Salvinorin A and related compounds as therapeutic drugs for psychostimulant-related disorders

ARTICLE *in* CURRENT DRUG ABUSE REVIEWS · OCTOBER 2014

4 AUTHORS, INCLUDING:

Rafael Guimarães dos Santos
Ribeirão Preto Medical School, University of …
35 PUBLICATIONS **114** CITATIONS
SEE PROFILE

João Paulo Machado-de-Sousa
University of São Paulo
41 PUBLICATIONS **394** CITATIONS
SEE PROFILE

Salvinorin A and Related Compounds as Therapeutic Drugs for Psychostimulant-Related Disorders

R.G. dos Santos[*,1], J.A.S. Crippa[1,2], J.P. Machado-de-Sousa[1,2] and J.E.C. Hallak[1,2]

[1]*Department of Neuroscience and Behavior, Ribeirão Preto Medical School, University of São Paulo, SP, Brazil*

[2]*National Institute for Translational Medicine (INCT-TM), CNPq, Brazil*

Abstract: Pharmacological treatments are available for alcohol, nicotine, and opioid dependence, and several drugs for cannabis-related disorders are currently under investigation. On the other hand, psychostimulant abuse and dependence lacks pharmacological treatment. Mesolimbic dopaminergic neurons mediate the motivation to use drugs and drug-induced euphoria, and psychostimulants (cocaine, amphetamine, and methamphetamine) produce their effects in these neurons, which may be modulated by the opioid system. Salvinorin A is a κ-opioid receptor agonist extracted from *Salvia divinorum*, a hallucinogenic plant used in magico-ritual contexts by Mazateca Indians in México. Salvinorin A and its analogues have demonstrated anti-addiction effects in animal models using psychostimulants by attenuating dopamine release, sensitization, and other neurochemical and behavioral alterations associated with acute and prolonged administration of these drugs. The objective of the present article is to present an overview of the preclinical evidence suggesting anti-addictive effects of salvinorin A and its analogues.

Keywords: Hallucinogens, psychedelics, psychostimulants, *Salvia divinorum*, salvinorin A.

INTRODUCTION

After cannabis, stimulants (cocaine and amphetamine) are the most consumed illegal recreational drugs worldwide [1, 2]. Among those seeking treatment for drug-related disorders in the Americans, cocaine remain the most prevalent primary drug of abuse [1]. Stimulant abuse causes considerable health problems in several countries [2-6]. Pharmacologists have been searching for drugs with therapeutic effects in psychostimulant-related disorders for decades, without success [5-6]. Thus, novel approaches are necessary to help those with problematic stimulant use who are seeking treatment.

The leaves of the hallucinogenic plant *Salvia divinorum* ("of the diviners") are eaten or drunk in a water infusion by the Mazatec Indians of Oaxaca, Mexico, for medicinal and ritual purposes [7-11]. Although *S. divinorum* is illegal in some countries, the plant is not regulated in many others, and several products derived from it (plants, dried leaves, extracts for smoking and tinctures for oral administration) are sold for young adults that use these products to induce powerful hallucinations [10-14].

In vitro and *in vivo* studies demonstrated that the only known and likely major active constituent of *S. divinorum* is the κ-opioid receptor agonist salvinorin A [10-12]. Other related chemicals are present in *S. divinorum*, such as salvinorins B-I, salvidivins A-D, salvinicins A-B, and divinatorins A-E, but little is known about their pharmacology [10-12]. Salvinorin A is the only non-nitrogenous natural κ-opioid receptor agonist currently known, and does not present affinity for other receptors associated with perceptual alterations produced by certain drugs, such as dopamine, serotonin, or glutamate [10-12]. Importantly, in contrast with classical hallucinogens (mescaline, LSD, psilocybin, DMT), salvinorin A does not behave as an agonist at the 5-HT_{2A} receptor [10-12].

Salvinorin A produces mental effects at only 4.5 μg/kg, making this compound the most active natural psychoactive product, almost in the same range as LSD [9, 10, 13-18]. This compound produces alterations on perceptions, mood, and on somatic sensations that are powerful but short-lived, lasting around 15 min [9, 10, 14-18].

