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ORIGINAL INVESTIGATION

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Effects of the plant-derived hallucinogen salvinorin A on basal dopamine levels in the caudate putamen and in a conditioned place aversion assay in mice: agonist actions at kappa opioid receptors

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Abstract *Rationale:* Salvinorin A is a naturally occurring hallucinogen derived from the plant *Salvia divinorum*. Salvinorin A is also a potent and selective kappa opioid receptor agonist in vitro. It has been shown that kappa agonists decrease dopamine levels in the caudate putamen and nucleus accumbens and cause conditioned place aversion in rodents. *Objectives:* To study the effects of salvinorin A on basal dopamine levels in the caudate putamen and nucleus accumbens, and to determine whether salvinorin A induces conditioned place preference or aversion and changes in locomotor activity in the mouse. *Methods:* In the first experiment, changes in dopamine levels in these brain regions after administration of salvinorin A were measured with in vivo microdialysis. In the second experiment, we examined whether salvinorin A led to conditioned place preference or aversion, and changes in locomotor activity during conditioning sessions. *Results:* The higher doses of salvinorin A studied (1.0 mg/kg and 3.2 mg/kg, i.p.) significantly decreased dopamine levels in the caudate putamen, but not in the nucleus accumbens, and this effect was completely blocked by pre-injection with 10 mg/kg of the kappa opioid receptor antagonist nor-binaltorphimine. The same doses of salvinorin A caused conditioned place aversion and decreased locomotor activity. *Conclusions:* The inhibitory effect of salvinorin A on striatal dopamine levels may contribute to its induction of conditioned place aversion and decreases in locomotion in mice. These findings are consistent with the in vitro characterization of salvinorin A as a kappa opioid receptor agonist. It is of interest that a compound such as salvinorin A, that lowers striatal dopamine levels and leads to conditioned place aversion in rodents, is self-administered by humans under certain conditions.

Keywords Salvinorin A · Dopamine · Microdialysis · Mice · Conditioned place aversion

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Introduction

Salvinorin A is the main active ingredient of *Salvia divinorum*, a psychoactive and hallucinogenic mint-like plant that has been used in traditional medical practices by the Mazatec Indian people of Oaxaca in Mexico (Valdes 1994). *Salvia divinorum*-based products (e.g., concentrated abstracts) are currently available in the United States and Europe, and widely available on the internet (Drug Enforcement Administration 2002). Recently, in vitro studies with radioligand binding assays and functional assays found that salvinorin A is a potent, selective and highly efficacious kappa opioid receptor agonist (Roth et al. 2002; Sheffler and Roth 2003; Chavkin et al. 2004).

Salvinorin A is therefore the first naturally occurring kappa opioid receptor agonist—and non-nitrogenous ligand—for opioid receptors to be studied. It has no structural resemblance to any known opioid ligand and represents a new class of kappa opioid selective compounds. Synthetic kappa opioid agonists, such as U-69593, U-50488 and R-84760, decrease dopamine levels in the nucleus accumbens and caudate putamen of rats and mice (Di Chiara and Imperato 1988; Donzanti et al. 1992; Spanagel et al. 1992; Devine et al. 1993; Zhang et al. 2004b). Activation of kappa opioid receptors induces a variety of behavioral effects. For example, the kappa opioid agonists U-50488, U-69593 and TRK-820 have aversive effects as measured by the conditioned place preference procedure in rats (Shippenberg and Herz 1987; Bals-Kubik et al. 1989; Suzuki et al. 1992; Mori et al. 2002). Moreover, U-50488 decreased cocaine-induced locomotor activity and conditioned place preference in rats (Crawford et al. 1995). Also, U-69593 attenuated cocaine-induced behavioral sensitization in rats (Heidbre-

der et al. 1993; Shippenberg et al. 1996). In addition, U-50488, U-69593 and cyclazocine were found to decrease cocaine self-administration in rats (Glick et al. 1995, 1998; Kuzmin et al. 1997; Schenk et al. 1999). The objectives of the present study were to determine whether salvinorin A has the same pharmacological profiles as the synthetic kappa opioid agonists mentioned above. Specifically, one part of the study examined the effect of salvinorin A on dopamine levels in the caudate putamen and the nucleus accumbens, and another determined whether salvinorin A caused conditioned place aversion in C57BL/6J mice. This, to our knowledge, is the first study to measure the effects of salvinorin A on dopamine levels and to show conditioned place aversion to salvinorin A in any species.

