Nor-BNI, a κ antagonist, had no effect on cocaine self-administration in rats (Glick et al. 1995) and monkeys (Negus 2004; Negus et al. 1997). One study showed that, only at low doses of cocaine, nor-BNI shifted the dose–response function of cocaine self-administration to the right in rats (Kuzmin et al. 1998), suggesting the decreased sensitivity of animals to the reinforcing effects of cocaine. In rats with extended access to cocaine, a hypothesized rodent model of cocaine dependence, 15 mg/kg of nor-BNI, the dose with a selective κ action, significantly decreased cocaine self-administration under a PR schedule only in LgA rats 5 days after the injection (Wee et al. 2009). However, when the dose of nor-BNI increased to 30 mg/kg, a high dose with μ and κ actions, the drug significantly decreased cocaine self-administration only in ShA rats right after the injection, a time point when μ actions of the drug were effective, whereas it did so only in LgA rats at the time points when selective κ actions of the drug were effective (Wee et al. 2009). Therefore, while acute stimulation of κ receptors may suppress cocaine self-administration, increased activation of the κ opioid system may contribute to the reinforcing actions of cocaine in cocaine dependence (Fig. 1).

In a CPP paradigm, a similar pattern was observed. Activation of κ receptors was shown to block cocaine-induced CPP in rodents (Crawford et al. 1995; Mori et al. 2002; Zhang et al. 2004). In a time-course study, however, U50488 enhanced cocaine-induced CPP when injected

60 min before cocaine conditioning, a time interval in which U50488 did not produce place aversion on its own, while it decreased cocaine-induced CPP when injected 15 min before cocaine conditioning, a time interval in which U50488 produced place aversion on its own (McLaughlin et al. 2006a). Co-pretreatment of cocaine with κ agonists (U50488, U69593) selectively abolished cocaine pretreatment-induced potentiation of cocaine CPP in rats (Shippenberg et al. 1996, 1998). On the other hand, nor-BNI had no effect on cocaine-induced CPP in sham rats, whereas it restored cocaine-induced CPP in rats that showed aversion to cocaine-associated chamber after CREB overexpression (Carlezon et al. 1998). Therefore, similar to the self-administration data, it appears that the stimulation of κ receptors antagonizes the rewarding effects of cocaine in CPP, perhaps by producing aversive effects although it can also enhance the rewarding effects of cocaine under a certain conditions. Consistent with this conclusion, in an intracranial self-stimulation paradigm, U69593 alone attenuated brain stimulation in rats, suggestive of a dysphoria-like state (Todtenkopf et al. 2004), and also antagonized cocaine-induced facilitation of brain stimulation in rats (Tomasiewicz et al. 2008).

Nicotine and cannabinoids

Data on the role of the κ opioid system in the reinforcing effects of nicotine and cannabinoid are scarce. One study showed that prodynorphin deletion slightly enhanced the sensitivity of mice to the reinforcing effect of nicotine (Galeote et al. 2009). However, gene deletion had no effect on nicotine-induced CPP and nicotine withdrawal symptoms in mice (Galeote et al. 2009). In one study, U50488 attenuated mecamylamine-precipitated nicotine withdrawal-induced place aversion in rats (Ise et al. 2002). With respect to cannabinoids, it was shown that Δ^9 -tetrahydrocannabinol (Δ^9 -THC)-induced place aversion was abolished in dynorphin knockout mice and κ receptor knockout mice implying an involvement of the κ opioid system in the dysphoric component of Δ^9 -THC (Ghozland et al. 2002; Zimmer et al. 2001). Consistent with this observation, nor-BNI and prodynorphin knockout enhanced, respectively, the acquisition of self-administration of WIN 55,212-2, a cannabinoid agonist, and the sensitivity of the reinforcing effect of the cannabinoid agonist in mice (Mendizabal et al. 2006), suggesting that the inhibition of the κ opioid system may enhance the reinforcing effect of WIN 55,212-2 by attenuating dysphoric-like effects of cannabinoids. Further research with animal models of nicotine dependence (O'Dell et al. 2007) and cannabinoid self-administration are merited.