Preclinical [19-50] and clinical [51-54] studies suggest that compounds that act as agonists of the κ-opioid receptor produce effects that are potentially beneficial for patients suffering psychostimulant-related disorders. Thus, the objective of the present text is to review data from preclinical and clinical studies suggesting that κ-opioid receptor agonists, including salvinorin A, may produce therapeutic effects in patients with psychostimulant-related disorders.

METHODS

The present review focused on studies conducted in the last 15 years evaluating the modulatory action of κ agonists on the effects of psychostimulants (*i.e.*, cocaine, amphetamine and methamphetamine). Preclinical and clinical studies published in English up to September 2014 were reviewed. Electronic searches were performed using PubMed.

*Address correspondence to this author at the Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Hospital das Clínicas, Terceiro Andar, Av. Bandeirantes, 3900, Ribeirão Preto, São Paulo, Brazil. Tel/Fax: + 55 16 3602 2703, E-mail: banisteria@gmail.com

1874-4737/14 $58.00+.00

κ-Opioid Receptor Agonists Modulate Dopaminergic Neurotransmission and the Effects of Psychostimulants

Studies in Rodents

Several studies in rodents showed that the effects produced by κ agonists are contrary to those produced by drugs such as cocaine, amphetamine and methamphetamine, which are all dopamine agonists [20, 21, 24-26, 28-33, 36-38, 40, 43-46, 49, 50]. For instance, these compounds do not modify basal dopamine levels, a hallmark of the stimulants [21, 25, 30]. κ-Opioid receptor agonists attenuate stimulant-induced increases in locomotor activity in rats [21, 29, 46]. κ-Opioid agonists also decrease responding maintained by cocaine and reduce the reinstatement of abolished cocaine and amphetamine use in rats [24, 28, 31, 32, 38, 46]. In mice, these compounds reduce the enhancement of dopamine release produced by non-neurotoxic doses of methamphetamine, and also inhibit the reduction of dopamine levels produced by neurotoxic doses of this stimulant [25].

Studies in Nonhuman Primates

Several studies investigated the pharmacology of κ agonists in monkeys [19, 22, 23, 26, 27, 33-35, 39-40, 48]. κ-Opioid agonists dose-dependently decrease self-administration of cocaine in monkeys [19, 22, 34, 35]. κ-Opioid agonists often induce vomiting and sedative effects, which typically occur only for a few days, since tolerance quickly develops [19, 22, 34, 35]. These undesirable behavioral effects could reduce the potential clinical uses of these drugs. Clinical trials with a large number of patients should be performed to elucidate the impact of these side-effects in clinical populations.

Administration of gradually increasing doses of κ-opioid agonists for 28 days do not produce alterations on biochemical parameters (hematocrit, white blood cells, urea nitrogen, creatinine, alanine aminotransferase and glucose) and dose-dependently decrease cocaine intake, which increases again after three weeks of treatment, suggesting the development of tolerance [22].

Research on the effects of κ agonists on stimulant-induced discrimination in monkeys report contradictory results, with studies reporting attenuation, enhancement or no significant effects [23, 27]. κ agonists also reduce the reinstatement of abolished cocaine use in monkeys [39].

Studies in Humans

Few studies assessed the human pharmacology κ agonists [51-53]. Acute intramuscular (i.m.) doses of the selective κ-agonist enadoline (20-160 μg/70 kg) produce hallucinatory- and dissociative-like side-effect such as depersonalization, visual alterations and confusion, as well as sedative effects, increases in urinary output and dizziness, having no significant effects on cardiovascular parameters, pupil size, skin temperature and respiratory rate in volunteers with poly-substance (opiates and cocaine) abuse histories [51]. High dose (160 μg/70 kg) enadoline produces intense psychedelic effects (*i.e.*, alterations on visual perception and self-awareness). Enadoline has no abuse potential and was safely administered in volunteers with drug-related disorders, although its perceptual and cognitive side-effects present an important limitation. However, these psychological effects are probably more prominent or maximized in standard abuse liability studies in which individuals who participate have drug-related problems and are poorly prepared for strong hallucinogenic effects. The salvinorin A studies conducted in healthy volunteers could have likely resulted in distressing psychedelic effects were it not for the fact that these participants were expecting and prepared for strong hallucinogenic effects (see below the Section *Human Psychopharmacology of Salvinorin A*).

