The American Journal on Addictions, 18: 272–276, 2009

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1080/10550490902925862

The Kappa-Opiate Receptor Impacts the Pathophysiology and Behavior of Substance Use

David Mysels, MD, MBA

Division on Substance Use Research, Columbia Presbyterian Medical Center/New York State Psychiatric Institution, New York, New York

There is increasing evidence that the kappa-opiate receptor, in addition to the mu-opiate receptor, plays an important role in substance use pathophysiology and behavior. As dopamine activity is upregulated through chronic substance use, kappa receptor activity, mediated through the peptide dynorphin, is upregulated in parallel. Dynorphin causes dysphoria and decreased locomotion, and the upregulation of its activity on the kappa receptor likely dampens the excitation caused by increased dopaminergic activity. This feedback mechanism may have significant clinical implications for treating drug dependent patients in various stages of their pathology. (Am J Addict 2009;18:272–276)

With regard to opiate receptors, research regarding substance use disorders has predominantly focused on the μ-opiate receptor. Activation of the μ-receptor has been implicated in anti-nocioception by opiates, as well as the euphoria and sense of reward associated with that class of drugs, as well as other substances of abuse, like cocaine and alcohol. Furthermore, treatments for dependence on opiates generally rely on their ability to compete with drugs of abuse by either blocking and inactivating the receptor (ie, naltrexone) or activating it with an attenuated (buprenorphine) or longer-acting (methadone) substrate that tends to possess less abuse liability than quicker acting, more potent opioids (heroin, morphine).

There is growing evidence that the κ-opiate receptor, and its associated peptide dynorphin, may play an important role in substance dependence as well. During cocaine binges, not only do dopamine levels rise in the brain, activating dopamine receptors, but there is a concomitant increase in μ and κ-receptor activity as well. Increased κ-receptor activation, via dynorphin, seems to lower dopamine levels.[1] The increase in pre-dynorphin mRNA in response to cocaine binges in rats is blocked by dopamine receptor antagonists.[2] Further data from animal studies indicate a directly proportional relationship between dopamine levels in the nucleus accumbens, substantia nigra, and striatum, and tonic dynorphin levels in these areas. As dopamine receptors are activated in these regions, dynorphin levels increase. Sivam et al. concluded that chronic dopaminergic stimulation (via cocaine in this study) was required to increase dynorphin levels in areas of the brain, and that acute sporadic use would not increase dynorphin levels or κ-agonism.[3] When dopamine receptors are blocked by an antagonist, the increased activation of κ-receptors/expression of dynorphin is also blocked,[4] an observation found more consistently with blockade of the dopamine-1 receptor subtype in relation to the dopamine-2 receptor subtype.[4,5] This reciprocal increase is noted in the ventral tegmental area as well, where acute increases in κ-receptor activity decrease dopamine levels in the prefrontal cortex.[5] However, κ-receptor activity does not seem to maintain dopamine tonicity in the prefrontal cortex. Chronically activated κ-receptors associated with decreased dopamine concentrations, reversible upon κ-antagonism, have also been noted in the hypothalamus.[6]

As dynorphin levels increase (ie, κ-receptors are activated), synaptic dopamine levels decline. Studies show that dynorphin blocks both the release, and increases the re-uptake, of dopamine in the synapse. It is apparent that through its substrate peptide dynorphin, κ-receptors function as part of a negative feedback loop to buffer increases in dopamine levels, favoring maintaining a steady tonic level. Increased dopamine levels in the nucleus accumbens, striatum, and the ventral tegmental area are inherent to the reward and salience that drive substance dependence. Data from animal studies suggest that ingestion of alcohol upregulates dopamine activity.[7] Alcohol administration has been found to increase PDYN mRNA expression in ventral and dorsal striatum and the nucleus accumbens, leading to an increased dynorphin concentration in these areas. This increase in dynorphin/kappa activity can last up to 21 days with abstinence.[8,9] Genetic knockout and pharmacological blockade of the kappa receptor both lead to enhanced dopamine activity and excretion.[10,11]

Received November 15, 2008; revised January 8, 2009; accepted January 19, 2009.

Address correspondence to Dr. Mysels, Columbia Presbyterian Medical Center/New York State Psychiatric Institution, Division on Substance Use Research, 1051 Riverside Drive, unit 120, New York, NY 10032. E-mail: myselsd@pi.cpmc.columbia.edu.

