

The hallucinogen derived from *Salvia divinorum*, salvinorin A, has κ -opioid agonist discriminative stimulus effects in rats

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Abstract

Data from clinical and preclinical studies converge implicating the plant-derived hallucinogen salvinorin A as an important pharmacologic tool; this psychoactive compound may expand scientific understandings on mammalian κ -opioid receptor systems. Human salvinorin A effects, consistent with κ -opioid receptor agonism, include antinociception, sedation, dysphoria and distorted perceptions. The experiments reported here measured salvinorin A (1–3 mg/kg, i.p.) discriminative stimulus properties in male Sprague–Dawley rats conditioned to recognize the discriminative stimulus cue generated by the well characterized κ -opioid agonist U-69593 (0.56 mg/kg, i.p.). At three distinct active doses, salvinorin A fully substituted for U-69593 without altering response rates. The lever choice pattern in U-69593 trained animals reverted to vehicle lever responding when a kappa selective antagonist compound, nor-BNI (4.5 nM, i.c.v.) was administered 1 h prior to salvinorin A, yet nor-BNI alone failed to impact the rate or pattern of subject responses. These findings confirm and extend results published after similar drug discrimination tests were performed in rhesus monkeys. The discussion section of this article highlights public concern over salvinorin A misuse and emphasizes several potential pharmacotherapeutic applications for salvinorin A or analogue compounds.

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1. Introduction

Salvinorin A is a structurally unique furanolactone neoclerodane diterpene and is the main active drug in *Salvia divinorum*, a ‘Mexican-mint’ sage plant belonging to the Lamiaceae family. Salvinorin A is both pharmacologically and chemically unique in that it represents the first non-nitrogenous, naturally occurring κ -opioid receptor selective agonist and the only known non-alkaloidal hallucinogen (Roth et al., 2002). *Salvia divinorum* has a long history of use for traditional spiritual purposes by Mazatec shamans of Oaxaca, Mexico (Valdés, 1994). More recently, the leaves and extracts of *S. divinorum*

have been misused for hallucinatory and mind-expanding effects (Bucheler et al., 2005). Cultivation and purchase of *Salvia divinorum* first appeared in young people from Mexican cities and has since spread through Europe, showing that global abuse of the drug is increasing. The use or possession of *Salvia divinorum* is not banned by most countries, which draws appeal from drug users. Attraction to the drug among recreational users can be attributed to hallucinogenic effects, which in doses above 200 μ g rival the synthetic hallucinogen lysergic acid diethylamide (LSD) in doses of 50–250 μ g (Bucheler et al., 2005). *Salvia* product abusers experience a psychic depersonalization condition, a unique sensation of being disconnected from one’s body.

Currently, few studies with salvinorin A have been performed in vivo. In mice, antinociceptive effects of the drug

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were shown using tail-flick and hot plate thermal nociceptive assays (McCurdy et al., 2006). Sedation and motor incoordinating effects of the drug were also shown in mice as disrupting climbing strategies in an inverted screen task (Fantegrossi et al., 2005). A forced swim test (Carlezon et al., 2006) revealed increased immobility accompanied by decreased swimming behaviors in rats, opposite to that seen by SSRIs, suggesting that salvinorin A produces pro-depressant like effects; however, salvinorin A elicits a complex spectrum of effects on mood-related variables. Indeed, clinic data suggest salvinorin A abuse is growing *because* of the complex mindset and mood changes invoked (Bucheler et al., 2005; National Drug Intelligence Center, 2007; Halpern, 2004). When leaves of *Salvia divinorum* are chewed or smoked, exposed individuals describe an intensely positive hallucinogenic experience (e.g., altered depth perception, heightened sensual and aesthetic appreciation, creative dream-like state). At least one case report secures mood-elevating effects from salvinorin A. This case documented a 26-year-old woman, depressed according to HAM-D scores, who remitted the symptoms of her depression with *Salvia divinorum* bought through a mail-order herbalist (Hanes, 2001). In line with the clinic report of a *Salvia* derivative's mood-elevating effects, Braida et al. (2007) showed reinforcing effects in a conditioned place preference test after injecting zebra fish with salvinorin.