Acute i.m. doses of enadoline (20-80 μg/kg) modestly reduce the reinforcing effects of intravenous (i.v.) cocaine in volunteers with poly-substance (opiates and cocaine) abuse histories [52]. Acute i.v. doses of the κ-receptor agonist/μ-receptor antagonist nalbuphine (5 mg/70 kg) slightly reduce the reinforcing effects of cocaine and significantly decrease diastolic blood pressure in current cocaine abusers [53]. The neuroendocrine alterations produced by cocaine administration to current cocaine abusers on luteinizing hormone, cortisol, and adrenocorticotropic hormone are attenuated by acute i.v. administration of nalbuphine (5 mg/70 kg), while effects on testosterone are not observed [54].

Human Psychopharmacology of Salvinorin A

The human pharmacology of inhaled (0.375-21 μg/kg [14, 18], 12 mg [17]), sublingual (up to 4 mg), and smoked (1,017 μg) [16] salvinorin A was investigated in healthy volunteers. Sublingual salvinorin A did not produce significant effects [15], while inhaled and smoked administration produced intense subjective effects that start in less than a minute, peak within 10 min, and return to baseline within 15-30 min [9, 10, 13-18]. These effects include hallucinatory and dissociative experiences, such as alterations in visual perception, time and spatial orientation, cognition, emotions and self-awareness, which are generally perceived as pleasurable by young adults. Improved mood and subjective well-being are also described, but salvinorin A does not seem to have euphoric properties or a high potential for abuse [9, 10, 13, 16-18]. Salvinorin A neuroendocrine effects include transient increases in cortisol and prolactin plasma levels, and neurophysiological effects include temporary reductions in resting EEG spectral power [17].

Salvinorin A is generally well-tolerated, and no serious adverse have been reported in controlled studies [14, 16-18]. Negative effects include anxiety- and psychotic-like reactions such as fear, panic, confusion, hallucinations and delusions, which are generally short-lived [9, 10, 13, 16-18]. Salvinorin A did not significantly increase heart rate or blood pressure [14, 17]. One study reported that salvinorin A produced dose-related impairments in recall/recognition memory [18], while other study reported a lack of cognitive deficits [17]. Some studies included follow-up assessments of 1 to 3 months, reporting an absence of persisting adverse effects [18]. Thus, the literature on the human pharmacology of salvinorin A suggests that this compound may be safely administered to healthy volunteers.

Salvinorin A and its Analogues Modulate Dopaminergic Neurotransmission and the Effects of Psychostimulants

Studies in Rodents

Several studies investigated the effects salvinorin A and its analogues in rodents after psychostimulant administration [36-38, 41, 42, 44, 45, 49, 50]. Salvinorin A inhibits the locomotor activity, rewarding effects, reinstatement of self-administration, sensitization, and striatum gene expression alterations produced by cocaine [36, 38, 41, 44]. Systemic and intrastriatal salvinorin A administration decrease dopamine levels in rats [37]. Extracellular dopamine levels were decreased whereas dopamine extraction fraction, which provides an estimate of dopamine uptake, was unaltered, indicating that salvinorin A decreases dopamine release but does not alter dopamine uptake. Repeated salvinorin A administration does not modify dopamine levels or uptake [37].

The salvinorin A analogue *β*-tetrahydropyran Sal B presents κ-opioid receptor binding affinity comparable to salvinorin A and shares the same potency of the parent compound in attenuating the reinstatement of cocaine self-administration [42]. Another analogues such as mesyl Sal B and the more potent MOM Sal B (2-methoxy-methyl salvinorin B) reduce the rewarding effects of cocaine [45, 50].