Effect of the κ opioid system on reinstatement of responding for drug self-administration

Data on the effects of κ agonists on reinstatement of extinguished responding for drug self-administration or CPP give a clearer view of the actions of κ agonists. An acute pretreatment with U69593 decreased cocaine- or amphetamine-primed reinstatement of responding for cocaine or amphetamine, respectively (Schenk and Partridge 2001; Schenk et al. 1999). However, U69593 did not alter the ability of other psychostimulants (amphetamine, GBR12909, WIN35428) to reinstate responding for cocaine self-administration in rats (Schenk et al. 1999, 2000). In contrast, κ agonists themselves reinstated responding for cocaine, an effect that was blocked by naltrexone and a CRF₁ receptor antagonist in monkeys (Valdez et al. 2007). Moreover, κ antagonists inhibited stress-induced, but not cocaine-primed, reinstatement of responding for cocaine in rats (Beardsley et al. 2005). Similarly, U50488, a κ agonist, induced reinstatement of extinguished cocaine-associated place preference (Redila and Chavkin 2008), and κ antagonists inhibited stress-induced, but not cocaine-primed, reinstatement of cocaine-associated CPP in mice (Carey et al. 2007; Redila and Chavkin 2008). Additionally, genetic deletion of κ receptors or prodynorphin also abolished stress-induced reinstatement of CPP in mice (Redila and Chavkin 2008). Therefore, the data clearly suggest that the κ opioid system plays a role in stress-induced drug seeking, and stimulation

or inhibition of κ receptors, respectively, induces or inhibits drug seeking via stress responses in laboratory animals. The reinstatement data further suggest that stress responses induced by κ agonists may underscore the observed increase in animals' sensitivity to the reinforcing/rewarding effect of cocaine by κ agonists in some studies (Kuzmin et al. 1997; McLaughlin et al. 2006a; Negus 2004).

Neural mechanisms of the dynorphin/ κ opioid system in the interactions with the reinforcing effects of drugs

The activation of the dynorphin system in the nucleus accumbens has been associated with activation of the dopamine system by cocaine and amphetamine. Activation of dopamine D_1 receptors stimulates a cascade of events that ultimately leads to cyclic adenosine monophosphate response element binding protein (CREB) phosphorylation and subsequent alterations in gene expression, notably activation of protachykinin expression and prodynorphin mRNA in the nucleus accumbens. Subsequent activation of the dynorphin system is hypothesized to decrease dopamine release via a negative feedback loop (Nestler 2004). The κ opioid system exerts tonic influences on dopamine neurons in the nucleus accumbens (Chefer et al. 2005), whereas it has no tonic activity on dopamine neurons in the ventral tegmental area (Margolis et al. 2006; Spanagel et al. 1992). Studies show that κ agonists decrease dopamine release or dopamine neuron activity in the nucleus accumbens (Maisonneuve et al. 1994; Spanagel et al. 1992; Xi et al. 1998), ventral tegmental area (Margolis et al. 2003), and prefrontal cortex (Heijna et al. 1990; Margolis et al. 2006), whereas nor-BNI produce the opposite effect in the nucleus accumbens (Spanagel et al. 1992). Similarly, a microdialysis study demonstrated that acute stimulation of κ receptors attenuated cocaine-evoked dopamine release in the dorsal striatum and nucleus accumbens (Gehrke et al. 2008). Repeated administration of U69593 for 3 days decreased the level of D_2 receptors in the nucleus accumbens (Izenwasser et al. 1998). The involvement of D_1 receptors in the dysphoric actions of the κ opioid system has also been demonstrated in rats (Shippenberg and Herz 1988). Therefore, the inhibitory actions of the κ opioid system on dopamine release, particularly in the ventral striatum, are postulated to underlie the behavioral effects of κ receptor ligands. A key role of CREB in mediating the dysphoric-like and depressive-like effects of κ agonists was the observation that the effect of U50488 on ICSS thresholds was absent in mutant mice expressing dominant-negative CREB (Dinieri et al. 2009).

