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κ Opioids as Potential Treatments for Stimulant Dependence

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Thomas E. Prisinzano,[1] Kevin Tidgewell,[1] and Wayne W. Harding[1]

[1]Division of Medicinal & Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242

ABSTRACT

Stimulant abuse is a major problem in the United States and the development of pharmacological treatments for stimulant abuse remains an important therapeutic goal. Classically, the "dopamine hypothesis" has been used to explain the development of addiction and dependence of stimulants. This hypothesis involves the direct increase of dopamine as the major factor in mediating the abuse effects. Therefore, most treatments have focused on directly influencing the dopamine system. Another approach, which has been explored for potential treatments of stimulant abuse, is the use of κ opioid agonists. The κ receptor is known to be involved, via indirect effects, in synaptic dopamine levels. This review covers several classes of κ opioid ligands that have been explored for this purpose.

KEYWORDS: kappa, opioid, self-administration, stimulant

INTRODUCTION

Drug dependence is a chronic, relapsing disorder in which compulsive drug-seeking and drug-taking behavior persists despite serious negative consequences.[1] The chronic use of abused drugs, such as central nervous system (CNS) stimulants, causes adaptive changes that lead to drug tolerance, physical dependence, drug craving, and relapse.[2] At present, there is no single theory to explain all aspects of drug dependence. Generally, addictive substances are able to act as positive reinforcers (producing pleasurable effects) or as negative reinforcers (relieving withdrawal symptoms).[1] However, environmental effects associated with drug use are also able to produce conditioned responses in the absence of drug.

Among the most widely abused substances in the world are the CNS stimulants cocaine (**1**) and methamphetamine (METH) (**2**) (Figure 1). The abuse of these compounds has had great effects on public health.[3,4] The National Drug Threat Survey data for 2003 indicates that 37.0% of state and local law enforcement agencies nationwide identify cocaine (both powder and crack) as their greatest drug threat, higher than any other drug type.[5] In addition to the problems associated with cocaine abuse, a rise in the abuse of METH has been noted in West Coast cities.[6] In less than 10 years, METH has grown from a problem limited to the Southwestern and Midwestern United States to one of nationwide concern.[7-9] The number of METH laboratory seizures increased from 8577 in 2001 to 9188 in 2002, to 9815 in 2003.[5] More than 51.0 kg of METH was seized in Iowa alone.[10] This highlights the growing problem of METH dependence. The primary market areas for METH are Los Angeles, Phoenix, San Diego, San Francisco, and the central states (Arkansas, Illinois, Indiana, Missouri, and Iowa).[5] State and local law enforcement agencies in the central states identify METH as their greatest drug threat.[5] These facts further illustrate the problem of METH dependence, as well as the pressing need for the development of stimulant abuse therapeutics in the central states such as Iowa.

Currently, there are various compounds being pursued as possible stimulant abuse therapeutics based on the "dopamine hypothesis."[11-15] The dopamine hypothesis considers the ability of stimulants to increase extracellular dopamine (DA) as being of primary importance in mediating the addictive effects of stimulants. The dopamine hypothesis explains some aspects of stimulant addiction, but other neurochemical mechanisms appear to be involved.[16-19] For example, cocaine has similar affinity for the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET).[20] Importantly, several studies indicate that the SERT and the NET also play a role in the pharmacological effects of cocaine.[21-24]

At present, there are no United States Food and Drug Administration (FDA)-approved therapeutic agents available for the treatment of stimulant abuse or for the prevention of its relapse. However, various agonist-like, replacement type of medications are currently being pursued.[11,25-28] This helps to support the hypothesis that agonist-substitution pharmacotherapy is a reasonable approach to developing pharmacotherapies for stimulant dependence.[28] However, additional approaches need to be explored.

Corresponding Author: Thomas E. Prisinzano, Division of Medicinal & Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242. Tel: (319) 335-6920; Fax: (319) 335-8766; E-mail: thomas-prisinzano@uiowa.edu

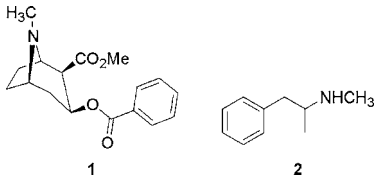

Figure 1. Structures of cocaine (**1**) and methamphetamine (**2**).