Salvinorin A does not appear to cause sedation, but may produce pro-depressive effects [44]. As with the parent compound, MOM Sal B do not cause sedation, but produces pro-depressive effects [45]. These pro-depressive effects could limit the therapeutic potential of these compounds.

Studies in Nonhuman Primates

Salvinorin A may function as a punisher for cocaine self-administration in monkeys [48]. Choices for cocaine options combined with salvinorin A decrease as a function of salvinorin A dose.

DISCUSSION

Endogenous κ-Opioid Systems Modulate the Effects of Psychostimulants

Psychostimulants inhibit the breakdown of monoamines (dopamine, serotonin and norepinephrine), which increases extracellular levels of these neurochemicals [5-6, 19-54]. Specifically, the main mechanism of action associated with the euphoria and abuse potential of stimulants is the increase in dopamine levels in the brain, and a growing preclinical and clinical literature suggest that dopamine uptake blockers and releasers (*d*-amphetamine, methamphetamine, methylphenidate, bupropion, and modafinil) may be efficacious for treating stimulant abuse and dependence [5-6]. However, methylphenidate and *d*-amphetamine have significant abuse and diversion potential, and bupropion and modafinil appear to have limited clinical efficacy [5-6]. Thus, new molecules should be explored for treating stimulant-related disorders.

Opioid receptor agonists are involved in the control of dopaminergic activity [19-54]. κ-Opioid receptors are expressed in brain regions rich in dopamine, such as the striatum, ventral tegmental area and nucleus accumbens (Nac) [19-22, 26, 33, 40, 43, 47, 49]. Dynorphin, a opioid peptide that seem to act as a endogenous κ receptor ligand, is abundant in the Nac [19-22, 26, 33, 40, 43, 47, 49].

Dynorphin is present in brain areas involved in the encoding and processing of perceptions, motivation, mood, stress, nociception, motor performance and vital signs (blood pressure, heart and respiratory rate, and body temperature) [26, 33, 40, 43, 47, 49]. In the Nac and other striatal dopaminergic nucleus such as the caudate putamen, dynorphin and other κ agonists decrease dopamine levels [20, 21, 24, 26, 33, 40, 43, 47, 49]. Differential regulation of dopamine levels by multiple signaling pathways and mechanism, such as dopamine release and reuptake in various brain regions, may explain why κ agonists such as dynorphin regulate addiction, stress, depression, sedation, and aversion [26, 33, 40, 43, 47, 49].

As κ agonists control dopaminergic transmission, these compounds also interact with psychostimulants [19-54]. Several cocaine-induced effects are inhibited by administration of κ agonists, including increases in dopamine levels [20, 26, 33, 37, 40, 49], rewarding effects [24, 26, 32, 33, 40-42, 46], increases in locomotion and stereotypy [20, 21, 26, 33, 36, 40, 44, 46, 49], alterations in gene expression [26, 33, 36, 43], and reinstatement of cocaine self-administration [24, 26, 28, 33, 38-40, 50]. In monkeys, κ agonists reduce cocaine intake [19, 26, 33-35, 40, 48]. Although some studies reported that chronic administration of κ agonists increased the motor performance and the dopamine overflow produced by cocaine [21, 37], most studies of acute and chronic administration of κ-opiod receptor agonists suggest that these compounds have anti-addictive effects [19-36, 38-54].

Cocaine also displays a reciprocal action on κ-opioidergic systems [19, 26, 33, 40, 43, 47, 49]. Cocaine increases the κ receptors, dynorphin, and dynorphin mRNA levels, and increased dynorphin and κ receptors are found in dopaminergic brain regions of deceased cocaine abusers [19, 26, 33, 40, 43, 47, 49].

