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Effect of the kappa-opioid receptor agonist, U69593, on reinstatement of extinguished amphetamine self-administration behavior

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Abstract

Previous research has indicated that pretreatment with the kappa-opioid receptor agonist, U69593, decreased the ability of experimenter-administered cocaine to reinstate extinguished cocaine self-administration behavior. This effect was specific to cocaine-produced drug seeking since U69593 failed to attenuate the ability of experimenter-administered amphetamine to reinstate extinguished cocaine self-administration behavior. One possibility is that U69593 selectively attenuates the behavioral effects of the drug that was originally self-administered. In order to test this hypothesis, the present study examined the effect of U69593 (0.0 or 0.32 mg/kg) on the reinstatement of extinguished amphetamine self-administration behavior produced by experimenter-administered injections of cocaine and amphetamine. Following extinction of amphetamine self-administration (0.04 mg/kg/infusion) the ability of cocaine (0.0, 5.0, 10.0 or 20.0 mg/kg) or amphetamine (0.0, 0.3, 1.0 or 3.0 mg/kg) to reinstate extinguished self-administration behavior was measured. Both drugs reinstated extinguished responding and the reinstatement was attenuated by pretreatment with U69593. The data indicate that the ability of U69593 to decrease drug seeking is not restricted to subjects experienced with cocaine self-administration. Self-administration history does, however, determine the effect of U69593 on amphetamine-produced drug seeking.

Keywords: Amphetamine; Cocaine; Drug seeking; Relapse; U69593; Kappa-opioid receptors

1. Introduction

Pretreatment with kappa-opioid receptor agonists modifies many of the behavioral effects of cocaine. For example, the ability of a cocaine-paired environment to acquire a preference was blocked by prior treatment with the kappa-opioid receptor agonist, U-50,488H (Crawford et al., 1995) and cocaine-produced hyperactivity was attenuated by pretreatment with the kappa-opioid receptor agonist, U69593 (Heidbreder et al., 1993). Several studies have also indicated that pretreatment with kappa-opioid receptor agonists decreased cocaine self-administration (Glick et al., 1995; Mello and Negus, 1998; Negus et al., 1997; Schenk et al., 1999).

Cocaine blocks the reuptake of dopamine, serotonin and norepinephrine (Kuczenski, 1983; Reith et al., 1997), but a number of studies have indicated that the increases in synaptic dopamine are critical for many of the behavioral effects (Heidbreder et al., 1996; Koob and Weiss, 1992). Kappa-opioid receptor agonists inhibit dopamine release and decrease cocaine-evoked dopamine overflow in the nucleus accumbens (Devine et al., 1993; Heidbreder and Shippenberg, 1994; Maisonneuve et al., 1994), providing a potential dopaminergic mechanism underlying the behavioral interactions between cocaine and kappa-opioid receptor agonists.

Some studies have suggested that effects of the kappa-opioid receptor agonist, U69593 (Lahti et al., 1985), are specific to cocaine. For example, pretreatment with U69593 decreased the discriminative stimulus properties of cocaine is some studies (Riberdy et al., 1995; Spealman and Bergman, 1992, 1994) but failed to attenuate the discriminative stimulus properties of amphetamine (Powell and Holtzman, 2000). In other studies, rats that received pretreatment with either morphine or cocaine were subsequently sensitized to the ability of these drugs to produce a conditioned place preference (Shippenberg and Heidbreder, 1995; Shippenberg and Rea, 1997; Shippenberg et al., 1996, 1998). When U69593 was coadministered with either cocaine or morphine during pretreatment, a blockade of cocaine- but not morphine-induced sensitization was produced (Shippenberg et al., 1998).

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Recently, we demonstrated that cocaine-produced cocaine seeking was blocked by pretreatment with the kappa-opioid receptor agonist, U69593 (Schenk et al., 1999, 2000). The effect of U69593 was specific since amphetamine-produced cocaine seeking was unaltered by pretreatment with this kappa-agonist (Schenk et al., 1999). One possibility for the specificity of effects of U69593 on cocaine-produced reinstatement is that the effects are restricted to those produced by the self-administered drug, but not by other drugs. This hypothesis was tested in the present study by examining the effect of pretreatment with U69593 on cocaine- and amphetamine-produced reinstatement of extinguished amphetamine self-administration behavior.