A large body of evidence indicates that κ opioid receptors may be involved in the modulation of some abuse-related effects of CNS stimulants.[29,30] Administration of cocaine or methamphetamine upregulates κ receptors.[31,32] Like other opioid receptors, κ receptors have a role in the modulation of immune responses,[33] as well as some effects on human immunodeficiency virus (HIV) in vitro.[34-36] Interestingly, κ receptors have a role in the modulation of dopamine levels.[37-44] In particular, κ receptor activation modulates DA uptake in the nucleus accumbens[45] and κ agonists directly inhibit dopamine neurons in the midbrain.[43] Repeated treatment with κ agonists alters D2 receptor density[46] and function,[47] as well as attenuating the locomotor effects of cocaine in rats.[48] Furthermore, administration of κ agonists in rats alters levels of the dopamine transporter,[49,50] decreases cocaine-induced dopamine levels, blocks cocaine-induced place preference, and attenuates cocaine-induced locomotor activity.[51,52] Furthermore, κ agonists also attenuated the reinstatement of extinguished drug-taking behavior.[53] These findings indicate that the κ opioid receptors may be involved in the antagonism of some abuse-related effects of cocaine, offering a pharmacological approach to treat cocaine abuse. However, κ opioid receptor agonists, while being effective in reducing cocaine self-administration in monkeys, produce side effects including sedation and vomiting.[29] It has been speculated that the addition of μ agonist/antagonist activity to the κ agonist might lessen the incidence of side effects and encompass a useful treatment for cocaine abuse.[54]

Previous pharmacological approaches identified apparent subtypes of κ opioid receptors.[55-60] The opioid receptors κ_1 and κ_2 were identified due to their preferential binding to arylacetamides and benzomorphans, respectively.[61,62] In addition, these subtypes show differences in the affinity and selectivity of the κ antagonist nor-BNI.[55,63-65] However, only one κ opioid receptor clone has been identified at the present time.[66] Recent work has suggested that the apparent receptor subtypes may actually be different affinity states of the same receptor.[67] The relevance of the proposed subtypes and/or different affinity states in reducing cocaine abuse has not been fully elucidated.

The present review focuses on κ agonists explored as potential stimulant abuse therapeutics. Interestingly, a selective partial κ agonist has not been evaluated as a potential stimulant abuse therapeutic. This type of compound has the potential to antagonize the effects of CNS stimulants like a full κ agonist but likely without the psychotomimetic side effects. This hypothesis, however, awaits further testing.

κ Opioid Receptor Agonists

The endogenous ligand for the κ receptor is dynorphin A (Dyn A).[68,69] It binds with subnanomolar affinity at κ receptors but is quite active at all 3 opioid receptors. Dyn A has been shown to significantly decrease basal dopamine levels, as well as block increases in dopamine levels, block the formation of conditioned place preference, and attenuate locomotion induced by 15 mg/kg of cocaine in mice.[52] There are also several classes of nonpeptide κ agonists that have been investigated as potential stimulant abuse therapeutics.[70,71] These include the benzomorphans, arylacetamides, epoxymorphinans, and natural products such as the *Iboga* alkaloids and neoclerodane diterpenes.

Cyclazocine, Bremazocine, and 8-CAC

Cyclazocine (Figure 2) is a benzomorphan originally synthesized in 1962 with mixed κ agonist and μ antagonist activity.[72] The treatment of rats with (±)-cyclazocine showed a dose dependent decrease in cocaine intake with no alteration of water intake.[73] In addition, (±)-cyclazocine significantly attenuated the increased dopamine levels induced by nicotine infusion and enhanced nicotine-induced increases in dopamine metabolites.[74] However, cyclazocine did not significantly alter cocaine self-administration in rhesus monkeys.[29] Interestingly, bremazocine, a structural analog and mixed κ agonist and μ antagonist, produced a significant and dose-dependent decrease in cocaine self-administration.[29] A recent study of cyclazocine in humans found that cocaine effects were consistently lower on the last administration following 4 days of pretreatment with cyclazocine compared with the first administration.[75] This study is suggestive of the utility of κ opioids to diminish acute effects of cocaine in humans.