With regard to other psychostimulants, κ agonists fail to reduce the reinstatement of amphetamine-induced cocaine intake [24]. On the other hand, κ agonists inhibit the reinstatement of amphetamine self-administration after cocaine or amphetamine intake [31]. The evidence for amphetamine-induced sensitization is contradictory, with some studies showing that κ agonists do not inhibit sensitization [20] while other studies report the contrary [29]. Methamphetamine-induced increases in dopamine concentrations and reductions in dopamine overflow are attenuated by κ-opioid receptor agonists [25]. In monkeys, κ agonists reduce the rewarding effects of amphetamine, although some doses of these compounds also potentiate the effects of amphetamine in some monkeys [27].

These results suggest that psychostimulant drugs have their own mechanisms of action related to specific pharmacological effects, such as sensitization and reinstatement of drug intake [20, 24, 27, 31].

Safety and Tolerability

Studies in monkeys reported emesis and sedative effects after chronic administration of some κ agonists [19, 23, 26, 34, 35]. In humans, these drugs may produce anxiety- and psychotic-like reactions [9, 10, 13, 16-18]. Thus, the intense subjective effects produced by salvinorin A [9, 10, 13-18] or the dysphoric effects, sedation and occasional distressing sensory and depersonalization effects produced by other κ-opioid agonists in humans [26, 33, 49, 51, 52], could be important limitations for the clinical use of these compounds.

However, studies in monkeys show that tolerance to emetic and sedative side-effects develops within a few days [19, 22, 23, 26, 34, 35], and clinical studies indicate that tolerance develops to κ-related psychedelic and dysphoric effects [26, 33, 35]. Thus, the rapid development of tolerance to side-effects could reduce toxicity and increase safety. On the other hand, some studies suggest that the reduction of stimulant intake produced by κ agonists has an inverted U shape [22, 26]. Thus, the therapeutic efficacy of these compounds could be reduced after some weeks of treatment, which represent an important limitation for a drug that will probably be used chronically.

Studies show that μ receptors also modulate the effects of psychostimulants, since most κ agonists that significantly attenuate cocaine intake have some affinity for these receptors [19, 22, 23, 26, 33-35], and studies in monkeys show that mixed κ/μ compounds have a better tolerability and safety profile when compared to selective κ agonists, producing only mild salivation [35]. Acute i.m. doses of κ-agonists are safely tolerated in combination with cocaine, but produce only a moderate attenuation of cocaine's subjective effects [52]. Acute i.v. doses of a κ-receptor agonist/μ-receptor antagonist are safely tolerated in combination with cocaine, slightly attenuate its subjective effects, and reduce the effects of this drug on ACTH, cortisol, and LH [53, 54]. Clinical trials are needed to investigate the safety and efficacy of these drugs after long-term administration.

Finally, it also must be considered that although salvinorin A possesses desirable anti-addictive effects with fewer side effects compared to traditional κ-opioid receptor agonists, the pharmacokinetic properties of salvinorin A are not desirable as an anticocaine pharmacotherapy [42, 43, 45, 49, 50]. Thus, new salvinorin A analogues are under investigation and show promising results [45, 49]. Studies in humans will be necessary to assess the tolerability and potential therapeutic effects of these drugs.

CONCLUSION

The problematic use of psychostimulants can cause a series of health, economic, and social costs to individuals and society. Although pharmacological treatments for opiate/opioid and nicotine abuse or dependence are available (methadone or buprenorphine, and nicotine patch etc., respectively) and several drugs for cannabis-related disorders are currently being investigated, there is no approved medication for the treatment of stimulant disorders.

The reviewed studies indicate that κ agonists decrease dopamine neurotransmission, possibly by decreasing dopamine release and increasing its uptake. Thus, these compounds could be beneficial for patients suffering stimulant-related disorders. Salvinorin A and its analogues show anti-addictive effects in several animal studies using psychostimulants as the drug under investigation. Although salvinorin A has been found to produce undesirable effects, the reduced side effect profile of salvinorin A compared to classic κ-agonists makes salvinorin A a compound of high therapeutic promise in treating drug abuse. The potential of salvinorin A and its analogues as pharmacotherapies can be further determined by characterization of the cellular signaling pathways responsible for therapeutic and undesirable effects. Moreover, it remains to be determined whether it is possible to separate these undesirable side effects from the anti-addictive effects. Further studies are warranted on the anti-addictive potentials of salvinorin A and its analogues.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] United Nations Office on Drugs and Crime. World Drug Report (2014). Vienna: United Nations 2014.