It is also apparent that increased production of dynorphin is significantly mediated through upregulation of cAMP response element binding protein (CREB) in the nucleus accumbens.[12,13]

The clinical importance of the direct association between activation of κ-receptors and dopamine receptors in brain regions intimately associated with the effects of substance dependence is manifest when the role and behavior of the κ-receptor is outlined. In addition to antinociceptive properties, which are mostly limited to attenuating internal visceral pain, with possibly some effects on thermal pain,[14] neuropathic and inflammatory pain,[15] the activation of κ-receptors tends to induce dysphoria[16–20] and hypokinesis in subjects. Conversely, antagonists to the κ-receptor tend to cause euthymia and normalized rate of locomotion, as evidenced by improved performance in various learned-helplessness models in animal subjects.[21–24] This makes sense when reflecting that κ-receptors and dynorphin seem to modulate dopamine levels in the hypothalamus and prefrontal cortex (mood) and the substania nigra (movement). Moreover, in studying the effects of prolonged κ-agonism in wild mice vs. κ-receptor knockout mice,[14] naltrexone administration precipitated many more withdrawal symptoms in the wild mice: increased body tremor, ptosis, jumping, sniffing, diarrhea, and generally higher withdrawal scores. These results imply that upregulated κ-agonism may be responsible for several aspects of the clinical experience of human opioid withdrawal, including dysphoria (a known κ-agonist effect), experience shakes, rhinorrhea, and diarrhea.

Researchers postulate that excess or chronic consumption of substances of abuse causes indirect upregulation of the κ-receptor/dynorphin system paralleling the known increase in dopaminergic stimulation, curbing use of the substances by attenuating the euphoria, reward, and hyperkinesis experienced by the user. Dynorphin production appears linked to overexpression of CREB in the nucleus accumbens. Carelezon et al. demonstrated that conditioned place aversion was generally noted as CREB levels increase in the nucleus accumbens in rats chronically exposed to cocaine, and that blocking the kappa opioid receptor negated this anhedonic effect.[25] Negus et al. demonstrated this by showing rhesus monkeys, addicted to cocaine, would cut down their cocaine self-administration in response to κ-receptor agonism.[26] This is demonstrated in autopsy studies of known cocaine users, who manifest decreased μ-receptor populations in the caudate and putamen, and significantly increased κ-receptor populations with elevation in expressed dynorphin mRNA, and decreased dopamine concentration in the same locales.[27] Studies show that the κ-receptor/dynorphin system remains upregulated several days after subjects cease using drugs of abuse.[3] This finding is consistent with the clinical observation that patients withdrawing from substances of abuse tend to exhibit dysphoria for several days before gradually moving toward euthymia.

The clinical assumption is that this persisting kappa upregulation may be what causes "abstinence syndrome," the persisting dysphoria, amotivation, and hypoactivity associated with early drug withdrawal. Strong evidence regarding this model has been demonstrated through animal models with opiates,[28,29] cocaine,[1–4,6,27] alcohol,[10,11] and marijuana.[30,31] Further animal studies show that by antagonizing κ-receptors during states of dysphoria (such as would be seen in early drug withdrawal) one can alleviate the subjects' negative affect without promoting further substance use.[23] However, in one study of chronic alcohol-consuming mice, administration of a kappa antagonist did lead to increased alcohol consumption,[32] while in another study kappa antagonist infusion prior to alcohol consumption in dependent rats resulted in decreased consumption.[33] Zimmer et al. demonstrated that mice lacking κ-receptors were not capable of experiencing the same conditioned place aversion to high-dose marijuana that wild type mice exhibit.[30]