As mentioned earlier, bremazocine has been shown to reduce cocaine-maintained behavior in rhesus monkeys.[29] An additional study found that pretreatment of bremazocine dose dependently decreased self-administration of cocaine,

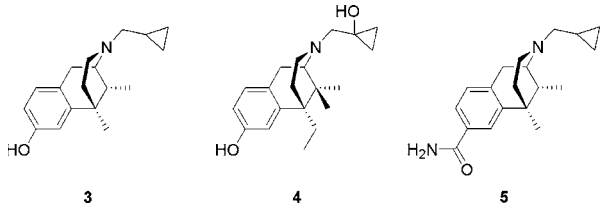

Figure 2. Structures of cyclazocine (**3**), bremazocine (**4**), and 8-CAC (**5**).

ethanol, and PCP.[76] This work also indicates that κ agonists attenuate self-administration of drug and nondrug reinforcers to smoked cocaine base, oral ethanol, PCP, and saccharin in rhesus monkeys. Furthermore, bremazocine reduces unrestricted free-choice ethanol self-administration in rats without affecting sucrose consumption.[77] This indicates the potential utility of bremazocine for ethanol dependence.

More recently, 8-CAC was synthesized to obtain a benzomorphan with a longer duration of action for potential use in treating cocaine abuse.[78] Additional testing showed that 8-CAC does not act as a μ opioid antagonist and that it is significantly longer acting than cyclazocine (15 hours vs 2 hours).[79] Acute administration of 8-CAC was found to reduce cocaine-maintained responding over a 10-fold range of cocaine unit doses.[80] However, doses of 8-CAC that decreased cocaine self-administration were similar to doses that decreased food-maintained responding. The results, however, suggest that mixed action κ/μ agonists might decrease cocaine self-administration with a lower incidence of undesirable effects. Other mixed κ/μ agonists also appear to offer advantages over selective κ agonists.[81]

U50,488, U69,593, AND R-84760

Several highly κ selective arylacetamides,[82-84] U50,488, U69,593, and R-84760 (Figure 3), have also been examined as potential stimulant abuse therapeutics. The first findings that κ agonists may be useful as functional cocaine antagonists were based on the actions of U50,488 in an in vivo microdialysis experiment in rats.[85] Maisonneuve et al showed that pretreatment with U50,488 attenuated the cocaine induced elevation of dopamine levels and that this phenomenon could be reversed by the κ opioid antagonist nor-BNI. Later work showed that U50,488 and fentanyl do not alter the discriminative stimulus effects of cocaine but U50,488 attenuates the cocaine induced responses.[86] Similarly, U50,488 produced dose-related decreases in self-administration of both morphine and cocaine.[87] A higher dose of U50,488 was needed to decrease the rate of water self-administration and the effect was fully reversible by treatment with nor-BNI. Furthermore, U50,488 significantly blocks intravenous (IV) administration of cocaine and decreases morphine intake in rats.[88] These results also indicate that κ activation seems to increase the sensitivity for drug reward. Interestingly, U50,488 was found to attenuate the discriminative effects of low-dose (3.0 mg/kg) but not high-dose (10.0 mg/kg) cocaine.[89] These results suggest that cocaine-opioid interactions are dependent on the training dose of cocaine. In addition, chronic administration of U50,488 produces a dose-dependent, κ−receptor-mediated, and often sustained decrease in cocaine self-administration of 2 different doses of cocaine in rhesus monkeys.[90] However, doses that decrease self-administration also produce decreases in food-maintained responding, emesis, and sedation. Further work with U50,488 showed variable results in rhesus monkeys trained to discriminate cocaine (0.4 mg/kg) from saline.[91] Recent behavioral work indicates that U50,488 produces a κ opioid−receptor-mediated increase in the relative reinforcing effects of cocaine compared with food.[92] This study suggests that chronic κ agonist treatment may mimic some effects of stress that modulate the reinforcing effects of abused drugs.