Materials and methods

Two separate experiments on the effects of salvinorin A were conducted, the first measuring changes in striatal and accumbal dopamine using microdialysis and the second examining the potential positive or negative hedonic properties of salvinorin A using a conditioned place preference/aversion paradigm. Different groups of mice were studied in each experiment. Of a total of 92 mice started in the study, the data from 88 were used in the final analyses.

Subjects

Male C57BL/6J inbred mice (Jackson Laboratory, Bar Harbor, ME) weighing 22–25 g were individually housed with free access to food and water in a light- (12-h/12-h light/dark cycle, lights on at 0700 hours) and temperature-(25°C) controlled room. Animal care and experimental procedures were conducted according to the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal Resources Commission on Life Sciences 1996). The experimental protocols used were approved by the Institutional Animal Care and Use Committee of The Rockefeller University.

Surgical procedures

After at least 1 week of acclimation, mice were anaesthetized with a combination of xylazine (8.0 mg/kg, i.p.) and ketamine (80 mg/kg, i.p.) and were placed in a stereotaxic frame modified for the mouse (David Kopf, Topanga, CA) for implantation of a guide cannula. A guide cannula (CMA/7, North Chelmsford, MA) was implanted into the caudate putamen (coordinates from bregma: A=0.65 mm, L=±2.00 mm and V=3.00 mm; Franklin and Paxinos 1997) or into the nucleus accumbens (coordinates from bregma: A=1.35 mm, L=±0.8 mm and V=4.50 mm; Franklin and Paxinos 1997). The guide cannula was fixed to the skull by dental acrylic. Mice were allowed 4–5 days to recover from surgery before any experimental procedure.

In vivo microdialysis

Dialysis probes (2 mm active region, CMA/7) were calibrated for dopamine recovery in vitro before each experiment, as previously described (Maisonneuve and Kreek 1994). Animals were randomly assigned to four groups (n=5). On the day before each dialysis experiment, mice were individually placed into microdialysis chambers with free access to food and water. Dialysis probes were then lowered into the caudate putamen and were perfused with artificial cerebrospinal fluid (aCSF) (146 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$, 1.0 mM $MgCl_2$) at a rate of 1.0 μl/min overnight. Following the overnight stabilization period (15–16 h), basal levels of dialysates were collected from freely moving mice every 20 min for 1 h at a flow rate of 1.0 μl/min. Then, each group received a different dose of salvinorin A, (0, 0.32, 1.0, 3.2 mg/kg, i.p.). Dialysate samples were collected every 20 min for a further 3 h after the injection. To determine whether the effect of salvinorin A on striatal dopamine is mediated by activation of kappa opioid receptors, the selective kappa opioid antagonist nor-binaltorphimine (nor-BNI; 10 mg/kg, i.p.) was administered 2 h before injection of the largest dose of salvinorin A in an additional group of six mice. Another group of seven mice was studied for 24 h to determine the time course of the highest dose of salvinorin A (3.2 mg/kg, i.p.).

To determine whether salvinorin A had the same effect on dopamine levels in the nucleus accumbens, two additional groups of mice were added to this study; one group was injected with the highest dose of salvinorin A (3.2 mg/kg, i.p.) while the control group was injected with physiological saline. Of 44 mice starting all dialysis studies, 4 were not included in the final analyses due to misplacement or loss of cannula.