In theory, a κ-receptor antagonist should attenuate early abstinence symptoms in humans as well. While pure κ-receptor antagonists exist, none has been tested on humans. Two prior studies[34,35] employed a creative pharmacological technique to manufacture a κ-antagonist from two compounds with known safety and tolerability to humans: naltrexone and buprenorphine. While naltrexone is an antagonist at all three opiate receptors (μ, δ, and κ), buprenorphine possesses partial agonism at the μ-receptor, while exhibiting strong antagonism at the κ-receptor.[36,37] Specifically, buprenorphine antagonizes kappa-opiate receptors with a Ki 0.072 nM,[38] while naltrexone antagonizes kappa-opiate receptors less strongly by a couple orders of magnitude, with a Ki of about 16nM.[39] Dynorphin A exhibits a Ki of 0.21 nM at the kappa receptor,[40] and should therefore be displaced by the higher affinity buprenorphine. In theory, by administering naltrexone at a dose sufficient to block an individual's mu-opiate receptors, subsequent administration of buprenorphine would manifest pure kappa antagonism since buprenorphine's mu-receptor agonism would have already been blocked by the naltrexone. These two studies were both 12-week open-label studies using a treatment of naltrexone 50 mg plus buprenorphine 4mg; however Gerra et al. used a control group maintained on naltrexone 50 mg daily.[35] Rothman et al. demonstrated 38% completion rate among treatment-seeking heroin addicts and a significant improvement of mood.[34] Gerra et al. demonstrated a 73.3% retention rate among treatment-seeking heroin addicts in the combination treatment group vs. 40% retention rate in the naltrexone-only group. Gerra et al. observed that the combination treatment group submitted 4.45% morphine positive urine toxicology screens, and 9.09% cocaine positive screens, while the naltrexone only group submitted 25% morphine positive and 33.3% cocaine positive.[35] These were statistically significant findings. The combination of buprenorphine and naltrexone shows promise as a treatment with improved retention and abstinence over naltrexone alone.

Mello et al. studied the prevention of reinstatement of cocaine use in chronically addicted rhesus monkeys, using naltrexone, buprenorphine, buprenorphine+naltrexone

(administered simultaneously) and buprenorphine+naltrexone (buprenorphine given 20 minutes after naltrexone). They found buprenorphine alone decreased reinstatement back to cocaine use, naltrexone alone and naltrexone simultaneously administered with buprenorphine had no efficacy. As for buprenorphine given after naltrexone, the efficacy was between that of naltrexone alone and buprenorphine, and was dependent on the dose of buprenorphine given.[41] The authors speculate that the μ-agonism of the buprenorphine was responsible for the effect of the treatment. However kappa-opiate receptor antagonism by the buprenorphine may have contributed to the efficacy of the naltrexone followed by buprenorphine model.

Conversely, it is also postulated that Kappa-opiate receptor agonists have a potential clinical role in the treatment of substance dependence. As discussed earlier, kappa receptors appear to be upregulated in parallel with increased dopaminergic activity during chronic substance use, with the apparent advantage of dampening down excitation in the hypothalamus and nucleus accumbens during these behaviors. In fact, there is significant literature linking this ability to reduce neural excitation in these areas with anticonvulsant properties, especially among patients with temporal lobe epilepsy and strong family histories of the condition.[42]

This "braking mechanism" is seemingly mediated through dynorphin's activity on the kappa-receptor that tends to decrease synaptic dopamine levels, and induce psychomotor retardation and dysphoria, in contrast to the euphoria and psychomotor stimulation induced by the substances of abuse via dopamine. It logically follows that kappa agonists may have the potential clinical use of preventing addicts from getting high and assist them in achieving abstinence. This approach has been studied in animal and human models, as there are kappa-opiate receptor agonists approved for use in humans. The results have been mixed, as there are questions regarding the tolerability and efficacy of this class of medications.

Kappa opiate receptor agonists have held promise for the field of pain management as they apparently have antinociceptive properties and lack the abuse liability of mu-receptor agonists.[43] However, at doses high enough for pain control, several troubling side effects emerge. Many studies demonstrate weakness, sweating, fatigue, vertigo, dizziness, lightheadedness and other aversive symptoms caused by kappa agonists.[42–44] Kappa agonists also induce dose-dependent mental status changes, ranging from anxiety, mood lability, disturbances of time and space, depersonalization/derealization, to frank visual disturbances described as pulsating waves in inanimate objects, and the sensation of melting into the floor.[42–44] In a study of rats, the kappa agonist U50,488 dose-dependently reduced prepulse inhibition to auditory gating, a hypothesized model for psychotic thought disorder.[45] A naturally occurring kappa-receptor agonist, Salvinorin A, is found in the plant Salvia divinorum, a mint found only in the Oaxaca region of Mexico, and used by indigenous people in religious ceremonies.[46] It has known hallucinogenic properties, similar to those described above, and its only active ingredient is the kappa agonist. It is the only known hallucinogen to act via this mechanism.[47] It is also hypothesized that postictal psychosis may be caused in part by acute upregulation of kappa activity as a by-product of a physiological attempt to create seizure control via dynorphin activity.[42] Lastly, kappa-receptor agonists are potent diuretics in animals and humans; they act by increasing free-water output while not increasing electrolyte excretion, thereby significantly lowering the urine's osmolality.[44,47–50]