Drug discrimination has long proven to be a reliable, robust, and selective model to discover the behavioral effects of various compounds. Drug discrimination is also endorsed as a test to infer neurological underlays and/or receptor mediation pathways for psychoactive drugs. Drug discriminating animals are rewarded for responding appropriately (i.e., correct lever-press sequence) after either a 'training' drug or its vehicle is administered. The discriminative stimulus properties of salvinorin A were studied in rhesus monkeys by Butelman et al. (2004). The Butelman study used a well characterized κ -opioid agonist, U-69593, to train responses under distinguishable stimulus conditions (i.e., training drug versus vehicle sessions). Butelman et al. (2004) reported κ -opioid receptor mediation of salvinorin A's psychotropic effects when subcutaneous injections of salvinorin A cross generalized to U-69593. Our search of the published literature revealed no rodent drug discrimination studies to verify κ -opioid receptor mediation of salvinorin A's effects. To fill this research gap, a group of ten Sprague–Dawley rats were trained to recognize the discriminative stimulus effects of U-69593, and generalization tests followed to discover whether or not rats would respond similarly to the interoceptive cue generated by salvinorin A (1–3 mg/kg, i.p.). In a second series of experiments, a subgroup of the U-69593 discriminating rats received pre-emption injections (i.c.v.) with the κ -opioid antagonist nor-BNI, before being injected with salvinorin A, to verify the proposed pharmacologic mode of action. Our expectation, as this experimental series started, was to note salvinorin A substitution for U-69593. While most *in vivo* and *in vitro* research data have supported κ -opioid receptor mediation of salvinorin A's central nervous system effects (Chavkin et al., 2004; Fantegrossi et al., 2005; McCurdy et al., 2006; Roth et al., 2002),

pause is taken while interpreting the findings in two non-human primate experiments where an incomplete reversal of salvinorin A effects was reported for monkeys pretreated with a κ -opioid receptor selective antagonist (Butelman et al., 2004, 2007).

2. Materials and methods

2.1. Subjects

Ten male Sprague–Dawley rats (Harlan Laboratories, Indianapolis, IN), weighing 280–340 g at the beginning of the experiments were subjects for this study. The rats were housed individually in plexiglass cages with free access to water in a temperature controlled room (23 ± 1 °C, with humidity $50 \pm 10\%$) scheduled for 12 h light/dark exposure cycles. Subjects for these experiments were drug naive and were maintained in facilities accredited by the Institutional Animal Care and Use Committee at Ohio Northern University. Rats were maintained at $\sim 80\%$ of their free feeding body weight in order to motivate operant responding for food rewards. Effort was expended to minimize animal suffering over the course of these experiments.

2.2. Apparatus

Operant conditioning chambers (Lafayette Instruments) constructed with left- and right-mounted response levers and a central food cup were used. Research Diet[®] (Natick, MA) 45-mg rat pellets rewarded conditioned behaviors. A 15-W white house light above the chamber's transparent ceiling was lit for all sessions. Chambers were set in sound-attenuating wooden cubicles with a fan motor to provide ventilation and mask noise. ABET[™] software controlled the experimental environment. Repeat conditioning induced a pairing of right chamber levers (red cue-light) to drug (U-69593) injection and left chamber levers (amber cue-light) to vehicle injection.

2.3. Drugs

U-69593 ((5 α ,7 α ,8 β)-(–)-*N*-methyl-*N*-[7-(pyrrolidinyl)-1-oxaspiro[4.5]-dec-8-yl]-benzeneacetamide; Sigma-Aldrich, St. Louis, MO) was dissolved in isotonic saline with 10 μ l of glacial acetic acid. Salvinorin A (isolated and purified from *Salvia divinorum* in Oxford, Mississippi (McCurdy laboratory)) was first dissolved in dimethylsulfoxide and then dissolved in isotonic saline for injection. Norbinaltorphimine dihydrochloride (nor-BNI) (Sigma-Aldrich, St. Louis, MO) was dissolved in isotonic saline. All drugs except nor-BNI were administered in a volume of 1 ml/kg. Doses were calculated as those of the bases. The doses and pre-injection intervals for U-69593, salvinorin A, and nor-BNI were selected from pilot studies or from previously published reports (McCurdy et al., 2006).