2. Methods

2.1. Subjects

Adult male Sprague–Dawley rats (Harlan, TX) weighing 325–350 g were used. Rats were housed individually in standard hanging polycarbonate cages in a temperature and humidity controlled facility at Texas A&M University. The colony is accredited by the American Association for the Accreditation of Laboratory Animal Care (AALAC) and was maintained on a 12-h light/dark cycle (lights on at 0800 h). All tests were conducted during the light portion of the cycle (beginning at 0900 h). Food and water were available ad libitum except during testing. Principles of laboratory animal care were followed (NIH publication no. 85-23, rev. 1985).

2.2. Surgery

Rats were implanted with a Silastic catheter in the external jugular vein under deep anesthesia produced by separate IP injections of ketamine (60.0 mg/kg) and pentobarbital (20.0 mg/kg). The external jugular vein was isolated and the tubing was inserted and fixed in place. The distal end of the tubing was passed subcutaneously to an exposed portion of the skull and fitted onto a 2-cm length of 22 gauge stainless steel tubing which was then attached to the skull using jeweler's screws embedded in acrylic dental cement.

Testing began 5–7 days following surgery. Each day following surgery, the catheters were infused with 0.1 ml of a sterile saline solution containing heparin (1.25 IU/ml), penicillin G potassium (250,000 IU/ml), and streptokinase (8000 IU/ml) to maintain catheter patency and to prevent infection and the formation of clots and fibroids.

2.3. Apparatus

Self-administration tests were conducted in standard operant chambers (Med Associates, ENV-001) equipped with two levers. Depression of one lever (the 'active' lever) resulted in a 12.0-s intravenous infusion (0.1 ml) of amphetamine (0.04 mg/kg/infusion). Depression of the other lever (the 'inactive' lever) was without programmed consequence. Coincident with drug infusions was the illumination of a stimulus light located above the active lever.

Rats were maintained in their home cages in the animal facility until testing. Immediately prior to each daily test session, the catheters were flushed with 0.1 ml of the heparin–penicillin–streptokinase solution and the exposed stainless steel tubing was attached to a length of microbore tubing that was connected through a swivel apparatus to a 20-ml syringe housed in a mechanical pump (Razel, Model A with 1 rpm motor). Drug delivery and data acquisition were controlled by an interfaced microcomputer using the OPN software package (Spencer and Emmett-Oglesby, 1985).

2.4. Procedure

2.4.1. Training

Acquisition of amphetamine self-administration was conducted during daily 2-h sessions. Every session began with an experimenter-delivered infusion of drug. Thereafter, each depression of the active lever (FR1 reinforcement schedule) resulted in an automatic infusion of amphetamine (0.04 mg/kg per infusion) paired with a stimulus light located directly above the active lever. The criterion for acquisition of drug self-administration consisted of at least (Bonate et al., 1997) 30 reinforced responses during the 2-h session (1.2 mg/kg amphetamine) and (Crawford et al., 1995) a 2:1 ratio of active/inactive lever responses for a minimum of 3 days.

Following acquisition, the response requirements were increased to FR5. Daily 2-h sessions were conducted until there was less than 20% variation in active lever responses on 3 consecutive days.

2.4.2. Test

Following acquisition and stabilization of amphetamine self-administration, reinstatement tests were conducted. The test consisted of three phases and was conducted in a single day. Phase 1 consisted of a 1-h period of amphetamine self-administration (0.04 mg/kg/infusion, FR-5). During Phase 2, the amphetamine solution was replaced with saline and extinction responding was measured for 3 h. At the start of Phase 3, during which saline was again the only solution available for self-administration, separate groups of rats ($n = 4–9$/group, see figures for specific group sizes) received U69593 (0.32 mg/kg, SC) or vehicle 15 min prior to an injection of cocaine (5.0, 10.0, 20.0 or 40.0 mg/kg ip) or amphetamine (0.3, 1.0 or 3.0 mg/kg ip). An additional group received a vehicle injection 15 min prior to an injection of vehicle at the start of Phase 3. This dose of U69593 was used because we have previously reported that it failed to attenuate the ability of amphetamine to reinstate extinguished cocaine-taking behavior although cocaine-produced reinstatement was attenuated (Schenk et al., 1999).