However, the behavioral effects of κ agonists do not appear to solely result from actions within the dopamine system. For example, although a single treatment of dynorphin or salvinorin A decreased dopamine release in the dorsal striatum (Zhang et al. 2004, 2005), three to five repeated injections of κ agonists had either no effect or augmented cocaine-, amphetamine-, and K^+ -evoked dopamine release (Fuentelba et al. 2006, 2007; Gehrke et al. 2008; Heidbreder et al. 1998). Additionally, three days of U69593 administration had no effect on basal dopamine dynamics in rats although it attenuated the quinpirole (a D_2 agonist)-induced decrease of dopamine level (Acri et al. 2001) while it potentiated quinpirole-induced locomotor sensitization in rats (Perreault et al. 2006). More importantly, whereas κ agonists can reinstate responding for extinguished cocaine self-administration, dopamine antagonists only inhibit context- or cocaine-induced reinstatement of responding for cocaine (Anderson et al. 2003, 2006; Crombag et al. 2002). Therefore, the behavioral effects of κ agonists are unlikely to be mediated only by actions within the dopamine system. The κ opioid system can also modulate glutamate and γ -aminobutyric acid (GABA) release in the striatum (Hjelmstad and Fields 2001, 2003; Rawls and McGinty 1998). Thus, this action may contribute to some of behavioral effects of κ receptor ligands.

One hypothesis that has gained support (Bruchas et al. 2009; Shippenberg 2009) is that the aversive and stress-like effects produced by the stimulation of κ receptors are responsible for

the antagonism of the reinforcing/rewarding effects of drugs and the reinstatement of drug seeking. Stress has been strongly associated with relapse to compulsive drug use in drug addiction (Koob 2009). The κ opioid system has been implicated in behavioral responses to stress (Knoll and Carlezon 2009). Moreover, the CRF system has long been implicated in drug addiction (Koob 1999a, b, 2008; Koob et al. 1993), and Valdez et al. (2007) showed that a CRF₁ receptor antagonist inhibited κ agonist-induced reinstatement of responding for cocaine in monkeys. Furthermore, Land et al. (2008) showed that nor-BNI inhibited swim stress-conditioned aversion of neutral odorant, whereas the drug had no effect on cocaine-conditioned preference of the odorant in mice, which strongly supports the role of the κ opioid system in an aversive, rather than rewarding, mechanism. Additionally, nor-BNI and prodynorphin deletion inhibited footshock-induced and CRF-induced place aversion in mice (Land et al. 2008). These results support the role of the κ opioid system in stress responses through an interaction with the CRF system. Whether CRF drives dynorphin and/or dynorphin drives CRF remains to be elucidated under different conditions.

The serotonergic system may also play a role in the dysphoric-like effects of activation of the κ opioid system. A local injection of DAMGO, a μ agonist, increased serotonin release in the dorsal raphe nucleus, whereas a local injection of U50488, a κ agonist, decreased it (Tao and Auerbach 2005). CRF administration activated κ receptors in the dorsal raphe nucleus in addition to the basolateral amygdala, dorsal hippocampus, ventral pallidum, ventral tegmental amygdala, nucleus accumbens and bed nucleus of stria terminalis (Land et al. 2008), and the local inhibition of κ receptors in the dorsal raphe nucleus abolished stress-induced enhancement of analgesia and reinstatement of cocaine-associated CPP in mice (Land et al. 2009). Similarly, κ receptors in the dorsal raphe nucleus were hypothesized to be responsible for the aversive effect of U50488 in mice (Land et al. 2009).