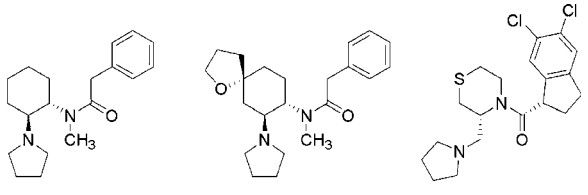

Figure 3. Structures of U50,488 (**6**), U69,593 (**7**), and R-84760 (**8**).

Various studies have shown arylacetamide **7** to modulate the neurochemical and behavioral effects of cocaine. The administration of U69,593 attenuates cocaine's discriminative stimulus properties, its conditioned reinforcing effects, its self-administration, and the reinstatement of extinguished drug-taking behavior.[53,93] In addition, U69,593 attenuates the psychomotor stimulant effects of amphetamine and cocaine and modulates neurotoxic effects of METH.[94,95] Furthermore, U69,593 attenuates the discriminative stimulus effects of amphetamine in squirrel monkeys.[96] However, this study also suggests that there are large individual differences in the ability of κ opioids to alter the discriminative effects of amphetamine.

Recently, the effects of R-84760 on basal levels of dopamine, cocaine-induced conditioned place preference, and cocaine-induced locomotor activity in mice were evaluated.[51] Arylacetamide R-84760 was found to decrease levels of dopamine in a dose-dependent manner. In addition, 0.1 mg/kg, i.p. of R-84760 blocked cocaine-induced conditioned place preference and also significantly attenuated cocaine-induced locomotion. Interestingly, R-84760 did not produce conditioned place aversion seen with other arylacetamides, such as U50,488 or U69,593.

NALFURAFINE (TRK-820)

Currently, the novel epoxymorphinan nalfurafine (TRK-820) is under investigation as an antipruritic.[97] Nalfurafine (Figure 4) is a high-affinity κ agonist.[98,99] Further pharmacological testing has shown this compound to produce potent antinociception in nonhuman primates[100] and to be more potent than U50,488H in mice.[101] Interestingly, nalfurafine does not produce the psychotomimetic effects in healthy human volunteers seen with other κ agonists[102] and

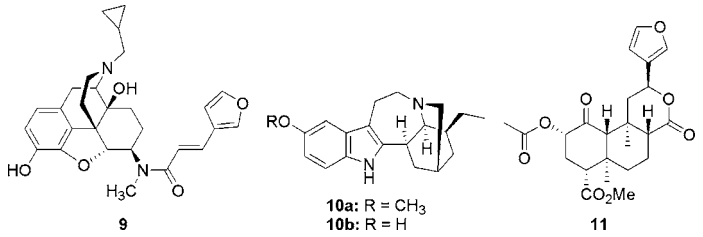

Figure 4. Structures of nalfurafine (**9**), ibogaine (**10a**), 12-hydroxyibogamine (**10b**), and salvinorin A (**11**).

develops lower tolerance in comparison to other κ agonists.[103] Behavioral testing in rats found nalfurafine to significantly attenuate the discriminative and rewarding effects of cocaine and that these effects were blocked by norBNI.[104] A low dose of nalfurafine (10–40 μg/kg) was found not to induce place preference or place aversion. However, a large dose (80 μg/kg) significantly induced place aversion. Further work has shown nalfurafine to attenuate the rewarding and locomotor effects of morphine in mice.[105] Additionally, nalfurafine decreased the mecamylamine-precipitated nicotine withdrawal aversive effect in rats chronically treated with nicotine.[105] Interestingly, nalfurafine did not completely substitute for U50,488 in rats trained to discriminate U50,488 from saline.[106] In cross substitution experiments, U50,488 was found to substitute for nalfurafine. These findings suggest that there are qualitative differences between the discriminative effects of U50,488 and nalfurafine.