2.4. Administration of norbinaltorphimine into the right lateral ventricle

Six rats were anesthetized with a mixture of ketamine plus xylazine (80 mg/kg plus 12 mg/kg, i.p.; Sigma-Aldrich, St. Louis, MO) and given diazepam (10 mg/kg, i.m.). Guide cannulae were then implanted using a Stoelting (model 51400) stereotactic frame, but coordinate measurements were taken manually with a plastic ruler. The skull was exposed, and a small hole was drilled unilaterally. The cannula was lowered to 1 mm above the target site (coordinates relative to bregma: A, –1.3; L, 1.0; V, 4.0), and, together with two additional screws, was embedded in dental cement.

The tips of the guide cannulae (25 gauge, Plastics One, VA, USA) extended beyond the skull by 1 mm. Microinjection of nor-BNI was done manually, with a Hamilton syringe, in a volume of 3 μ l. Intracerebroventricular injection (i.c.v.) doses were instilled over a 60 s period, and followed by a 2 μ l of saline flush. The injection cannula was left in place for 60 additional seconds. Although six of the ten U-69593 discriminating animals underwent surgery to implant intracerebroventricular cannulae, a nor-BNI-blocked dose effect curve for

salvinorin A was only determined in five subjects because the i.c.v. cannula dislodged from supportive dental cement in one surgically prepared animal.

2.5. Experimental procedure

2.5.1. Training with U69,593 as a discriminative stimulus

Training sessions occurred from Monday to Saturday, between 1100 and 1800 h. Early training was arranged on a double alternation schedule—daily sessions exposed all subjects three times per week to U-69593 (0.56 mg/kg) injections and three times per week to saline injections. As the right lever was arbitrarily paired with training drug, consecutive responses at the right lever (FR-10) were reinforced by the delivery of a food pellet on the days designated for U-69593 injection. Responses emitted on the opposite lever (FR-10) produced food pellet rewards on the days designated for saline injection. Injections of U-69593 or saline were given i.p. 10 min before subjects were placed into operant chambers. Responses on the incorrect lever reset the response count on the correct lever. All training sessions ended after 20 min, when animals were returned to home cages and given a sufficient quantity of Purina Laboratory Chow to sustain ~80% of their expected free-fed weight.

Drug-induced stimulus control was assumed to be present when the animals consistently selected the appropriate lever (U-69593 or vehicle) first in three vehicle plus three training-drug consecutive sessions. Our training procedure also stipulates rats must emit 80% of all lever press responses at the correct lever and a minimum of 80 lever presses must be emitted for a training session to be counted. Once this level of performance was achieved, testing with various doses of salvinorin A was initiated.

2.5.2. Pilot tests to resolve salvinorin A dose range

The sparse literature describing salvinorin A effects in rats made it difficult to specify an appropriate salvinorin A dosage range for substitution tests. Therefore, pilot tests were conducted to scrutinize salvinorin A effects on spontaneous locomotion and to detect dose-dependent influences on treated subjects' responsiveness to stimuli. The pilot test series consisted of six open-field observing sessions, 30 min in duration, to assess salvinorin A influences in a separate group of naïve female rats with no operant conditioning history. Pilot test rats were watched in an open field environment—an exploratory environment wherein experimenters introduced cues to elicit a variety of spontaneous reactive behaviors (e.g., righting reflex, response to pencil-pokes, reaction to food stimuli). Six discrete doses of salvinorin A were assessed during pilot tests: (i) 0.1 mg/kg, (ii) 0.3 mg/kg, (iii) 1.0 mg/kg, (iv) 3.0 mg/kg, (v) 5.6 mg/kg, (vii) 10 mg/kg. Data from pilot tests suggested 0.1 mg/kg and 0.3 mg/kg as “no-effect” doses, and all doses above the 1.0 mg/kg dose produced motor incoordination during the last 15 min of observation plus dose-dependent catalepsy at times proximal to i.p. drug administration. The 5.6 mg/kg and 10 mg/kg doses also produced salivation/drooling and forelimb tremor. After completing the pilot tests and consulting the relevant literature, the 1.0–3.0 mg/kg range was considered optimal to reflect salvinorin A discriminative stimulus effects.