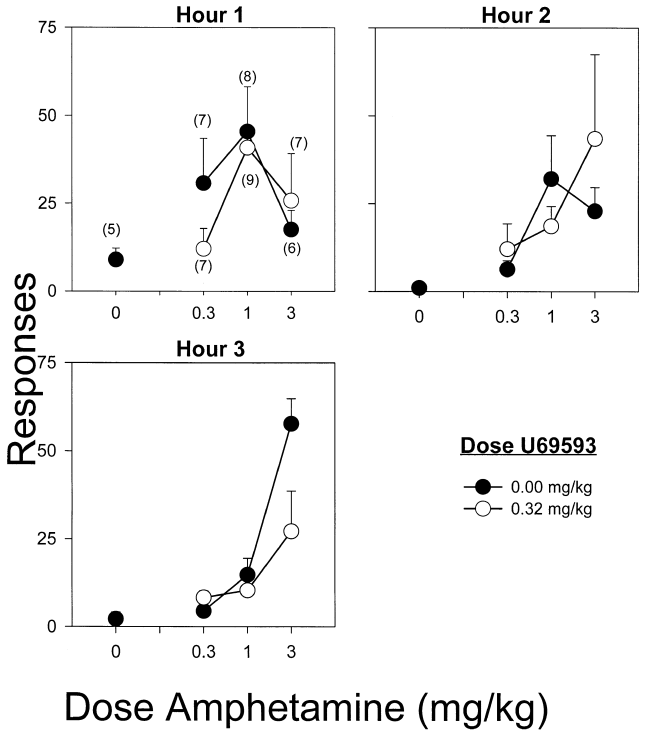

Fig. 1. Time course for the ability of various doses of amphetamine to reinstate extinguished amphetamine self-administration behavior. Responses (+S.E.M.) on the previously amphetamine-associated lever during each hour of the 3-h period that comprised Phase 3 are shown. Sample sizes are shown in parentheses above each symbol in the panel depicting the data for Hour 1.

A high percentage of rats that were treated with the 40.0 mg/kg dose of cocaine, either in combination with the vehicle or 0.32 mg/kg dose of U69593, died following treatment. Therefore, data from the surviving rats were not used in any analyses. For the remaining groups, responding was measured for the 3 h that comprised Phase 3.

2.4.3. Drugs

Cocaine-HCl (NIDA) and D-amphetamine sulfate (Sigma, St. Louis, MO) were dissolved in a sterile saline vehicle. U69593 (NIDA) was dissolved in an aqueous solution of 25% propylene glycol. Intravenous infusions were in a volume of 100 μl, subcutaneous and intraperitoneal injections were given in a 1.0 ml/kg volume. All drug doses were calculated based on salt weights.

2.4.4. Data analyses

Responses on the lever that had previously resulted in an infusion of amphetamine were recorded for each hour of Phase 3. The number of responses produced during each hour were analyzed using a two-way analysis of variance (U69593 Dose × Amphetamine or Cocaine Dose) followed by Tukey–HSD post hoc tests for pairwise comparisons where appropriate. Data are expressed as the average number of responses + S.E.M.

3. Results

Fig. 1 shows the time course for the ability of amphetamine to reinstate extinguished amphetamine-taking behavior. These data are presented for each hour of the 3-h period that comprised Phase 3 of the test. For the vehicle pretreated groups, the doses of 0.3 and 1.0 mg/kg amphetamine produced the greatest number of responses during Hour 1. There was a delay in the effect of the highest dose of amphetamine (3.0 mg/kg) which produced a high rate of responding during Hour 3 of the test. An ANOVA (Amphetamine Dose × Hour) conducted on the data from the vehicle control animals revealed a significant effect of Amphetamine Dose [$F(3,69) = 7.561$, $P < .001$] and a significant interaction between Amphetamine Dose and Hour [$F(6,69) = 4.381$, $P = .001$]. Tukey post hoc tests were performed to determine which doses of amphetamine produced a greater number of responses than the group that received a vehicle injection. During Hours 1 and 2, none of the amphetamine doses produced responses that were significantly greater than the number of responses produced following the vehicle injection. During Hour 3, however, the dose of 3.0 mg/kg produced responding that was significantly greater than responding produced following the injection of vehicle ($P = .002$).