Adaptations in the dynorphin/ κ opioid system during chronic exposure to drugs of abuse

In postmortem studies of cocaine abusers, increased immunoreactivity of dynorphin or κ receptors in the caudate and ventral pallidum was found, which suggests an upregulated κ opioid system in cocaine dependence (Frankel et al. 2008; Hurd and Herkenham 1993; Staley et al. 1997). Similarly, cocaine self-administration or administration increased prodynorphin mRNA in the striatum of rats and monkeys (Daunais et al. 1993; Fagergren et al. 2003; Hurd et al. 1992; Schlussman et al. 2005). In alcohol self-administration/administration, prodynorphin mRNA and the release of prodynorphin-derived peptides were shown to increase in the nucleus accumbens of rats during early and protracted ethanol withdrawal (Lindholm et al. 2000; Przewlocka et al. 1997). Prolonged heroin self-administration (6 weeks) also significantly increased prodynorphin mRNA expression in the central nucleus of amygdala and nucleus accumbens shell but not in the dorsal striatum and nucleus accumbens core, in rats (Solecki et al. 2009). This increased κ opioid activity induced by abused drugs is consistent with manifestation of withdrawal-related negative emotional states in drug addiction (Fig. 1). Consequently, although κ agonists can acutely antagonize the reinforcing effects of abused drugs, presumably in part via an action to decrease dopamine release (Nestler 2001), the use of κ antagonists may be beneficial in treating drug addiction by antagonizing motivational withdrawal symptoms, thereby reducing relapse to drug use, a core symptom of drug addiction. One clinical study tested the hypothesis that the potent κ antagonism of buprenorphine combined with naltrexone would improve compliance compared with naltrexone treatment alone (Gerra et al. 2006). The results showed significantly enhanced compliance and drug abstinence from heroin and cocaine compared with naltrexone alone in heroin-dependent humans (Gerra et al. 2006). These findings were postulated to be attributable to less aversive responses of the buprenorphine/naltrexone combination compared with naltrexone alone. This study further supports the hypothesis of the therapeutic potential of κ antagonists in drug addiction.

Summary

Findings in conditioned place preference/aversion and intracranial self-stimulation studies clearly indicate that κ agonists produce, respectively, aversive-like and dysphoric-like effects in laboratory animals. Data in stress-induced reinstatement of CPP or responding for a drug corroborate the stress-like effect of κ agonists. Consistent findings in drug self-administration and drug-induced CPP studies are that the stimulation of κ receptors generally antagonizes the reinforcing/rewarding effects of cocaine, morphine, heroin, and ethanol, whereas κ receptor blockade has no consistent effect (Table 2). These observations suggest that the κ opioid system is not directly involved in the reinforcing/rewarding mechanism but modulates them by producing punishing/aversive effects. Under certain conditions, however, κ agonists can enhance the sensitivity of animals to the reinforcing or rewarding effect of cocaine. Considering that stress can also enhance the sensitivity to the reinforcing (Covington et al. 2005; Covington and Miczek 2001) and rewarding effect of a drug (McLaughlin et al. 2003), the enhanced sensitivity may result from the stress-like effects of κ agonists (McLaughlin et al. 2006b). In a drug-dependent-like state associated with compulsive drug use, κ receptor blockade was effective in reducing the increased intake of ethanol and cocaine (Table 3). The role of the κ opioid system in physical withdrawal symptoms of morphine and nicotine was equivocal suggesting that the increase of drug intake during the development of drug dependence may be related to the κ opioid-mediated development of negative emotional states. Thus, when a state of drug dependence is reached, the inhibition of κ receptors may be effective in attenuating compulsive drug intake. Consistent with this hypothesis, the data from animal models of reinstatement indicate that the κ receptor stimulation can induce reinstatement of drug seeking by producing stress-like effects in animals (Table 4). Consequently, the inhibition of the κ opioid system is a potential target for blocking compulsive drug use and vulnerability to relapse during drug abstinence.

