Abstract  Rationale: Previous research has shown that kappa-opioid receptor agonists decrease intravenous cocaine self-administration. These agents also block the development of sensitization that occurs following repeated exposure to cocaine, which is thought to be important in the maintenance and reinstatement of compulsive drug-seeking behavior. Objectives: This study was designed to determine the effects of the kappa-opioid receptor agonist, U69593, on the maintenance of cocaine self-administration and on the ability of a priming injection of cocaine to reinitiate drug-seeking. Methods: During daily test sessions, the dose-effect curve (0.015–1.0 mg/kg per infusion) was obtained by either repeatedly reducing the cocaine dose from a starting dose of 1.0 mg/kg per infusion or by repeatedly doubling the cocaine dose from a starting dose of 0.015 mg/kg per infusion. The effect of U69593 (0.0 or 0.32 mg/kg) on responding reinforced by different cocaine doses was determined. The effect of U69593 on the reinstatement of extinguished cocaine-taking behavior was measured in other groups. Results: U69593 decreased responding maintained by low doses of cocaine, regardless of whether cocaine doses were presented in an ascending or descending order. Responding maintained by high doses was unaffected. In animals which received pretreatment with U69593, the priming effects of cocaine were significantly attenuated. The effects of U69593 were specific, since amphetamine-induced cocaine-seeking was not altered by prior administration of U69593. Conclusions: These findings demonstrate that U69593 attenuates cocaine self-administration and the reinstatement of drug-taking behavior which occurs in response to experimenter-administered cocaine. It is suggested that U69593 may decrease low dose cocaine self-administration by decreasing the priming effects of cocaine.

Key words  Cocaine · Self-administration · U69593 · Kappa-opioid · Drug abuse · Relapse

Introduction

Preclinical studies have shown that sensitization can develop to the behavioral effects of cocaine. For example, the prior repeated exposure to cocaine increases the ability of cocaine to produce hyperlocomotion (Post and Rose 1976; Kalivas and Stewart 1991), decreases the latency to acquisition of cocaine self-administration (Horger et al. 1990) and facilitates the ability of environmental stimuli previously associated with the administration of cocaine to develop conditioned reinforcing properties (Lett 1989; Shippenberg and Heidbreder 1995; Shippenberg et al. 1996). These data are of particular interest in view of the postulated role of sensitization in the addiction process (Weeks 1975; Robinson and Berridge 1993; Stewart and Badiani 1993; Schenk and Partridge 1997).

Cocaine blocks the reuptake of norepinephrine, serotonin and dopamine (Reith et al. 1983). However, increases in synaptic dopamine following acute administration of this drug have generally been the mechanism attributed to many of the behavioral effects (de Wit and Wise 1976; Kelley and Iverson 1976; Ritz et al. 1987, 1988; Wise and Bozarth 1987; Di Chiara 1995). A number of neurochemical systems modulate the response of central dopaminergic systems. Among these, kappa-opioid agonists produce effects that are opposite to effects produced by dopaminergic agonists. Thus, kappa-opioid agonists decrease synaptic dopamine levels (Di Chiara and Imperato 1988b; Werling et al. 1988;Spanagel et al. 1990; Manzarares et al. 1991; Heidbreder et al. 1996), thereby opposing the effects of dopamine agonists.
An involvement of kappa-opioid receptor systems in modulating the acute effects of cocaine and the development of sensitization following repeated administration of cocaine has recently been suggested. Pretreatment with the selective kappa-opioid receptor agonist (trans-\(\text{dL}\))-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-benzeneacetamide) methane sulfonate hydrate (U50,488H) blocked the ability of cocaine to produce a conditioned place preference in rats (Crawford et al. 1995) and repeated exposure to the kappa opioid agonist, (5a, 7a, 8b)-(−)-N-methyl-N-(7-(1-pyrrolidinyl)1-oxaspiro (4,5) dec-8-yl) benzeneacetamide (U69593), decreased the hyperactivity produced by acute exposure to cocaine (Heidbreder et al. 1998). Furthermore, the enhancement of cocaine-induced place preference conditioning (Shippenberg et al. 1996) and the sensitized hyperlocomotor response (Heidbreder et al. 1995) produced by prior administration of this psychostimulant was prevented by co-administration of the kappa-opioid receptor agonists, U69593 and U50,488H.