[2] van Amsterdam J, Pennings E, Brunt T, *et al*. Physical harm due to chronic substance use. Regul Toxicol Pharmacol 2013; 66: 83-7.

[3] Nutt DJ, King LA, Phillips LD, *et al*. Drug harms in the UK: a multicriteria decision analysis. Lancet 2010; 376: 1558-65.

[4] Morgan CJ, Noronha LA, Muetzelfeldt M, *et al*. Harms and benefits associated with psychoactive drugs: findings of an international survey of active drug users. J Psychopharmacol 2013; 27: 497-506.

[5] Haile, CN, Mahoney JJ 3rd, Newton TF, *et al*. Pharmacotherapeutics directed at deficiencies associated with cocaine dependence: focus on dopamine, norepinephrine and glutamate. Pharmacol Ther 2012; 134: 260-77.

[6] Stoops WW, Rush CR. Agonist replacement for stimulant dependence: a review of clinical research. Curr Pharm Des 2013; 19: 7026-35.

[7] Schultes RE, Hofmann A. Plants of the gods: their sacred, healing and hallucinogenic powers. Rochester: Healing Arts Press 1992.

[8] Ott J. Pharmacotheon: entheogenic drugs, their plant sources and history. Kennewick: The Natural Products Co. 1993.

[9] Diaz JL. *Salvia divinorum*: a psychopharmacological riddle and a mind-body prospect. Curr Drug Abuse Rev 2013; 6: 43-53.

[10] Zawilska JB, Wojcieszak J. *Salvia divinorum*: from Mazatec medicinal and hallucinogenic plant to emerging recreational drug. Hum Psychopharmacol 2013; 28: 403-12.

[11] Casselman I, Nock CJ, Wohlmuth H, *et al*. From local to global – fifty years of research on *Salvia divinorum*. J Ethnopharmacol 2014; 151: 768-83.

[12] Prisinzano TE. Psychopharmacology of the hallucinogenic sage *Salvia divinorum*. Life Sci 2005; 78: 527-31.

[13] González D, Riba J, Bouso JC, *et al*. Pattern of use and subjective effects of *Salvia divinorum* among recreational users. Drug Alcohol Depend 2006; 85: 157-62.

[14] Johnson MW, MacLean KA, Reissig CJ, *et al*. Human psychopharmacology and dose-effects of salvinorin A, a kappa opioid agonist hallucinogen present in the plant *Salvia divinorum*. Drug Alcohol Depend 2011; 115: 150-5.

[15] Mendelson JE, Coyle JR, Lopez JC, *et al*. Lack of effect of sublingual salvinorin A, a naturally occurring kappa opioid, in

humans: a placebo-controlled trial. Psychopharmacology 2011; 214: 933-9.

[16] Addy PH. Acute and post-acute behavioral and psychological effects of salvinorin A in humans. Psychopharmacology 2012; 220: 195-204.

[17] Ranganathan M, Schnakenberg A, Skosnik PD, *et al*. Dose-related behavioral, subjective, endocrine, and psychophysiological effects of the κ opioid agonist Salvinorin A in humans. Biol Psychiatry 2012; 72: 871-9.

[18] MacLean KA, Johnson MW, Reissig CJ, *et al*. Dose-related effects of salvinorin A in humans: dissociative, hallucinogenic, and memory effects. Psychopharmacology 2013; 226: 381-92.

[19] Negus SS, Mello NK, Portoghese PS, *et al*. Effects of kappa opioids on cocaine self-administration by rhesus monkeys. J Pharmacol Exp Ther 1997; 282: 44-55.

[20] Shippenberg TS, Rea W. Sensitization to the behavioral effects of cocaine: modulation by dynorphin and κ-opioid receptor agonists. Pharmacol Biochem Behav 1997; 57: 449-55.