2.5.3. Discrimination tests with salvinorin A

When a rat met testing criteria for consistent U-69593 discrimination performance, test sessions were planned to present salvinorin A doses in an irregular order. Ultimately, all subjects received the range of salvinorin A doses (1.0 mg/kg, 1.9 mg/kg, and 3.0 mg/kg), but the order of dose presentations varied among subjects. Test sessions were identical to training sessions with the exception that 10 consecutive responses on either lever produced food delivery. When salvinorin A substitution tests commenced, a single alternation schedule between training drug, saline vehicle, and salvinorin A was followed. Rats were considered eligible for substitution testing only after completing two prior training sessions (U-69593 plus vehicle) at an accuracy level of at least 80% and after emitting their first response (FR10) at the correct lever. If the accuracy of trained animals deteriorated relative to stated criteria, further training sessions were given before testing was reinstated.

2.5.4. Discrimination tests with nor-BNI pretreatment

Following the discrimination tests with salvinorin A, similar tests were done with a pretreatment of the κ -opioid antagonist nor-BNI. Rats were given

nor-BNI (10 mg/ml solution, 3 μ l, i.c.v.) 60 min before the administration of salvinorin A. The discrimination tests then preceded as described above. To demonstrate stimulus control from the same training dose of U-69593, probe tests (2 min at the start of each training session) were performed with U-69593 or saline. In order to rule out the possibility that behavioral changes were due to nor-BNI during sessions of κ -opioid antagonist and salvinorin A co-administration, extra control sessions were scheduled for each test animal. Thus, a preliminary control session measured nor-BNI (10 mg/ml solution, 3 μ l, i.c.v.) against nor-BNI's vehicle (saline, i.c.v.). After noting that nor-BNI failed to alter behavior relative to its vehicle, a second i.p. saline control session was scheduled. Data from the i.p. saline control session was statistically analyzed against data collected in sessions of nor-BNI and salvinorin A co-administration.

2.6. Data analysis

Data from salvinorin A test sessions were analyzed for similarity to U-69593 by determining the mean percentage of responses on the U-69593-associated lever. An a priori decision was made to deem 80% or more U-69593-lever responding, during salvinorin A test sessions, as full generalization. In addition to monitoring U-69593 appropriate responding, the total number of lever presses in each session was recorded and response rates were tabulated to reflect non-specific effects on behavior. The response rate data were graphed after conversion to a percentage of the average saline session response rate (mean in 5 saline injection sessions). Finally, reinforcement pellets earned in each 20 min testing session was recorded and caloric equivalent tabulated to adjust post-session feedings.

The data of primary interest are the proportion of responses made on the drug-state appropriate lever during salvinorin A test sessions. Because the drug-lever selection data is difficult to interpret when the subject is severely impaired, data from sessions in which responding was less than 0.06 responses/min were excluded from determination of the mean percentage of U-69593-lever responding. Data from sessions exceeding the 0.06 responses/min threshold were used in a General Linear Model (GLM) analysis to distinguish any significant effects related to salvinorin A dose. This GLM statistical analysis was applied for salvinorin A testing sessions both with and without prior nor-BNI injection. The variance of GLM mean measures was further examined in Dunnett's *t* posteriori comparison tests where appropriate. Calculations were performed using SPSS, version 10 software. A similar GLM analysis was undertaken to discover whether or not salvinorin A significantly affected rats' responding rates.

3. Results

Drug discriminative stimulus control was shown unequivocally for U-69593, and the mean number of training periods to establish discrimination was 85 (\pm 3) sessions. At all three active doses, salvinorin A displayed a rapid onset of action (i.e., 10 min for visible effects). Results from substitution tests with salvinorin A are shown in Fig. 1. Salvinorin A fully substituted for the U-69593 interoceptive cue. Salvinorin A, administered at either the 1 mg/kg or 3 mg/kg dosage resulted in 96% subject responding at the drug appropriate lever, while the middle dose of salvinorin A, 1.9 mg/kg, yielded 88% drug appropriate responding in U-69593-trained rats. A GLM statistical analysis confirmed cross generalization of salvinorin A to U-69593 [$F(3,18) = 8.37$, $p < 0.01$], and post hoc tests proved all salvinorin A doses were statistically different from vehicle ($p < 0.05$).

The effects of salvinorin A on response rates are shown in Fig. 2. While specific doses of salvinorin A had influence over bar press rates, no statistically significant change in rats' responding rates was revealed [$F(3,18) = 0.23$, $p > 0.98$].