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Glossary

Positive reinforcement	defined as the process by which presentation of a stimulus (drug) increases the probability of a response (nondependent drug-taking paradigms)
Punishment	defined as the process by which presentation of a stimulus (drug) decreases the probability of a response (nondependent drug-taking paradigms)
Negative reinforcement	defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking)
Reward	defined as a stimulus (drug) that increases the probability of a response, but usually includes a positive hedonic connotation
Stress	anything that causes an alteration in psychological homeostatic processes
Neuroadaptation	changes in function of a given neuronal system to a drug
Noxious (aversive) stimulus	stimuli that arouse emotional reactions stimulus of distress, and the termination of them induces relief

Fig. 1.

Neurocircuitry associated with the positive reinforcement of drugs of abuse and the negative reinforcement of dependence and how it changes in the transition from nondependent drug taking to dependent drug taking (Modified with permission from Koob and Le Moal 2008). Key elements of the reward circuit are dopamine (DA) and opioid peptides at both the ventral tegmental area (VTA) and nucleus accumbens, which are activated during initial use and the early binge/intoxication stage of the addiction cycle. Key elements of the stress circuit are corticotropin-releasing factor (CRF) and norepinephrine (NE) neurons that converge on γ -aminobutyric acid (GABA) interneurons in the central nucleus of the amygdala, which are activated during the development of dependence. The hypothesis elaborated here is that in nondependent animals, opioid peptides that preferentially activate μ opioid receptors have a facilitatory effect on the positive reinforcing actions of drugs of abuse but that opioid peptides that preferentially activate κ opioid receptors have an inhibitory effect on the positive reinforcing actions of drugs of abuse. In contrast, in dependent animals, the μ opioid system is compromised via tolerance-like neuroadaptations, and the κ opioid system becomes either activated or sensitized indirectly by drugs of abuse via the dopaminergic-CREB system and via an interaction with the stress system, manifesting its influence on compulsive drug seeking. Mu and κ receptors are distributed across all of these brain regions and the spinal cord. For example, “a high correlation between μ receptor mRNA expression and binding is observed in the striatal clusters and patches of the nucleus accumbens and caudate-putamen, diagonal band of Broca, globus pallidus and ventral pallidum, bed nucleus of the stria terminalis, most thalamic nuclei, medial and cortical amygdala, mammillary nuclei, presubiculum, interpeduncular nucleus, median raphe, raphe magnus, parabrachial nucleus, locus coeruleus, nucleus ambiguus, and nucleus of the solitary tract. Differences in μ receptor mRNA and binding distributions are observed in regions such as the neocortex, olfactory bulb, superior colliculus, spinal trigeminal nucleus, and spinal cord, which might be a consequence of receptor transport to presynaptic terminals.” With respect to κ receptor distribution, “a high degree of correlation between κ_1 receptor mRNA expression and binding is observed in regions such as the nucleus accumbens, caudate-putamen, olfactory tubercle, bed nucleus of the stria terminalis, medial preoptic area, paraventricular nucleus, supraoptic nucleus, dorsomedial, and ventromedial hypothalamus, amygdala, midline thalamic nuclei, periaqueductal gray, raphe nuclei, parabrachial nucleus, locus coeruleus, spinal trigeminal nucleus, and the nucleus of the

solitary tract. Differences in κ_1 receptor binding and mRNA distribution in the substantia nigra pars compacta, ventral tegmental area, and neural lobe of the pituitary might be due to receptor transport” [Koob and Le Moal (2006), Opioids. *In Neurobiology of Addiction pp. 152–153*. Academic press, London]. The *arrows* indicate the increase of activities in the positive and negative reinforcement circuits, and the relative differences in the size of the arrows represent the relative differences in the activities