Kappa agonists have demonstrated inconsistent efficacy in substance use models. Negus et al. demonstrated that the kappa agonists ethylketocyclazocine (EKC) and U50,488 both significantly reduced self-administration of cocaine by rhesus monkeys at the peak of the cocaine dose-effect curve.[26] The monkeys were administered the treatments multiple times daily over ten days without developing tolerance to the kappa agonist's apparent reduction of preference for cocaine. However, individual monkeys also developed aversion to their food as well as cocaine, more often during treatment with U50,488 than EKC. They also developed emesis and sedation, but grew tolerant to these effects rapidly. Suzuki et al. demonstrated that the kappa agonist U50,488 was able to attenuate preference for morphine in cocaine discriminative rats at a significantly lower dose (2–4 mg/kg) than that required to attenuate preference for cocaine (8 mg/kg), which they say is consistent with other studies.[51] Using a novel kappa agonist, TRK-820, Hasebe et al. demonstrated that the kappa agonist significantly decreased reward from cocaine and morphine in a rat model.[52] Walsh et al. tested whether the kappa agonist enadoline would reduce self-administration of cocaine in humans.[53] At rather large doses (80 mcg/kg), enadoline seemed to mildly reduce the pleasure derived from acute administration of cocaine, but it had no effect on reducing self-administration. However, this study demonstrated that this relatively high dose was well tolerated by human subjects, even when concomitantly administered with cocaine.[53]

Another potential therapeutic application for kappa agonists may be in the treatment of mania. Cohen and Murphy demonstrated significant and rapid reduction of manic symptoms using two doses of intramuscular pentazocine two hours apart.[54] Psychosis and dysphoria were not observed side effects. In light of the fact that 14–65% of patients in a treatment setting for bipolar disorder have a drug use disorder, compared to 6–14% of the general population[55] and 56% of patients diagnosed with bipolar disorder have a lifetime substance use disorder,[56] kappa-agonist therapy may hold promise as a unique treatment in this population.

Kappa agonists also have been studied in models of alcohol consumption. Acute kappa agonist treatment, presumably by counteracting dopamine reward, decreased ethanol consumption in rats.[57] Chronic exposure to a kappa agonist during a period of abstinence was associated with increased alcohol consumption in rats.[58] In a model of current abuse, kappa agonists can decrease alcohol consumption, while in a model of recent abstinence the kappa-induced dysphoria may trigger relapse.

The hypothesized feedback loop of an upregulated kappa agonist response to the dopaminergic stimulation by substances of abuse is not only interesting from a physiological standpoint, but seems to hold significant clinical promise. In the model, when chronic users are removed from their drug supply, unopposed kappa agonism leads to a state of dysphoria and lethargy, known as "abstinence syndrome." The addition of a kappa receptor antagonist may allay some of these symptoms, allowing for a smoother and more attainable detoxification.

According to the ECA study, 18% of people with a history of major depressive disorder also have a lifetime drug use disorder. Furthermore, having a drug use disorders makes one nearly five times more likely than those without one to have a major depressive episode.[56] Animal experiments suggest kappa antagonists may possess antidepressant-like effects. With κ-receptor antagonism seemingly able to ameliorate withdrawal dysphoria in several substances of abuse, there is speculation that this process may have application in the treatment of polysubstance use disorders with comorbid depressive disorders,[51,59] a particularly challenging clinical constellation.

Conversely, kappa agonists may play a role in outpatient settings where patients still have access to substances of abuse. When administered in temporal proximity with the drug of abuse, the kappa agonist could potentially dampen the high from the drug, decreasing the likelihood of relapse. As stated earlier, kappa agonists may have a special role in the treatment of bipolar disorder with comorbid substance use disorder. However, while kappa antagonists do not appear to elicit significant side effects, the clinical utility of kappa agonists may be limited by significant diuresis and mental status changes they tend to incur.