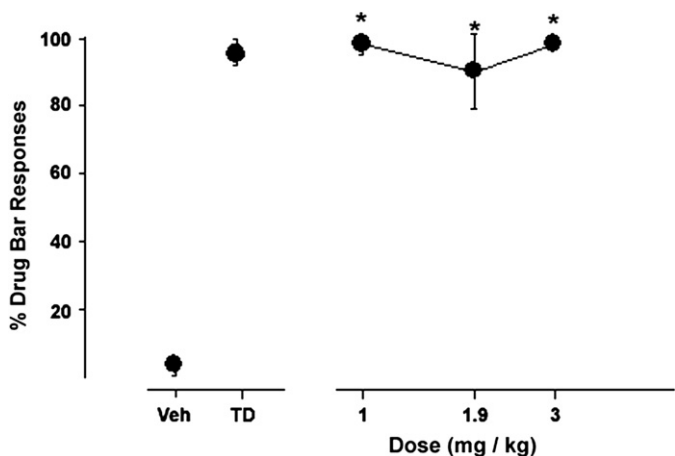


Fig. 1. Stimulus generalization (% DBR) following three doses of salvinorin A (1.0–3.0 mg/kg, i.p.) in male rats ($n = 10$) trained to discriminate U-69593 (0.56 mg/kg, i.p.) from saline. Lever selection data are plotted as group mean; error bars show standard error of the mean. Data points above Veh and TD represent the results of control tests with saline and training drug (U-69593). Significant differences from vehicle session choice patterns are designated by an asterisk.

Visual inspection of graphed means for rats' percent control response rate shows salvinorin A provoked a slight decrease in the rate of bar pressing at the 1 mg/kg and the 3 mg/kg dose levels, but no rate change was apparent in sessions testing the middle dose (1.9 mg/kg).

The discriminative effects of salvinorin A were blocked by nor-BNI (4.5 nM, i.c.v.) in all subjects. In support of this, pre-session injections of nor-BNI completely reverted the lever selections of rats that later received salvinorin A (1 mg/kg, 1.9 mg/kg, 3 mg/kg, i.p.). As shown in the upper panel of Fig. 3, during the sessions of nor-BNI and salvinorin A co-

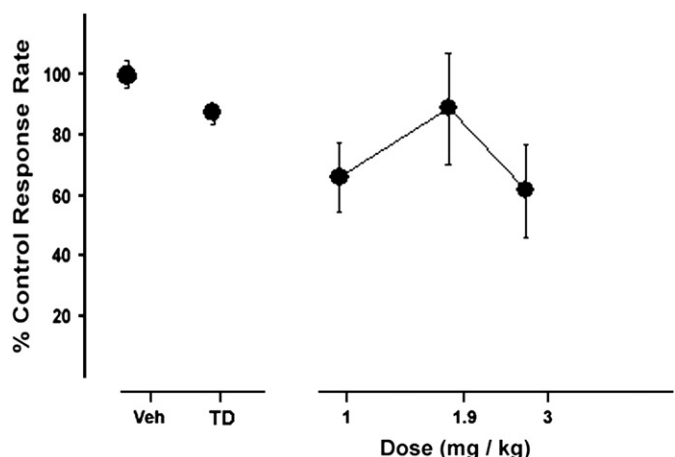


Fig. 2. Mean response rates, expressed as a percentage of vehicle control response rates (% CRR) in male rats ($n = 10$) trained to discriminate U-69593 (0.56 mg/kg, i.p.) from saline during salvinorin A substitution tests. The total number of responses emitted on both levers during salvinorin A test sessions was divided by the session duration (1200 s) for each rat, and data from individual rats were averaged for each test condition. Data points above Veh and TD represent the results of control tests with saline and training drug (U-69593; 1.0 mg/kg). Data points show group mean; error bars show standard error of the mean.