Recent data have shown that the kappa-opioid receptor agonist, U50,488H, alters cocaine self-administration (Glick et al. 1995; Kuzmin et al. 1997; Negus et al. 1997; Mello and Negus 1998). In one study (Glick et al. 1995), acute administration of U50,488 to rats decreased responding maintained by a high dose of cocaine, and it was suggested that these findings reflected a rightward shift in the dose-effect curve and a decrease in the positive reinforcing effects of cocaine associated with self-administration. In rhesus monkeys, similar findings have been reported following acute as well as chronic treatment with kappa-opioid receptor agonists (Negus et al. 1997; Mello and Negus 1998). However, since the dose-effect curve for cocaine self-administration is in the shape of an inverted-U, with both high and low doses producing low rates of responding, a decrease in cocaine-maintained responding may also indicate a leftward shift in the dose-effect curve (Koob et al. 1987; Caine and Koob 1994; Mello and Negus 1996). As a result, changes in responding maintained by a single dose of cocaine cannot be unambiguously interpreted as indicative of an increase or decrease in the reinforcing properties of the drug.

In the present study, the effect of the selective kappa-opioid receptor agonist, U69593 (Lahti et al. 1985) upon self-administration of a large range of cocaine doses was determined and compared to effects obtained following administration of the dopaminergic antagonist, flupenthixol, and the dopaminergic agonist, GBR 12909. Additionally, the ability of cocaine to serve as a cue for the reinitiation of extinguished cocaine-taking behavior, which has been proposed to reflect drug-seeking behavior (De Wit and Stewart 1981; Worley et al. 1994; Weisenborn et al. 1996), was evaluated in control subjects and in those which were pretreated with U69593 prior to cocaine.

**Materials and methods**

**Subjects**

Male Sprague-Dawley rats (Harlan, Tex., USA) weighing 325–350 g were used. They were housed individually in hanging polycarbonate cages. The humidity and temperature were controlled and food and water were freely available except during testing. The colony was maintained in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care and principles of laboratory animal care (NIH publication No. 85-23, revised 1985) were followed.

**Surgery**

Rats were implanted with a Silastic catheter in the external jugular vein. Briefly, the rats were deeply anesthetized with ketamine (60.0 mg/kg) and pentobarbital (20.0 mg/kg). The external jugular vein was isolated, the catheter was inserted and the distal end (22 ga stainless steel tubing) was passed subcutaneously to an exposed portion of the skull where it was fixed to embedded jeweler’s screws with dental acrylic. Each day, 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 prevent infection and the formation of clots and fibrin. The rats were allowed 5 days after surgery for recovery.

**Apparatus**

Self-administration testing was carried out in standard operant chambers (Med Associates, ENV-001) equipped with two levers. Depression of one lever (the active lever) resulted in an intravenous infusion of cocaine HCl, dissolved in sterile physiological saline and heparin (3 IU/ml). Depression of the other lever (the inactive lever) was without programmed consequence.

Rats were maintained in the animal colony except during testing. Immediately prior to each daily test, the catheter lines were infused with 0.1 ml of the heparin-penicillin-streptokinase solution and the portion of the catheter comprised of stainless steel tubing was connected to a length of microbore tubing that was connected to the syringe. At the end of each test, the lines were again infused with 0.1 ml of the heparin-penicillin-streptokinase solution, the stainless steel tubing was plugged and the animal was returned to its home cage. Drug delivery and data acquisition were controlled by the OPN software package (Spencer and Emmett-Oglesby 1985). Cocaine deliveries were made via mechanical pumps (Razel, Model A with 1 rpm motor equipped with 20.0 ml syringes).

**Procedure**

**Training**

Acquisition of cocaine self-administration was monitored during daily 2-h sessions. Each session began with an experimenter-delivered infusion of cocaine. Thereafter, depression of the active lever produced automated cocaine infusions (0.5 mg/kg per infusion) according to an FR1 schedule of reinforcement. The criterion for acquisition of cocaine self-administration consisted of at least 30 reinforced responses (15.0 mg/kg) during the 2-h session and a ratio of active/inactive lever responses of 2:1. Self-administration was considered to be acquired when these criteria were met for 3 consecutive days.

Following acquisition, the response requirements were increased to FR5. Daily 2-h sessions were conducted until there was less than 20% variation in responding on 3 consecutive days. During training and subsequent tests, the cocaine infusion was always paired with the illumination of a stimulus light located directly above the active lever. All training and test sessions began with an experimenter-delivered infusion of cocaine.