Determination of dialysate dopamine levels

Dopamine concentration in the dialysates was measured by means of high-performance liquid chromatography (HPLC) with electrochemical detection (ESA, North Chelmsford, MA). The HPLC system consisted of an ESA 540 autosampler, an ESA 582 solvent delivery system, a reverse-phase C18 column and an ESA microdialysis cell (Model 5014B). The MD-TD mobile phase was purchased from ESA and was delivered at a rate of 0.5 ml/min. Chromatograms were integrated and compared with standards using the ESA 501 chromatography system.

Drugs

Salvinorin A was purchased from Biosearch Technologies (Novato, CA), dissolved in 10% ethanol, followed by 10% Tween 80 and then 80% $d H_2O$, and administered intraperitoneally. Nor-BNI 2HCL (Sigma, St. Louis, MO) was dissolved in physiological saline and administered intraperitoneally.

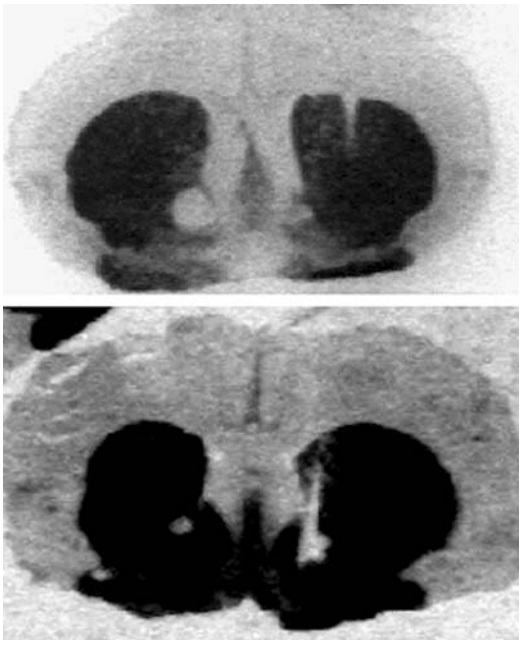

Fig. 1 Placement of the dialysis probes. The micrographs show the probe placement in the caudate putamen (*upper panel*) and the nucleus accumbens (*lower panel*) of representative mice used in this study

Histological verification of probe placement

Following microdialysis, the mice were decapitated after brief exposure to CO_2, and their brains were removed for histological evaluation. Frozen sections were cut to verify the correct placement of dialysis probes. Figure 1 shows photomicrographs of a tissue section from the brain of representative mice used in this study, showing probe placement in the caudate putamen (upper panel) and in the nucleus accumbens (lower panel).

Mouse place preference chambers

The mouse place preference chambers (model ENV-3013, MED Associates, Georgia, VT) had three distinct compartments that could be separated by removable doors. Data were collected from individual infrared photobeams on a photobeam strip, with six beams in the white and black compartments and two beams in the smaller central gray compartment. The center compartment had a "neutral" smooth gray floor. The black compartment was 16.8×12.7×12.7 cm with a stainless-steel grid rod floor. The white compartment (also 16.8×12.7×12.7 cm) had a stainless-steel mesh floor.

Determinations of conditioned place preference/aversion and associated locomotor activity