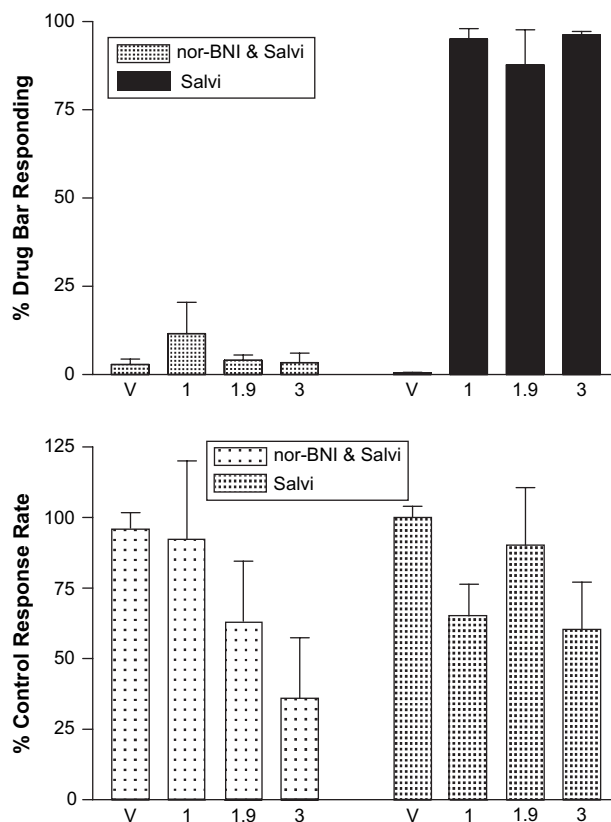


Fig. 3. Upper panel: the left series of bars plots antagonism of the discriminative stimulus effects of salvinorin A (1.0–3.0 mg/kg, i.p.; expressed as % DBR), and salvinorin A vehicle, during nor-BNI (4.5 nM, i.c.v.) co-administration sessions. The right side plots % DBR data during sessions without nor-BNI pre-administration. Salvinorin A cross generalization tests used male rats trained to discriminate U-69593 (0.56 mg/kg, i.p.) from saline. Lever selection data are plotted as group mean; error bars show standard error of the mean. Lower panel: the left series of bars shows response rates tabulated during salvinorin A generalization tests (1.0–3.0 mg/kg, i.p.; expressed as % CRR) and indicates a salvinorin A vehicle session rate, while nor-BNI (10 mg/kg, i.c.v.) co-administration was stipulated. The right side plots % CRR data during sessions without nor-BNI pre-administration. Salvinorin A cross generalization tests used male rats trained to discriminate U-69593 (0.56 mg/kg, i.p.) from saline. % CRR is plotted to show group mean; error bars show standard error of the mean.

administration, subjects overwhelmingly emitted vehicle lever responses. However, data collected while concomitantly dosing antagonist and agonist do not indicate differences in bar press rates (Fig. 3, lower panel). In other words, pre-treatment with the κ -opioid selective antagonist compound revoked drug appropriate responding but had no impact on the rate of lever pressing.

4. Discussion

The present study targets a broader general awareness of the sage plant-derived hallucinogen, salvinorin A. The illicit use of easy access hallucinogenic compounds, like salvinorin A, is a reemerging health problem, particularly among well-educated young adults and teenagers (Hunt, 1997; Schuster et al., 1998). Salvinorin A is misused because intake of this

herb, by smoking or leaf-chewing, produces a short-lived inebriant state with intense, bizarre feelings of depersonalization (Halpern and Pope, 2001). Readers may view it odd that any ‘out-of-body’ or depersonalized state would be desired; on the other hand, the cohort groups sanctioning use of this drug defend it vigorously. Supporters of recreational *Salvia divinorum* use claim, while certain elements in the drug trip may cause discomfort, bad trip experiences are likely to be trumped by positive experiences (Giroud et al., 2000; Sheffler and Roth, 2003). Since *Salvia divinorum* extracts are hallucinogenic and act principally through opioid receptors, experts in this field of study view *Salvia* products as ‘narcotic’.