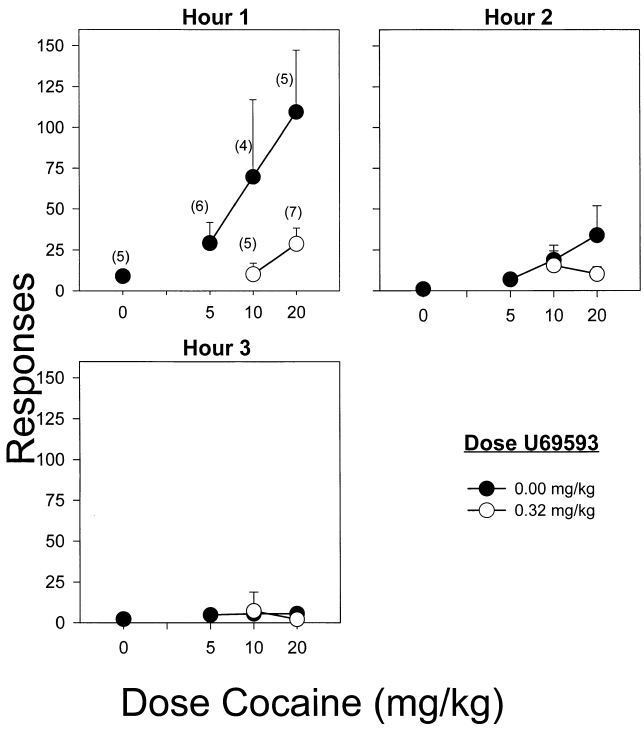

Fig. 2. Time course for the ability of various doses of cocaine to reinstate extinguished amphetamine self-administration behavior. Responses (+S.E.M.) on the previously amphetamine-associated lever during each hour of the 3-h period that comprised Phase 3 are shown. Sample sizes are shown in parentheses above each symbol in the panel depicting the data for Hour 1.

An ANOVA (Dose U69593 × Dose Amphetamine) was conducted on the data from Hour 3. The effect of Amphetamine Dose [$F(2,38) = 22.366$, $P < .001$], U69593 Dose [$F(1,38) = 5.156$, $P = .029$] and the interaction [$F(2,38) = 4.841$, $P = .013$] were significant. Tukey post hoc tests revealed that responding produced following the injection of 3.0 mg/kg amphetamine was decreased by prior administration of 0.32 mg/kg U69593 ($P = .009$).

Fig. 2 shows the time course for the ability of cocaine to reinstate extinguished amphetamine-taking behavior. Cocaine produced a dose-dependent reinstatement of responding and this effect was restricted to the first hour of the 3-h period that comprised Phase 3. An ANOVA (Cocaine Dose × Hour) conducted on the data from the vehicle control animals revealed a significant effect of Cocaine Dose [$F(3,48) = 4.323$, $P = .009$] and Hour [$F(2,48) = 9.514$, $P < 0.001$]. Tukey post hoc tests revealed that the dose of 20.0 mg/kg cocaine produced responding that was greater than responding produced following the vehicle injection ($P = 0.009$). An ANOVA performed on the data from Hour 1 (Cocaine Dose × U69593 Dose) revealed a significant effect of U69593 Dose [$F(1,17) = 7.018$, $P = 0.017$].

4. Discussion

Both cocaine and amphetamine reinstated extinguished amphetamine self-administration behavior. The effects of cocaine were restricted to the first hour following the injection and prior administration of U69593 attenuated cocaine-produced reinstatement of responding. The effects of amphetamine were only significant during the third hour of the test and only the highest dose (3.0 mg/kg) produced a significant reinstatement of extinguished drug-taking behavior. U69593 attenuated responding produced by this dose of amphetamine during this time period.

In previous reports, specific effects of U69593 on drug seeking were demonstrated. In rats trained to self-administer cocaine, U69593 attenuated the ability of cocaine to reinstate extinguished drug taking but failed to attenuate the effects of amphetamine (Schenk et al., 1999) or other drugs (Schenk et al., 2000). In the present study, the ability of cocaine and amphetamine to reinstate extinguished responding of animals that had received training in amphetamine self-administration was examined. Both drugs reinstated extinguished responding at doses that were comparable to those that reinstated extinguished cocaine-taking behavior. One difference between the results of the present study and our previous studies is that amphetamine produced a relatively low rate of responding when compared to responses produced following extinction of cocaine self-administration (Schenk et al., 2000). In spite of this low baseline level of responding, reinstatement produced by a high dose of amphetamine was attenuated by prior administration of U69593.