Because salvinorin A decreased dopamine levels at doses of 1.0 mg/kg and 3.2 mg/kg, effects of the same doses of salvinorin A on the development of conditioned place preference or aversion and locomotor activity were studied. Six groups of mice (n=8 each group) were studied. Each group received one of the following combinations of two injections (with a 2-h interval) before being placed in a conditioned place preference chamber as described above: vehicle+vehicle; vehicle+salvinorin A (1.0 mg/kg); vehicle+salvinorin A (3.2 mg/kg); nor-BNI+vehicle; nor-BNI+salvinorin A (1.0 mg/kg); nor-BNI+salvinorin A (3.2 mg/kg). Experiments were performed in a dimly lit, sound-attenuated chamber as described above. The study used an unbiased, counterbalanced design in which mice were randomly assigned to either the drug or saline compartment on the first day. Half the animals had white and half had black chambers as the drug-paired side. During the pre-conditioning session, each animal was placed in the center gray compartment with free access to the black and white compartments. The time spent in each compartment and the locomotor activity within the compartments were recorded for 30 min. Locomotor activity was assessed by the number of "crossovers" defined as breaking the beams at either end of the conditioning compartment. During the conditioning sessions, mice were placed in and restricted to the appropriate compartment for 30 min after drug or saline injection. The animals were injected with drug and saline on alternate days, for a total of eight conditioning sessions with four drug and four saline trials for each animal. The post-conditioning test session was performed on the day after the last conditioning session, and was identical to the pre-conditioning session: each mouse had free access to both white and black compartments. The schedule of sessions is shown in Table 1. The difference between the pre- and post-conditioning sessions in the amount of time spent on the drug-paired compartment was used to determine whether the mice had developed a conditioned place preference or aversion to salvinorin A.

Data analysis

A separate preliminary two-way (group×sample) analysis of variance (ANOVA) was used to assure that there were no significant differences during the baseline hour. Then, the mean dopamine levels over the 3-h period after administration of salvinorin A, expressed as percentage change from mean basal levels of dopamine in dialysate, were examined by one-way ANOVA followed by Newman–

Table 1 Protocol for conditioned place preference study. *CS* conditioning session

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Week 1	Pre-CS	CS	CS	CS	CS	–	–
Week 2	CS	CS	CS	CS	Post-CS		

Keuls post-hoc tests to identify significant differences between conditions. The effect of salvinorin A on the formation of a conditioned place preference or aversion, and associated locomotor activity in the conditioning chamber, were examined using two-way ANOVA (pretreatment× drug condition), followed by Newman–Keuls post-hoc tests. Since a preliminary three-way ANOVA of locomotor activity across the four conditioning sessions (pretreatment×dose×session) showed no significant main effect of session, nor any significant interaction effect involving session, giving no evidence of change in locomotor activity across sessions, the session factor was dropped; mean crossovers during the four conditioning sessions for each mouse were used in the final analysis.

Results

Effect of salvinorin A on dopamine levels in the caudate putamen

The dose–response effect of salvinorin A on dopamine levels in the caudate putamen of C57BL/6J mice is shown in Fig. 2 with each 20-min sample shown in panel A and mean percentage change from basal levels in panel B. One-way ANOVA showed that dopamine levels in the caudate putamen expressed as percentage change from basal levels were significantly affected by salvinorin A injections, in a dose-dependent manner ($F_{4,17}$=28.95, P< 0.000001). Newman–Keuls post-hoc tests showed that dopamine levels in the caudate putamen were significantly lower in response to the two higher doses of salvinorin A (1.0 mg/kg and 3.2 mg/kg) than to vehicle control (P< 0.005 and P<0.0002, respectively). Pre-injection of the kappa receptor antagonist nor-BNI (10 mg/kg, i.p.) blocked the effect of the highest dose of salvinorin A (3.2 mg/kg) on dopamine levels.

The time course of the effect on dopamine levels in the caudate putamen of the 3.2-mg/kg dose of salvinorin A was examined in a separate group of seven mice, with results shown in Fig. 3. Dopamine levels measured in 20-min dialysate samples, taken hourly after administration of salvinorin A, showed an initial decrease and remained at the reduced level for 10 h, but were at basal levels by the next morning, 23 h later.