Behavior analysts define a narcotic ‘cue’ as, “the discriminative stimulus complex which is exclusively associated with the specific central actions of a narcotic drug” (Colpaert et al., 1975). Results from the present study show salvinorin A produces a discriminative stimulus complex in rats similar to that of the κ -opioid agonist U-69593. This finding, together with salvinorin A’s high and selective affinity at κ -opioid receptors in vitro (Roth et al., 2002) and replicate demonstrations of salvinorin A’s κ -opioid like signal transduction cascade (Vortherms et al., 2007; Wang et al., 2005) support κ -opioid receptor mediation of the subjective effects of salvinorin A. In this experimental series, we showed salvinorin A induction of drug appropriate lever selections in U-69593 trained rats, but lever selections reverted to the vehicle designated lever when the kappa selective antagonist compound nor-BNI was administered by intracerebroventricular injection. The possibility that non-specific effects of nor-BNI were responsible for its surmounting salvinorin A substitution for U-69593 can be ruled out, since nor-BNI alone provoked responses at the vehicle designated lever. The antagonist reversal of conditioned responses reported here is consistent with results published by Zhang et al. (2005), showing nor-BNI blockade of salvinorin A-induced place aversion and a decrease in dopamine levels in the nucleus accumbens. Likewise, reversal of conditioned responses in this experimental series falls in line with a report describing zebra fish swim pattern changes after intramuscular injection of salvinorin A in a conditioned place preference test when paired with nor-BNI (Braidia et al., 2007). More data to bolster the scientific claim that salvinorin A’s effects are κ opioid receptor mediated were published from a series of experiments that used κ opioid receptor knockout mice as subjects. Ansonoff et al. (2006) showed κ opioid receptor knockout mice do not respond to salvinorin A when analgesia and temperature are used as readouts. On the other hand, a partial (~66%) block of salvinorin A substitution for U-69593 in drug discriminating monkeys was reported by Butelman et al. (2004). A different antagonist was used in the Butelman study, namely GNTI. GNTI resembles nor-BNI pharmacologically by virtue of its κ -opioid selectivity (Jones and Portoghese, 2000). However, Butelman and colleagues injected GNTI peripherally before measuring cross generalization between salvinorin A and U-69593. Even while granting GNTI likeness to nor-BNI, differences in the species used and routes of administration distinguish our experiments from the discrimination tests in Butelman et al. (2004), which rationalizes an outcome disparity.

Salvinorin A did not systematically decrement rats’ response rates as dose increased. Visual inspection of the graphed response rate data (Fig. 2) shows an inverted U shaped dose effect curve. Our search of the drug discrimination literature revealed precedence for this type of response rate curve, exemplified when the κ -opioid agonist probes E-2078 and R-84760 were administered to ascertain cross substitution in U 50488-trained and TRK-820-trained animals, respectively (Mori et al., 2004). Another aspect of the salvinorin A precipitated changes to bar press rates warrants mention because, in the pilot segment of our investigations, non-specific motor impairment (e.g., motor incoordination, motor depression, catalepsy) was specified for naïve rats that received salvinorin A injections in the 3–10 mg/kg dosing range. Since a systematic response rate decrement was not concluded during salvinorin A drug discriminating sessions, the possibility remains open that discordant motor effects, in discriminating relative to naïve rats, are reflecting cross-tolerance (Colpaert, 1978). If acceptance is granted for this interpretation, then the analyst asserts that animals receiving daily doses of U-69593 may manifest tolerance to the motor sedative effects of many κ -opioid receptor agonists. Further, tolerance to the motor effects of *Salvia* products seem to manifest in dosing ranges lower than that required for tolerance to narcotic cuing. Finally, the slow and uncoordinated motor performance we detected after administering 3–10 mg/kg salvinorin A to naïve animals is consistent with the test outcomes reported for salvinorin A when mice were examined (Fantegrossi et al., 2005; Zhang et al., 2005).

Together, these data provide empirical verification that the salvinorin A discriminative stimulus cue is κ -opioid receptor mediated in rats. These findings corroborate conclusions about the central origin of salvinorin A’s narcotic cue in monkeys (Butelman et al., 2004). An important question arises when κ -opioid receptor mediation of salvinorin A effects is contemplated: how can research teams, focused on medicinal product development, harness a therapeutic effect from *Salvia* plant extracts or related synthetic analogues? It is instructive to recall the ubiquity of κ -opioid receptor expression in central and peripheral neural circuits (Barry and Zuo, 2005). Moreover, recent data critically implicate distinct κ -opioid receptor isotypes (e.g. κ_1 , κ_2 , κ_3 opioid receptors) in pain signaling (McCurdy et al., 2006; Przewlocki et al., 1983), food intake (Morley and Levine, 1983), mood (Carlezon et al., 2006; Pfeiffer et al., 1986) and drug seeking behaviors (Glick et al., 1995; Kuzmin et al., 1997; Schenk et al., 1999; Walsh et al., 2001). Therefore, a proliferation of interest in *Salvia divinorum* should soon emerge to identify κ -opioid agonist and/or antagonist compounds as antinociceptive, antidepressant, and addiction therapies.

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