Table 1Comparison of actions of μ and κ opioid receptors

Parameter	μ Receptor	κ Receptor	Reference
Feeding	Stimulation	Stimulation	(Cooper et al. 1985; Gosnell et al. 1987; Jackson and Cooper 1985; Morley et al. 1985)
Drinking	Decrease	Increase	(Hartig and Opitz 1983; Locke et al. 1982)
Locomotion	Increase	Decrease	(Iwamoto 1981)
Place conditioning	Preference	Aversion	(Mucha and Herz 1985)
Submissive behavior	Decrease	Increase	(Benton 1985; Benton et al. 1985)
Seizures	Convulsant	Anticonvulsant	(Lee et al. 1989; Tortella et al. 1986, 1987)
Urinary output	Antidiuretic	Diuretic	(Smith et al. 2008)
Body temperature	Hyperthermia	Hypothermia	(Chen et al. 2005; Handler et al. 1992)
Dopamine release	Increase	Decrease	(Di Chiara and Imperato 1988)
Serotonin release in dorsal raphe	Increase	Decrease	(Tao and Auerbach 2002, 2005)

The cited studies are representative work

Table 2Effects of κ opioid system on the reinforcing effects of drugs in nondependent animals

Drug	κ Receptor agonism	κ Receptor antagonism
Heroin/morphine	↓ (Glick et al. 1995; Kuzmin et al. 1997; Xi et al. 1998) – (Shippenberg et al. 1998)	– (Glick et al. 1995; Negus et al. 1993; Xi et al. 1998)
Alcohol	↓ (Cosgrove and Carroll 2002; Lindholm et al. 2001; Logrip et al. 2008, 2009; Matsuzawa et al. 1998, 1999; Nestby et al. 1999)	↑ (Matsuzawa et al. 1999; Mitchell et al. 2005) ↓ (Logrip et al. 2008) – (Doyon et al. 2006; Matsuzawa et al. 1998; Williams and Woods 1998)
Cocaine	↓ (Carlezon et al. 1998; Crawford et al. 1995; Glick et al. 1995; Mello and Negus 1998; Mori et al. 2002; Negus et al. 1997; Schenk et al. 1999, 2001; Shippenberg et al. 1996, 1998; Tomasiewicz et al. 2008; Zhang et al. 2004) ↑ (Kuzmin et al. 1997; McLaughlin et al. 2006a; Negus 2004) – (Schenk et al. 2001)	↓ (Kuzmin et al. 1998) – Carlezon et al. 1998; Glick et al. 1995; Negus 2004; Negus et al. 1997; Wee et al. 2009)
Nicotine	NA	↑ (Galeote et al. 2009) – (Galeote et al. 2009)

↓, decrease; ↑, increase, –, no effect, NA: not available

Table 3Effect of κ opioid system on withdrawal-related motivational effects of drugs in dependent animals

Drug	κ Receptor agonism	κ Receptor antagonism
Heroin/morphine	↓ (Khazan et al. 1983; Young and Khazan 1983)	↑ (Spanagel et al. 1994) ↓ (Simonin et al. 1998) – (Negus and Rice 2009)
Alcohol	↑ (Holter et al. 2000)	↓ (Holter et al. 2000; Walker and Koob 2008)
Cocaine	NA	↓ (Wee et al. 2009)
Nicotine	↓ (Ise et al. 2002)	– (Galeote et al. 2009)

↓, decrease; ↑, increase; –, no effect; NA, not available

Table 4Effect of κ opioid system on reinstatement of extinguished responding

Drug	κ Receptor agonism	κ Receptor antagonism
Cocaine/amphetamine	<p>↑ (Redila and Chavkin 2008; Valdez et al. 2007)</p> <p>↓ (Schenk and Partridge 2001; Schenk et al. 1999)</p> <p>– (Schenk et al. 1999, 2000)</p>	<p>↓ (Beardsley et al. 2005; Carey et al. 2007; Redila and Chavkin 2008)</p>

↓, decrease; ↑, increase; –, no effect