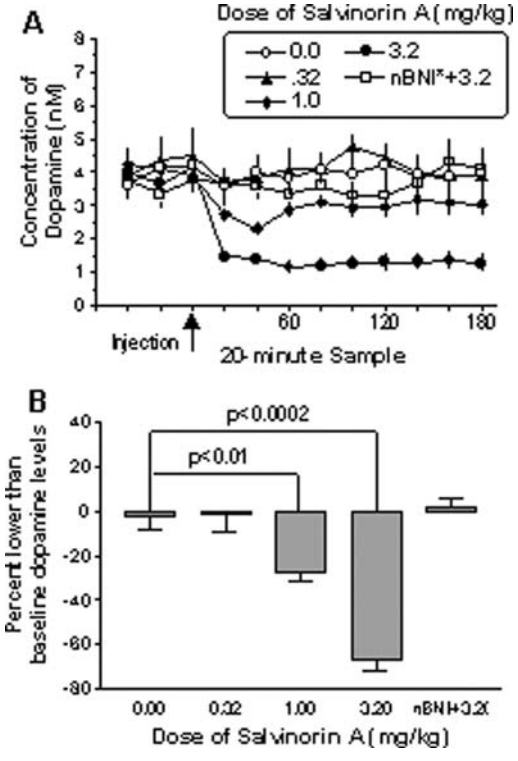

Fig. 2 **a** The dose–response effect of salvinorin A on dopamine levels in the caudate putamen of C57BL/6J mice with 20-min samples of dialysate for 1 h before and 3 h after injection (*arrow*) of salvinorin A. The *asterisk* (*) indicates that nor-BNI was administered 2 h before salvinorin A. **b** The mean percentage lowering from basal levels of dopamine after injection of each dose. It may be seen that salvinorin A dose dependently affected dopamine levels and that pre-injection of nor-BNI blocked the reduction of dopamine levels produced by salvinorin A. There were four or five mice in each dose group

Effect of salvinorin A on dopamine levels in the nucleus accumbens

To determine whether salvinorin A has similar effects on dopamine levels in the nucleus accumbens, the highest dose of salvinorin A tested (3.2 mg/kg) was injected i.p. and dopamine levels were measured in six additional C57 BL/6J mice, with a control group of five mice that received the 0.0-mg/kg dose (vehicle). Dopamine levels in dialysate from the nucleus accumbens of each group are shown in Table 2. Note the expected lower basal levels of dopamine in nucleus accumbens than in caudate putamen, as we have previously found in this strain (Zhang et al. 2001).

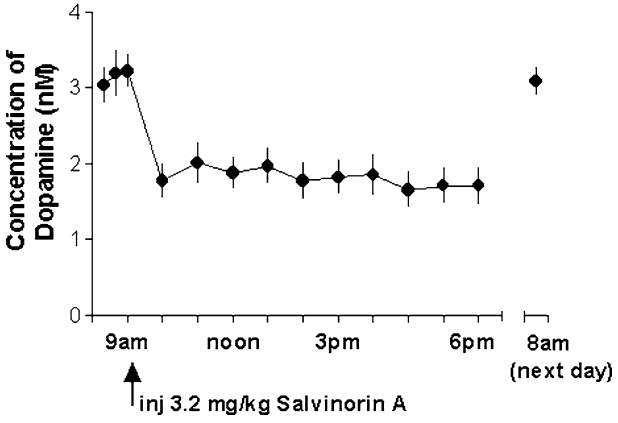

Fig. 3 The time course of the effect of the highest dose of salvinorin A tested (3.2 mg/kg) on dopamine levels in the dialysate from the caudate putamen is shown in an additional group of six C57BL/6J mice

Table 2 Effect of salvinorin A on basal dopamine levels in the caudate putamen and nucleus accumbens in the C57BL/6J mice

	Basal dopamine (nM)	Percentage decrease from baseline
Caudate putamen	4.0±0.1	66.6±1.7
Nucleus accumbens	0.8±0.0	2.1±2.0