[21] Heidbreder CA, Schenk S, Partridge B, *et al*. Increased responsiveness of mesolimbic and mesostriatal dopamine neurons to cocaine following repeated administration of a selective kappa-opioid receptor agonist. Synapse 1998; 30: 255-62.

[22] Mello NK, Negus SS. Effects of kappa opioid agonists on cocaine- and food-maintained responding by rhesus monkeys. J Pharmacol Exp Ther 1998; 286: 812-24.

[23] Negus SS, Mello NK. Effects of kappa opioid agonists on the discriminative stimulus effects of cocaine in rhesus monkeys. Exp Clin Psychopharmacol 1999; 7: 307-17.

[24] Schenk S, Partridge B, Shippenberg TS. U69593, a kappa-opioid agonist, decreases cocaine self-administration and decreases cocaine-produced drug-seeking. Psychopharmacology 1999; 144: 339-46.

[25] El Daly E, Chefer V, Sandill S, *et al*. Modulation of the neurotoxic effects of methamphetamine by the selective κ-opioid receptor agonist U69593. J Neurochem 2000; 74: 1553-62.

[26] Mello NK, Negus SS. Interactions between kappa opioid agonists and cocaine. Preclinical studies. Ann N Y Acad Sci 2000; 909: 104-32.

[27] Powell KR, Holtzman SG. Modulation of the discriminative stimulus effects of *d*-amphetamine by mu and kappa opioids in squirrel monkeys. Pharmacol Biochem Behav 2000; 65: 43-51.

[28] Schenk S, Partridge B, Shippenberg TS. Reinstatement of extinguished drug-taking behavior in rats: effect of the kappa-opioid receptor agonist, U69593. Psychopharmacology 2000; 151: 85-90.

[29] Vanderschuren LJ, Schoffelmeer AN, Wardeh G, *et al.* Dissociable effects of the κ-opioid receptor agonists bremazocine, U69593, and U50488H on locomotor activity and long-term behavioral sensitization induced by amphetamine and cocaine. Psychopharmacology 2000; 150: 35-44.

[30] Acri JB, Thompson AC, Shippenberg T. Modulation of pre- and postsynaptic dopamine D2 receptor function by the selective kappa-opioid receptor agonist U69593. Synapse 2001; 39: 343-50.

[31] Schenk S, Partridge B. Effect of the kappa-opioid receptor agonist, U69593, on reinstatement of extinguished amphetamine self-administration behavior. Pharmacol Biochem Behav 2001; 68: 629-34.

[32] Schenk S, Partridge B, Shippenberg TS. Effects of the kappa-opioid receptor agonist, U69593, on the development of sensitization and on the maintenance of cocaine self-administration. Neuropsychopharmacology 2001; 24: 441-50.

[33] Shippenberg TS, Chefer VI, Zapata A, *et al*. Modulation of the behavioral and neurochemical effects of psychostimulants by κ-opioid receptor systems. Ann N Y Acad Sci 2001; 937: 50-73.

[34] Cosgrove KP, Carroll ME. Effects of bremazocine on self-administration of smoked cocaine base and orally delivered ethanol, phencyclidine, saccharin, and food in rhesus monkeys: a behavioral economic analysis. J Pharmacol Exp Ther 2002; 301: 993-1002.

[35] Bowen CA, Negus SS, Zong R, *et al*. Effects of mixed-action κ/μ opioids on cocaine self-administration and cocaine discrimination by rhesus monkeys. Neuropsychopharmacology 2003; 28: 1125-39.

[36] Chartoff EH, Potter D, Damez-Werno D, *et al*. Exposure to the selective κ-opioid receptor agonist salvinorin A modulates the behavioral and molecular effects of cocaine in rats. Neuropsychopharmacology 2008; 33: 2676-87.

[37] Gehrke BJ, Chefer VI, Shippenberg TS. Effects of acute and repeated administration of salvinorin A on dopamine function in the rat dorsal striatum. Psychopharmacology 2008; 197: 509-17.