A clinician utilizing therapy based on the kappa system would need to maintain vigilance regarding the patient's current substance use, preferring to use kappa antagonists during abstinence and kappa agonists during relapses. Since kappa activity dampens the reward and excitation from drugs of abuse, a patient still using drugs may get an even stronger high, unopposed by dynorphin. Conversely, a dysphoric patient in a drug-abstinent milieu receiving kappa agonist treatment may exhibit worsened depression, possibly leading to relapse.

The application of kappa opiate-receptor agonists and antagonists to the treatment of substance use disorders clearly invites further investigation. While compelling animal and human data already exist regarding this model in terms of opiate and cocaine dependence, and alcohol dependence, few trials have applied the kappa upregulation theory to marijuana and nicotine studies.[30,31,52] Evidence of treatment effects of kappa ligands for affective pathology (mania by agonists and depression with antagonists), would suggest pursuing further study of the dually diagnosed population.

REFERENCES

1. Kreek MJ. Cocaine, dopamine, and the endogenous opioid system. *J Addict Dis*. 1996;15:73–96.
2. Spangler R, Zhou Y, Maggos CE, Zlobin A, Ho A, Kreek MJ. Dopamine antagonists and "bing" cocaine effects on rat opioid and dopamine transporter mRNAs. *NeuroReport*. 1996;7:2196–2200.
3. Sivam SP. Cocaine selectively increases striatonigral dynorphin levels by a dopaminergic mechanism. *J Pharmacol Exp Ther.* 1989;250:818–824.
4. Smiley PL, Johnson M, Bush L, Gibb JW, Hanson GR. Effects of cocaine on extrapyramidal and limbic dynorphin systems. *Pharmacology*. 1990;253:938–943.
5. Shippenberg TS, Zapata A, Chefer VI. Dynorphin and the pathophysiology of drug addiction. *Pharmacol Ther*. 2007;116:306–321.
6. Bhargava HN, Gulati A, Ramarao P. Binding characteristics of 3HSCH 23390 in spinal cord and discrete brain regions of κ-opiate tolerant-dependent and abstinent rats. *Pharmacology.* 1991;42:121–127.
7. Yoshimoto K, McBride WJ, Lumeng L, Li TK. Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens. *Alcohol.* 1991;9:17–22.
8. Gulya K, Orpana AK, Sikela JM, Hoffman PL. Prodynorphin and vasopressin mRNA levels are differentially affected by chronic ethanol ingestion in the mouse. *Brain Res Mol Brain Res*. 1993;20:1–8.
9. Lindholm S, Ploj K, Franck J, Nylander I. Repeated ethanol administration induces short- and long-term changes in enkephalin and dynorphin tissue concentrations in rat brains. *Alcohol*. 2000;22:165–171.
10. Zapata A, Shippenberg TS. Endogenous K-opioid receptor systems modulate the responsiveness of mesoaccumbal dopamine neurons to ethanol. *Alcohol Clin Exp Res.* 2006;30:592–597.
11. Doyon WM, Howard EC, Shippenberg TS, Gonzales RA. K-opioid receptor modulation of accumbal dopamine concentration during operant ethanol self-administration. *Neuropharmacol*. 2006;51:487–496.
12. Todtenkopf MS, Marcus JF, Portoghese PS, Carlezon WA. Effects of k-opioid receptor ligands on intracranial self-stimulation in rats. *Psychopharmacology*. 2004;172:463–470.
13. Carlezon Jr. WA, Duman RS, Nestler EJ. The many faces of CREB. *TRENDS in Neurosciences*. 2005;28:436–445.
14. Simonin F, Valverde O, Smadja C, et al. Disruption of the κ-opioid receptor gene in mice enhances sensitivity to chemical visceral pain, impairs pharmacological actions of the selective κ-agonist U-50,488H and attenuates morphine withdrawal. *EMBO J*. 1998;117:886–897.
15. Wang Z, Gardell LR, Ossipov MH, et al. Pronociceptive actions of dynorphin maintain chronic neuropathic pain. *J Neurosci*. 2001;21:1779–1786.
16. Newton SS, Thome J, Wallace TL, et al. Inhibition of cAMP response element-binding protein or dynorphin in the nucleus accumbens produces an antidepressant-like effect. *J Neurosci*. 2002;24:10883–10890.
17. Ukai M, Suzuki M, Mamiya T. Effects of U-50,488H, a κ-opioid receptor agonist, on the learned helplessness model of depression in mice. *J Neural Transm.* 2002;109:1221–1225.
18. Gaveriaux-Ruff C, Kieffer BL. Opioid receptor genes inactivated in mice: the highlights. *Neuropeptides.* 2002;36):62–71.
19. Vortherms TA, Roth BL. Salvinorin A: from natural product to human therapeutics. *Mol Interv*. 2006;6:257–265.
20. Bruchas MR, Land BB, Aita M, et al. Stress-induced p38 mitogen-activated protein kinase activation mediates κ-opioid-dependent dysphoria. *J Neurosci*. 2007;27:11614–11623.
21. Mague SD, Pliakas AM, Todtenkopf MS, et al. Antidepressant-like effects of κ-opioid receptor antagonists in the forced swim test in rats. *J Pharmacol Exp Ther.* 2003;305:323–330.
22. McLaughlin JP, Marton-Popvici M, Chavkin C. Kappa opioid receptor antagonism and prodynorphin gene disruption block stress-induced behavioral responses. *J Neurosci*. 2003;23:5674–5683.
23. Beardsley PM, Howard JL, Shelton KL, Carroll FI. Differential effects of the novel κ-opioid receptor antagonist, JDTic, on reinstatement of cocaine-seeking induced by foot shock stressors vs. cocaine primes and its antidepressant-like effects in rats. *Psychopharmacology.* 2005;183:118–126.
24. Reindl JD, Rowan K, Carey AN, Peng X, Neumeyer JL, McLaughlin JP. Antidepressant-like effects of the novel κ-opioid antagonist MCL-144B in the forced-swim test. *Pharmacology.* 2008;81:229–235.