Salvinorin A-induced conditioned place aversion

The development of a conditioned place aversion in mice by salvinorin A injection is shown in Fig. 4, with reduced time spent in the drug-paired chamber. Two-way ANOVA revealed that there was a significant main effect of dose of salvinorin A ($F_{2, 42}$=6.22, P<0.005). Newman–Keuls post-hoc tests showed that both doses of salvinorin A (1.0 mg/kg and 3.2 mg/kg, i.p.) produced conditioned place aversion compared with the control group (P<0.001 and P<0.01, respectively). Pretreatment with nor-BNI (10 mg/kg, i.p.) also showed a significant main effect ($F_{1, 42}$=19.33, P< 0.0001), and there was a significant drug condition×pretreatment interaction ($F_{2, 42}$=5.23, P<0.01). Newman–Keuls post-hoc tests showed that pre-injection of nor-BNI blocked the formation of conditioned place aversion induced by both doses of salvinorin A (1.0 mg/kg and 3.2 mg/kg, i.p.).

Salvinorin A decreased locomotor activity

The effect of salvinorin A on locomotor activity in the conditioning chamber, measured as number of crossovers from one end of the compartment to the other, is shown in Fig. 5. Two-way ANOVA (pretreatment×dose) showed

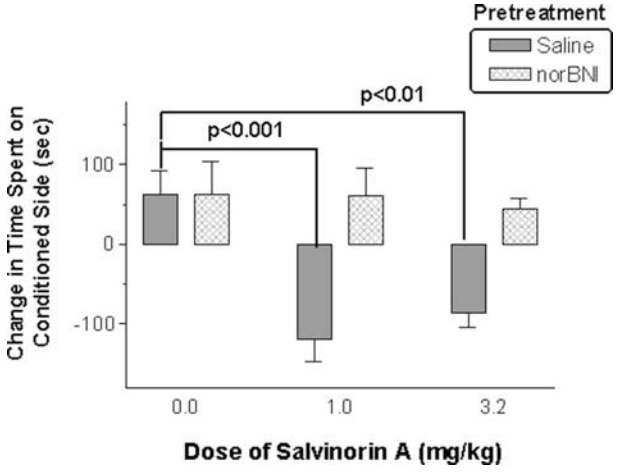

Fig. 4 Conditioned place preference produced by salvinorin A (n=8 per group). Both doses of salvinorin A induced a decrease in time spent in the drug-paired compartment. Pre-injection of nor-BNI in saline-treated mice did not lead to a significant change in time spent in the drug-paired compartment compared with that for saline control. Pre-injection of nor-BNI (10 mg/kg, i.p.) prior to salvinorin A blocked the salvinorin A-induced decrease in time spent in the drug-paired compartment at both doses

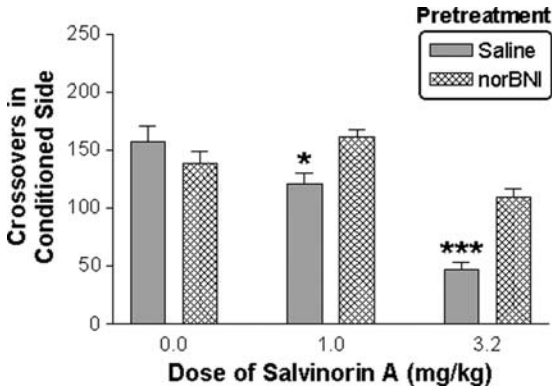

Fig. 5 Effect of salvinorin A on locomotor activity (n=8 per group, the same mice shown in Fig. 4). Locomotor activity in the drug-paired compartment expressed as mean (±SEM) number of crossovers in 30 min in the four drug-conditioning sessions. Salvinorin A produced a decrease in locomotor activity in the conditioned place preference chamber. Pre-treatment of nor-BNI (10 mg/kg, i.p.) by itself failed to change locomotor activity in the drug-paired compartment compared with saline control, but it did attenuate salvinorin A-induced decreases in locomotor activity

that there was a significant main effect of both pretreatment with nor-BNI ($F_{1, 42}$=14.00, P<0.001) and dose of salvinorin A ($F_{2, 42}$=35.27, P<0.000001). There was also a significant pretreatment×dose interaction ($F_{2, 42}$=10.70, P<0.0002). Newman–Keuls post-hoc tests revealed that animals that did not receive pretreatment with nor-BNI before salvinorin A showed lower levels of locomotor activity at both doses (1.0 mg/kg and 3.2 mg/kg, i.p.) than the zero-dose control groups (P<0.05 and P<0.0002, respectively). Furthermore, pretreatment with nor-BNI attenuated the lowering of locomotor activity induced by these doses of salvinorin A (1.0 mg/kg and 3.2 mg/kg, i.p.).