IBOGAINE

Ibogaine is a naturally occurring indole alkaloid isolated from the root, rootbark, stems, and leaves of the African shrub *Tabernanthe iboga*.[107] This plant has been used by indigenous peoples in low doses to combat fatigue and hunger and in higher doses as a sacrament in religious rituals.[108,109] Interest in ibogaine as a drug abuse therapeutic has been based on anecdotal reports of its efficacy in eliminating, in a single dose, the withdrawal symptoms and long-term drug craving for cocaine and heroin.[108] The psychopharmacology of ibogaine is complex due to its affinity for several receptors, transporters, and ion channels.[107] In addition, its primary metabolite, 12-hydroxyibogamine, is also biologically active.[110,111] Among these are the dopaminergic, serotonergic, adrenergic, muscarinic, NMDA, and opioidergic receptor systems.[112] The mechanism by which ibogaine exerts its anti-addictive effects is presently unknown although several receptor systems have been implicated in its activity.[113,114] However, it has been speculated that its κ agonist actions contribute to its effects on stimulant self-administration.[115,116]

In self-administration studies in rats, a single injection of ibogaine (40 mg/kg, i.p.) produced a significant decrease in cocaine intake.[117,118] Cocaine-induced locomotor activity is decreased by ibogaine in rodents.[119,120] Pretreatment of ibogaine has been shown to reduce the neuroadaptations produced by chronic cocaine administration in rats.[121] Under open label conditions of opioid detoxification in 33 human subjects, ibogaine eliminated signs of opioid withdrawal and drug seeking behavior in 25 cases.[122] This effect was sustained throughout the 72-hour period of posttreatment. The potential neurotoxic effects of ibogaine have raised concerns over its clinical use.[123] However, analogs of ibogaine are currently being explored as potentially safer medications.[124-128]

SALVINORIN A

Recently, salvinorin A, the presumed active component of the hallucinogenic Mexican mint *Salvia divinorum*, was found to be a potent and selective κ agonist in vitro using a screen of 50 receptors, transporters, and ion channels.[129] Functional studies also demonstrated that salvinorin A is a potent and selective agonist at both cloned κ and native κ opioid receptors expressed in guinea pig brain. Surprisingly, salvinorin A was found to be more efficacious than U50,488 or U69,593 and similar in efficacy to Dyn A as a κ opioid receptor agonist.[130] A recent report compared the activity of salvinorin A to epoxymorphinan nalfurafine.[99] Binding affinities using [^{3}H]diprenorphine at κ receptors found nalfurafine (K_i = 75 pM) to have higher affinity than salvinorin A (K_i = 7.9 nM). Both compounds were found to be full agonists in the [^{35}S]GTP-γ-S binding assay with nalfurafine (EC_{50} = 25 pM) >> salvinorin A (EC_{50} = 2.2 nM). Interestingly, salvinorin A was found to be 40-fold less potent in promoting internalization of the hKOR compared with U50,488 and showed little anti-scratching activity and no antinociception in mice.[99]

There has been only one report of behavioral testing of salvinorin A in nonhuman primates.[131] All subjects (n = 3) dose-dependently emitted ≥90% U69,593-appropriate responding after subcutaneous injection of salvinorin A (0.001–0.032 mg/kg). Quadazocine (0.32 mg/kg), an opioid antagonist, blocked the effects of salvinorin A. However, the long-lasting κ selective antagonist GNTI (1 mg/kg; 24 hours pretreatment) antagonized the effects of salvinorin A in 2 of 3 monkeys. These findings are consistent with the in vitro characterization of salvinorin A as a κ agonist. Therefore, based on its similar mechanism of action to the previously described compounds, salvinorin A has the potential to reduce cocaine self-administration. However, the ability of salvinorin A to block cocaine self-administration has not been reported to date.

CONCLUSION

At present, there are no FDA-approved therapeutic agents available for the treatment of stimulant abuse or for the

prevention of its relapse. Many types of medications are currently being pursued based on the "dopamine hypothesis." However, additional approaches need to be explored. κ Opioid receptor agonists offer an indirect approach to the modulation of some abuse-related effects of CNS stimulants. Both selective and nonselective κ opioids have been shown to attenuate stimulant self-administration in a variety of animal models. A selective partial κ agonist, however, has not been evaluated to date. While highly selective κ agonists attenuate stimulant self-administration in nonhuman primates, they are associated with behavioral side effects such as sedation and emesis. Mixed-action κ agonists decrease stimulant self-administration with a lower incidence of undesirable effects. The full extent to which κ agonists antagonize stimulant self-administration remains to be determined.

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