[38] Morani AS, Kivell B, Prisinzano TE, *et al*. Effect of kappa-opioid receptor agonists U69593, U50488H, spiradoline and salvinorin A on cocaine-induced drug-seeking in rats. Pharmacol Biochem Behav 2009; 94: 244-9.

[39] Rüedi-Bettschen D, Rowlett JK, Spealman RD, *et al*. Attenuation of cocaine-induced reinstatement of drug seeking in squirrel monkeys: kappa opioid and serotonergic mechanisms. Psychopharmacology 2010; 210: 169-77.

[40] Wee S, Koob GF. The role of the dynorphin-κ opioid system in the reinforcing effects of drugs of abuse. Psychopharmacology 2010; 210: 121-35.

[41] Potter DN, Damez-Werno D, Carlezon WA Jr., *et al*. Repeated exposure to the κ-opioid receptor agonist salvinorin A modulates extracellular signal-regulated kinase and reward sensitivity. Biol Psychiatry 2011; 70: 744-53.

[42] Prevatt-Smith KM, Lovell KM, Simpson DS, *et al*. Potential drug abuse therapeutics derived from the hallucinogenic natural product salvinorin A. Medchemcomm 2011; 2: 1217-22.

[43] Butelman ER, Yuferov V, Kreek MJ. κ-Opioid receptor/dynorphin system: genetic and pharmacotherapeutic implications for addiction. Trends Neurosci 2012; 35: 587-96.

[44] Morani AS, Schenk S, Prisinzano TE, *et al*. A single injection of a novel kappa opioid receptor agonist salvinorin A attenuates the expression of cocaine-induced behavioral sensitization in rats. Behav Pharmacol 2012; 23: 162-70.

[45] Morani AS, Ewald A, Prevatt-Smith KM, *et al*. The 2-methoxy methyl analogue of salvinorin A attenuates cocaine-induced drug seeking and sucrose reinforcements in rats. Eur J Pharmacol 2013; 720: 69-76.

[46] Smith MA, Cole KT, Iordanou JC, *et al*. The mu/kappa agonist nalbuphine attenuates sensitization to the behavioral effects of cocaine. Pharmacol Biochem Behav 2013; 104: 40-6.

[47] Trifilieff P, Martinez D. Kappa-opioid receptor signaling in the striatum as a potential modulator of dopamine transmission in cocaine dependence. Front Psychiatry 2013; 4: 44.

[48] Freeman KB, Naylor JE, Prisinzano TE, *et al*. Assessment of the kappa opioid agonist, salvinorin A, as a punisher of drug self-administration in monkeys. Psychopharmacology 2014; 231: 2751-8.

[49] Kivell BM, Ewald AW, Prisinzano TE. Salvinorin A analogs and other kappa-opioid receptor compounds as treatments for cocaine abuse. Adv Pharmacol 2014; 69: 481-511.

[50] Walsh SL, Strain EC, Abreu ME, *et al*. Enadoline, a selective kappa opioid agonist: comparison with butorphanol and hydromorphone in humans. Psychopharmacology 2001; 157: 151-62.

[51] Walsh SL, Geter-Douglas B, Strain EC, *et al*. Enadoline and butorphanol: evaluation of κ-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. J Pharmacol Exp Ther 2001; 299: 147-58.

[52] Mello NK, Mendelson JH, Sholar MB, *et al*. Effects of the mixed mu/kappa opioid nalbuphine on cocaine-induced changes in subjective and cardiovascular responses in men. Neuropsychopharmacology 2005; 30: 618-32.

[53] Goletiani NV, Mendelson JH, Sholar MB, *et al*. Opioid and cocaine combined effect on cocaine-induced changes in HPA and HPG axes hormones in men. Pharmacol Biochem Behav 2009; 91: 526-36.

[54] Simonson B, Morani AS, Ewald AW, *et al*. Pharmacology and anti-addiction effects of the novel κ opioid receptor agonist Mesyl Sal B, a potent and long-acting analogue of salvinorin A. Br J Pharmacol 2015; 172: 515-31.

Received: August 29, 2014 Revised: October 8, 2014 Accepted: October 15, 2014