Discussion

This study demonstrated that the naturally occurring hallucinogen salvinorin A dose dependently decreased dopamine levels in the caudate putamen of C57BL/6J mice, effects similar to those previously found with synthetic kappa opioid agonists (Di Chiara and Imperato 1988; Donzanti et al. 1992; Spanagel et al. 1992; Devine et al. 1993; Zhang et al. 2004b). Moreover, salvinorin A at the same dose induced conditioned place aversion and decreased locomotor activity. Both effects were blocked by pre-injection of the kappa opioid receptor antagonist nor-BNI.

In vivo microdialysis studies in rats showed that basal dopamine levels in the nucleus accumbens and dorsal striatum were lower following perfusion of the synthetic kappa opioid agonist U-69593 into the nucleus accumbens (Spanagel et al. 1992) or systemic injections of the kappa agonists, U-50488 or bremazocine (Di Chiara and Imperato 1988). In agreement with these findings, acute administration of salvinorin A dose dependently decreased basal dopamine level in the caudate putamen of C57BL/6J mice. This dopamine-lowering effect of salvinorin A is

most likely due to activation of kappa opioid receptors in the caudate putamen, because pre-injection of the selective kappa opioid receptor antagonist nor-BNI blocked this effect of salvinorin A on dopamine.

In contrast to our findings in the caudate putamen, the highest dose of salvinorin A tested (3.2 mg/kg, i.p.) did not cause significant decreases in dopamine levels in the nucleus accumbens in mice. This finding was unexpected because, in the rat, other kappa opioid receptor agonists have been reported to decrease dopamine levels in the nucleus accumbens. However, we have found no studies of the effect of kappa agonists on dopamine levels in the nucleus accumbens in the mouse. Both in situ hybridization and receptor binding studies have shown that kappa opioid receptor mRNA and kappa binding sites are present in the nucleus accumbens in the mouse (DePaoli et al. 1994; Jamensky and Gianoulakis 1997). The lack of alteration in dopamine levels induced by salvinorin A (3.2 mg/kg, i.p.), therefore, is very interesting and remains to be explained.

Previous studies showed that the classic hallucinogen lysergic acid diethylamide (LSD), presumably acting on serotonergic receptors for its hallucinogenic effect (Harvey 2003; Roth et al. 2002), induced conditioned place preference in rats (Parker 1996; Meehan and Schechter 1998). 3,4-Methylenedioxymethamphetamine (MDMA) was also found to produce conditioned place preference in rodents (Meyer et al. 2002; Robledo et al. 2004). However, other hallucinogens (e.g., mescaline) have apparent aversive effects in the rodent (Cappell and LeBlanc 1971). In contrast, the synthetic kappa opioid agonists U-50488H, U-69 593 and TRK-820 produced conditioned place aversion in rats (Shippenberg and Herz 1987; Bals-Kubik et al. 1989; Suzuki et al. 1992; Mori et al. 2002). Interestingly, the hallucinogen salvinorin A, a kappa selective agonist without affinity at serotonergic receptors, produced conditioned place aversion. This effect may be related to its lowering of dopamine levels, since both doses of salvinorin A that produced conditioned place aversion also decreased dopamine levels. Furthermore, these doses of salvinorin A decreased locomotor activity in the conditioned place preference chamber. The fact that the formation of a conditioned place aversion was blocked and the inhibition of locomotor activity was attenuated by pre-treatment with the selective kappa opioid antagonist nor-BNI, suggest that activation of kappa opioid receptors underlies both the aversive and locomotor effects of salvinorin A.

The effect of the synthetic kappa opioid agonist R-84760 on dopamine levels in the caudate putamen was recently examined under similar experimental conditions in the same strain of mice (Zhang et al. 2004b). Salvinorin A is less potent than R-84760, since systemic administration of 0.1 mg/kg R-84760 decreased dopamine level in the caudate putamen to approximately 50% of the baseline; whereas, at a dose of 0.32 mg/kg, salvinorin A did not significantly affect dopamine levels in the caudate putamen of mice. The dose–response study reported above showed that two doses of salvinorin A (1.0 mg/kg and 3.2 mg/kg, i.p.) revealed a fast onset effect of lowering dopamine levels in the caudate putamen, similar to our finding with R-84760. These findings are consistent with a previous study in rhesus monkeys (Butelman et al. 2004). In the present study, salvinorin A was also shown to have a long duration of action (at least 10 h), similar to R-84760. Behavioral studies in mice revealed that R-84760 failed to induce conditioned place aversion at 0.1 mg/kg. However, at both doses tested herein (1.0 mg/kg and 3.2 mg/kg, i.p.), salvinorin A produced conditioned place aversion. Interestingly, both R-84760 and salvinorin A decreased locomotor activity in conditioning sessions.

The fact that salvinorin A decreased striatal dopamine levels and produced a place aversion suggests that this drug would possibly be aversive to humans. However, numerous studies have found compounds that are self-administered by humans to produce aversive effects in rodents. For example, cannabinoids (e.g., THC) are self administered in humans, although the synthetic cannabinoid CP 55,940 produced conditioned place aversion in rats (McGregor et al. 1996; Robinson et al. 2003). Also, phencyclidine, a compound that is also abused by humans, was found to be aversive in rats (Kitaichi et al. 1999). Thus, compounds from particular pharmacological classes that produce aversive effects in rodents may have abuse potential under certain conditions in humans.

The abuse property of salvinorin A may result from its ability to produce “psychotomimetic” or “hallucinogenic” effects in humans, which may be pleasurable to some people. Whether this is a result of alteration of the dopaminergic system remains to be determined. While other kappa agonists have been studied for the potential treatment of cocaine addiction in both pre-clinical and clinical models (Glick et al. 1995; Kuzmin et al. 1997; Schenk et al. 1999; Walsh et al. 2001), their diverse side effects, such as sedation, may limit their therapeutic use. The hallucinogenic effect of the naturally occurring kappa opioid agonist salvinorin A studied here may limit it as a candidate therapeutic agent.

Of interest, a very recent study in mice (Wang et al. 2005) suggests that salvinorin A may not have behavioral (e.g., antinociceptive) effects similar to those of synthetic κ-agonists. Furthermore, Wang et al. reported that salvinorin A had a lesser propensity to cause κ-receptor internalization and downregulation in vitro than synthetic k-agonists, such as U-69593 or TRK-820. It is unknown at this time whether these potentially unique features of salvinorin A underlie its powerful hallucinogenic effects in humans.

The present studies provide, to our knowledge, the first available data on the profile of salvinorin A on these neurobiological and behavioral effects, previously observed with kappa agonists in rodents (i.e., a decrease in extracellular dopamine levels in the striatum and place aversion). These results are consistent with previous findings in rats and mice, focusing on synthetic or peptidic kappa opioid agonists (Heidbreder et al. 1993; Crawford et al. 1995; Shippenberg et al. 1996; Suzuki et al. 1992; Zhang et al. 2004a). These studies indicate that this widely available hallucinogen produces in vivo effects that are qual-

itatively similar to those of synthetic kappa agonists, consistent with its in vitro profile as a selective, high efficacy kappa agonist (Chavkin et al., 2004).

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