25. Carlezon Jr. WA, Thome J, Olson VG, et al. Regulation of cocaine reward by CREB. *Science*. 1998;282:2272–2275.
26. Negus SS, Mello NK, Portoghese PS, Lin C. Effects of κ-opioids on cocaine self-adnministration by Rhesus Monkeys. *J Pharmacol Exp Ther.* 1997;282:44–55.
27. Hurd YL, Herkenham M. Molecular alterations in the neostriatum of human cocaine addicts. *Synapse.* 1993;13:357–369.
28. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA*. 1988;85:5274–5278.
29. Acquas E, Di Chiara G. Depression of mesolimbic dopamine transmission and Sensitization to Morphine During Opiate Abstinence. *J Neurochem*. 1992;58:1620–1625.
30. Zimmer A, Valjent E, Konig M, et al. Absence of delta-9-tetrahydrocannabinol dysphoric effects in dynorphin-deficient mice" *J Neurosci*. 2001;21:9499–9505.
31. Ghozland S, Matthes HWD, Simonin F, Filliol D, Kieffer B, Maldonado R. Motivational effects of cannabinoids are mediated by κ-opioid and κ-opioid receptors. *J Neurosci*. 2002;22:1146–1154.
32. Mitchell JM, Liang MT, Fields HL. A single injection of the kappa opioid antagonist norbinaltorphimine increases ethanol consumption in rats. *Psychopharmacology.* 2005;182:284–392.
33. Walker BM, Koob GF. Pharmacological evidence for a motivational role of kappa-opioid systems in ethanol dependence. *Neuropsychopharmacology.* 2008;33:643–652.
34. Rothman RB, Gorelick DA, Heishman SJ, et al. An open-label study of a functional opioid kappa antagonist in the treatment of opioid dependence. *J Subst Abuse Treat*. 2000;18:277–281.
35. Gerra G, Fantoma A, Zaimovic A. Naltrexone and buprenorphine combination in the treatment of opioid dependence. *J Psychopharmacol*. 2006;20:806–814.
36. Negus SS, Dykstra LA. Kappa antagonist properties of buprenorphine in the shock titration procedure. *Euro J Pharmacol*. 1988;156:77–86.
37. Leander JD. Buprenorphine is a potent κ-opioid receptor antagonist in pigeons and mice. *Euro J Pharmacol*. 1988;151:457–461.
38. Romero DV, Partilla JS, Zheng Q, et al. Opioid peptide receptor studies. 12. Buprenorphine is a potent and selective mu/kappa antagonist in the [^{35}S]-GTP-gamma-S functional binding assay. *Synapse.* 1999;34:83–94.
39. Giordano AL, Nock B, Cicero TJ. Antagonist-induced up-regulation of the putative epsilon opioid receptor in rat brain: comparison with kappa, mu, and delta opioid receptors. *J Pharmacol Exp Ther*. 1990;255:536–540.
40. Kumar V, Guo D, Marella M, et al. Use of receptor chimeras to identify small molecules with high affinity for the dynorphin A binding domain of the k opioid receptor. *Bioorganic & Molecular Chemistry Letters*. 2008;18:3667–3671.
41. Mello NK, Lukas SE, Mendelson JH, Drieze J. Naltrexone-buprenorphine interactions: effects on cocaine self-administration. *Neuropsychopharmacology.* 1993;9:211–224.
42. Bortolato M, Solbrig MV. The price of seizure control: dynorphins in interictal and postictal psychosis. *Psychiatry Res*. 2007;151:139–143.
