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Research report

The effects of amphetamine, butorphanol, and their combination on cocaine self-administration

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HIGHLIGHTS

- The effects of an opioid-stimulant combination were examined on cocaine intake.
- Rats were treated with butorphanol, amphetamine, the drug combination, or vehicle.
- Butorphanol and the drug combination reduced cocaine intake on an FR schedule.
- The drug combination reduced cocaine intake on a PR schedule.
- These data support the use of an opioid-stimulant therapy under some conditions.

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ABSTRACT

There have been recent calls to examine the efficacy of drug-combination therapies in the treatment of substance use disorders. The purpose of the present study was to examine the ability of a novel stimulant-opioid combination to reduce cocaine self-administration, and to compare these effects to those of each drug administered alone. To this end, male Long-Evans rats were implanted with intravenous catheters and trained to self-administer cocaine under positive reinforcement contingencies. Once self-administration was acquired, rats were divided into four different groups and treated chronically for 20 days with (1) saline, (2) the psychomotor stimulant and monoamine releaser amphetamine, (3) the mu/kappa opioid agonist butorphanol, or (4) a combination of amphetamine and butorphanol. During chronic treatment, cocaine self-administration was examined on both fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement. On the FR schedule, butorphanol significantly decreased cocaine self-administration, but this effect was not enhanced by amphetamine. On the PR schedule, amphetamine and butorphanol non-significantly decreased cocaine self-administration when administered alone but significantly decreased cocaine self-administration when administered in combination. These data suggest that under some conditions (e.g., when the response requirement of cocaine is high), a dual stimulant-opioid pharmacotherapy may be more effective than a single-drug monotherapy.

1. Introduction

In 2012, 639,000 Americans tried cocaine for the first time and 1.1 million Americans met diagnostic criteria for a cocaine use disorder [30]. Despite the continuing public health problems associated with cocaine abuse, there are currently no FDA-approved medications for the treatment of cocaine use disorders. Previous research has indicated that endogenous mu and kappa opioids play a critical role in cocaine reward and reinforcement [6,33], and the mixed mu/kappa agonists butorphanol and nalbuphine reduce cocaine self-administration in laboratory animals [35,15,13,12,21]. Despite these positive findings, controlled studies with opioids in cocaine-abusing populations have failed to demonstrate consistent efficacy on measures of cocaine self-administration (e.g., [32]). In recent years, stimulant-based therapies employing indirect dopamine agonists have shown positive responses in treatment-seeking populations [5,19]. