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Tolerance to cocaine in brain stimulation reward following continuous cocaine infusions

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ABSTRACT

This study examined tolerance to cocaine's threshold-lowering effect in brain stimulation reward (BSR) following continuous cocaine infusions and secondly, used the nitric oxide synthase inhibitor Nω-nitro-L-arginine methyl ester (L-NAME) to determine NO's involvement in the development of cocaine tolerance. Animals were continuously infused with saline or cocaine (30 mg/kg per day) via osmotic minipump for 14 days and injected daily with saline or L-NAME (30 mg/kg, i.p.) following BSR testing. Saline-treated animals continuously infused with saline showed stable BSR thresholds across the 14-day infusion period. Saline-treated animals continuously infused with cocaine showed markedly lowered BSR thresholds on Day 1 followed by a progressive increase in BSR thresholds across the infusion period – indicating the development of tolerance. L-NAME-treated animals continuously infused with cocaine showed stimulation thresholds that were not significantly different from saline-treated animals continuously infused with cocaine.

A cocaine challenge injection (10 mg/kg, i.p.) administered 3 and again at 10 days following minipump removal revealed that saline-treated animals continuously infused with saline showed lowered BSR thresholds. Saline-treated animals continuously infused with cocaine displayed lowered BSR thresholds that were not significantly different from saline-infused animals. L-NAME treated animals continuously infused with cocaine showed higher BSR thresholds to a challenge 3 days following pump removal. However, stimulation thresholds for this group failed to reach statistical significance on both days (i.e., Days 3 and 10) following pump removal.

Results showed that animals continuously infused with cocaine develop robust tolerance to cocaine's threshold-lowering effect during the 14-day infusion period. Tolerance to cocaine's threshold-lowering effect was short-lived and dissipated soon after minipump removal. L-NAME treatment failed to significantly alter the development of tolerance to cocaine's threshold-lowering suggesting that NO does not have a primary role in the development of cocaine tolerance.

1. Introduction

Cocaine addiction is associated with a pattern of drug taking that often occurs in "binges." Binges are periods of drug use that typically last from several hours to days. A binge is usually terminated when an addict depletes his/her drug supply. An important feature of a drug addict's bingeing cycle can be closely mimicked in the behaving animal by implanting animals with a minipump that continuously delivers drug. This method of continual drug delivery mimics the high plasma concentrations of drug that addicts maintain during a bingeing cycle and more closely resembles the human binge pattern of drug administration (King et al., 1992, 1993) than animal studies that employ daily intermittent drug injections. Thus, the continuous infusion paradigm may represent a more suitable animal model for studying the neuroadaptive changes that occur with repeated drug use in the cocaine addict.

Previous studies employing the use of the continuous infusion paradigm have revealed that animals receiving continuous cocaine via osmotic minipump delivery display low levels of locomotor activity across consecutive days of drug exposure (Reith et al., 1987) and display less cocaine-induced stereotypy following a cocaine-challenge injection administered 1 (Inada et al., 1992) and 7 days after terminating continuous cocaine administration (King et al., 1992; Reith et al., 1987). This diminished responsiveness to cocaine's locomotor-activating and stereotypic effects is known as behavioral tolerance. Tolerance is a neuroadaptive response that occurs with prolonged drug exposure and it results in a diminished responsiveness to the drug (Koob and Bloom, 1988). Cocaine-induced tolerance is produced by the frequent administration of high doses of cocaine (for a review see Hammer et al., 1997). Unlike stimulant-induced sensitization (i.e., amphetamine, cocaine), cocaine-induced tolerance appears to be context independent

Abbreviations: BSR, Brain stimulation reward; L-NAME, Nω-nitro-L-arginine methyl ester.

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with Pavlovian mechanisms having little to no role in its expression (reviewed in Hammer et al., 1997).

Previous clinical studies have reported that acute tolerance develops to cocaine's subjective and cardiovascular effects (Ambre et al., 1988; Fischman and Schuster, 1982; Fischman et al., 1985). Furthermore, Sherer (1988) reported that volunteer drug addicts administered continuous cocaine infusions reported tolerance to the "rush" but not to the "high" produced by intravenous cocaine. Consistent with these findings are studies showing that animals allowed to intravenously self-administer cocaine develop tolerance to cocaine's reinforcing effects (Emmett-Oglesby and Lane, 1992; Li et al., 1994; reviewed in Schenk and Partridge, 1997).

Addictive drugs (e.g., cocaine, heroin) produce their reinforcing effects via dopamine modulation in the mesolimbic system (Bozarth, 1987; Wise and Bozarth, 1987). The mesolimbic reward substrate can be either electrically or chemically activated. Electrical activation of this reward substrate is produced by delivering brief pulses of electrical stimulation through a stimulating electrode placed into either the medial forebrain bundle at the level of lateral hypothalamus or into the ventral tegmental area. Chemical activation can be produced by the pharmacological actions of stimulant drugs that stimulate dopamine release (e.g., amphetamine) or block dopamine reuptake (e.g., amphetamine, cocaine) in the nucleus accumbens terminal region. It has been well documented that manipulations that enhance dopamine activity through increased release or inhibited re-uptake facilitate brain stimulation reward [BSR] (i.e., lower BSR thresholds) while manipulations that block or impair dopamine activity decrease BSR lever-pressing rates and elevate BSR thresholds (Black and Cooper, 1970; Cooper et al., 1974; Crow, 1972; Himwich and Alpers, 1970; Phillips et al., 1975). The interaction between electrical and chemical activation can be used to detect the mood-elevating or positive subjective effects produced by addictive drugs (Kornetsky et al., 1979; Reid, 1987). The increased lever-press rates and lowering of BSR thresholds following stimulant administration (for a review see Wise, 1996) are indicative of an enhancement of reward and correlate with the euphoric effects produced by these drugs. Besides measuring the euphoric effects produced by addictive drugs, the BSR method has also been used to detect the dysphoric effects commonly associated with cocaine withdrawal (Kenny et al., 2003; Markou and Koob, 1991).

The molecular mechanisms underlying the development of tolerance to cocaine's effects are not well understood. However, previous studies have shown that nitric oxide (NO) mediates changes in neural sensitivity (i.e., tolerance, sensitization) that often accompany repeated drug administration (Babey et al., 1994; Byrnes et al., 2000; Herman et al., 1995; Itzhak, 1996; Manzanedo et al., 2009; Pudiak and Bozarth, 1993; Santamarta et al., 2005). Thus, changes in neural sensitivity that alter an individual's responsiveness to abused drugs likely contribute to the development and maintenance of an addiction (Robinson and Berridge, 1993; Schenk and Partridge, 1997). This study examined tolerance to cocaine's threshold-lowering effect in BSR following continuous cocaine infusions and secondly, used the nitric oxide synthase (NOS) inhibitor Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME) to assess NO's involvement in the development of tolerance to cocaine's threshold-lowering effect in BSR. NOS is the synthesis enzyme that breaks down arginine and converts it to NO and citrulline.

2. Materials and Methods

2.1. Subjects

Male, Long-Evans rats (Harlan Sprague–Dawley, Indianapolis, IN), weighing 275–350 g at the beginning of the experiment were individually housed with food and water freely available in their home cages. The animal colony was maintained at a constant temperature (22 ± 2 °C) and humidity (50 ± 5 % relative humidity) with a 14-h light/10-h dark illumination cycle. All behavioral testing occurred during the light phase of the light/dark cycle at the same time every day (±30 min). All experiments described in this paper were conducted in accordance with the Declaration of Helsinki and with the Guide for Care and Use of Laboratory Animals as adopted and promulgated by the United States National Institutes of Health.

2.2. Apparatus

Brain stimulation reward thresholds were measured in operant chambers (26 × 47 × 38 cm high) that contained a lever mounted 8 cm above the floor. A stimulation lead connected to an electrical commutator allowed unrestricted movement of the animal during behavioral testing. Each operant chamber was housed in a ventilated, sound-attenuating chamber provided with dim illumination.

2.3. Stimulation parameters

Each lever press produced a 300 msec train of monophasic cathodal stimulation pulses (300 μsec pulse width). The electrode was shunted to ground between stimulation pulses to prevent tissue damage from capacitance buildup (Mundl, 1980). All stimulation parameters except frequency were held constant throughout the experiment.

2.4. Drugs

Cocaine hydrochloride (National Institute on Drug Abuse, Rockville, MD) was administered via osmotic minipump and intraperitoneally (i.p.). Cocaine hydrochloride used to fill minipumps was dissolved in 0.9% sterile physiological saline and it contained 0.3% sodium metabisulfate that prevented drug degradation. Cocaine hydrochloride used for i.p. injections was dissolved in 0.9% physiological saline, sterilized by filtration (0.22 μm filter), and stored at room temperature. Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME; Sigma Chemical, St. Louis, MO) was dissolved in sterile 0.9% physiological saline and was freshly prepared each day. All drug dosages refer to the drug salts. The dose of L-NAME (30 mg/kg) examined was based on previous studies showing that this dose of L-NAME attenuates stimulant-induced sensitization (Celik et al., 1999; Pudiak and Bozarth, 1993) and haloperidol-induced supersensitivity (Pudiak and Bozarth, 1997).

2.5. Minipump Preparation

Osmotic minipumps (model 2ML2; ALZA Corp., Palo Alto, CA) were filled with either 2.2 ml of 81 mg/ml cocaine hydrochloride or 0.9% physiological saline. Each pump's infusion rate was 5.0 μl/hr across 14 days (0.120 ml/day). The cocaine concentration used for cocaine minipumps was based on the mean body weight of the group (mean = 324 g) and was calculated to yield an approximate cocaine dose of 30 mg/kg per day. To ensure the minipumps were operating at their nominal flow rate during the time of surgical implantation, each pump was placed inside a saline-filled beaker immersed in a water bath warmed to 37 °C for a minimum of 4 hours before implantation. Each osmotic minipump delivered solution continuously for 14 days. Following the surgical removal of osmotic minipumps on Day 14, a syringe needle was inserted into each minipump and the residual fluid was withdrawn and measured. This allowed for a quick check, in addition to the behavioral data, that the pump was not operationally defective.

2.6. Surgical preparation

2.6.1. Electrode surgery

Each rat was surgically implanted with a chronically indwelling, stainless steel, monopolar-stimulating electrode (0.25 mm diameter) in the medial forebrain bundle at the level of the lateral hypothalamus. The monopolar electrode was insulated with Formvar except at the cross section of the tip. Two to three stainless steel screws mounted in