The differential effects of U69593 on the ability of amphetamine to reinstate extinguished cocaine versus amphetamine self-administration behavior suggest that the effect of U69593 is, at least partly, determined by the drug that has been self-administered. Thus, amphetamine-produced reinstatement of extinguished cocaine self-administration behavior was not attenuated by prior administration of U69593 (Schenk et al., 1999) but the ability of amphetamine to reinstate extinguished amphetamine self-administration was attenuated. In contrast, cocaine-produced reinstatement of extinguished drug-taking behavior was disrupted by U69593 for rats that had a history of either cocaine (Schenk et al., 1999, 2000) or amphetamine (present results) self-administration. The role of kappa-opioid receptor mechanisms in amphetamine- but not cocaine-produced reinstatement is, therefore, dependent on self-administration history.

During self-administration training, rats receive substantial exposure to the self-administered drug and this exposure undoubtedly led to behavioral as well as neurochemical sensitization. It has been suggested that drug-seeking is associated with the development of behavioral sensitization (De Vries et al., 1998) and some studies have shown that there is cross-sensitization between the behavioral effects of cocaine and amphetamine (Bonate et al., 1997; Horger et al., 1992; Kalivas and Weber, 1988; Schenk et al., 1991; Taylor and Horger, 1999), suggesting common neuroadaptations as a result of preexposure.

Other studies suggest that repeated exposure to cocaine and amphetamine might produce behavioral sensitization through different mechanisms. For example, coadministration of the D1 dopamine antagonist, SCH 23390, during pretreatment prevented the development of behavioral sensitization to amphetamine (Pierre and Vezina, 1998; Vezina, 1996) but failed to attenuate the development of behavioral sensitization to cocaine (Mattingly et al., 1994, 1996). Lesions of the prefrontal cortex attenuated the development of behavioral sensitization to cocaine (Pierce et al., 1998; Tzschentke and Schmidt, 2000) but not to amphetamine (Tzschentke and Schmidt, 2000). Further, whereas repeated injections of amphetamine into the ventral tegmental area produced behavioral sensitization to a systemic injection of either cocaine or amphetamine (Kalivas and Weber, 1988), repeated injections of cocaine into this site failed to produce behavioral sensitization to a systemic injection of cocaine (Steketee, 1998).

The present data provide additional differences between the effects of repeated exposure to cocaine and amphetamine and suggest that following experience with self-administered amphetamine but not cocaine, a kappa-opioid receptor mechanism mediates amphetamine-produced drug-seeking. Following experience with cocaine self-administration U69593 failed to attenuate amphetamine-produced drug seeking (Schenk et al., 1999) suggesting that it is mediated by other mechanisms.

Recently, it was demonstrated that the motor-activating effect of amphetamine was attenuated by pretreatment with U69593 (Gray et al., 1999; Vanderschuren et al., 2000).

Systemically administered U69593 also prevented calcium dependent amphetamine-stimulated dopamine release in the nucleus accumbens (Gray et al., 1999). Kappa-opioid receptors in the nucleus accumbens are localized presynaptically and are associated with synaptic vesicles (Meshul and McGinty, 2000). It was suggested, therefore, that the kappa-opioid receptor agonist produced inhibition of basal dopamine and drug-stimulated increases in synaptic dopamine may reflect an inhibition of vesicular release via these receptors (Meshul and McGinty, 2000). This may explain the ability of U69593 to block both amphetamine-produced (Gray et al., 1999; Vanderschuren et al., 2000) and cocaine-produced (Heidbreder et al., 1993; Vanderschuren et al., 2000) motor activation, cocaine-produced conditioned place preference (Crawford et al., 1995), discriminative stimulus properties of cocaine (Riberdy et al., 1995; Spealman and Bergman, 1992, 1994) and cocaine self-administration (Glick et al., 1995; Mello and Negus, 1998; Negus et al., 1997; Schenk et al., 1999) which have all been attributed to effects on mesocorticolimbic dopamine substrates. Repeated exposure to amphetamine through self-administration might enhance these effects thereby rendering reinstatement more sensitive to kappa-opioid receptor agonist effects.

Acknowledgments

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