43. Pfeiffer A, Brantl V, Herz A, Emrich HM. Psychotomimesis mediated by kappa opiate receptors. *Science*. 1986;233:774–776.
44. Walsh SL, Strain EC, Abreu ME, Bigelow GE. Enadoline, a selective kappa opioid agonist: comparison with butorphanol and hydromorphone in humans. *Psychopharmacol*. 2001;157:151–162.
45. Bortolato M, Ary GN, Frau R, et al. Kappa opioid receptor activation disrupts prepulse inhibition of the acoustic startle in rats. *Biological Psychiatry*. 2005;57:1550–1558.
46. Roth BL, Baner K, Westkaemper R, et al. Salvinorin A: a potent naturally occurring nonnitrogenous kappa opioid selective agonist. *Proc Natl Acad Sci*. 2002;99:11934–11939.
47. Peters GR, Ward NJ, Antal EG, Lai PY, deMaar EW. Diuretic actions in man of a selective kappa opioid agonist: U-62,066E. *J Pharmacol Exp Ther.* 1987;240:128–131.
48. Pfeiffer A, Knepel W, Braun S, Meyer HD, Lohman H, Brantl V. Effects of a kappa-opioid agonist on adrenocorticotropic and diuretic function in man. *Horm Metab Res*. 1986;18:842–848.
49. Reece PA, Sedman AJ, Rose S, Wright DS, Dawkins R, Rajagopalan R. Diuretic effects, pharmacokinetics, and safety of a new centrally acting kappa-opioid agonist (CI-977) in humans. *J Clin Pharmacol*. 1994;34:1126–1132.
50. Qi W, Ebenezar K, Samhan MA, Smith FG. Renal responses to the k-opioid receptor agonist U-50488H in conscious lambs. *Am J Physiol Regul Integr Comp Physiol.* 2007;293:162–168.
51. Suzuki T, Mori T, Tsuji M, et al. Differential effects of μ-, δ-, and κ-opioid receptor agonists on the discriminative stimulus properties of cocaine in rats. *Euro J Pharmacol*. 1997;324:21–29.
52. Hasebe K, Kawai K, Suzuki T, et al. Possible pharmacotherapy of the opioid kappa receptor agonist for drug dependence. *Ann NY Acad Sci.* 2004;1025:404–413.
53. Walsh SL, Geter-Douglas B, Strain EC, Bigelow GE. Enadoline and Butorphanol: Evaluation of k-agonists on cocaine pharmacodynamics and cocaine self-administration.*J Pharmacol Exp Ther*. 2001;299:147–158.
54. Cohen BM, Murphy B. The effects of pentazocine, a kappa agonist, in patients with mania. *Int J Neuropsychopharm*. 2008;11:243–247.
55. Levin FR, Hennessy G. Bipolar disorder and substance abuse. *Biol Psychiatry.* 2004;56:738–748.
56. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA.* 1990;264:2511–2518.
57. Lindholm S, Werme M, Brene S, Franck J. The selective κ-opioid receptor agonist U50,488H attenuates voluntary ethanol intake in the rat. *Behav Brain Res*. 2001;120:137–146.
58. Holter SM, Henniger MSH, Lipkowski AW, Spannagel R. Kappa-opioid receptors and relapse-like drinking in long-term ethanol-experienced rats. *Psychopharmacol*. 2000;153:93–102.
59. McCann DJ. Potential of buprenorphine/naltrexone in treating polydrug addiction and co-occurring psychiatric disorders. *Clin Pharmacol Ther.* 2008;83:627–630.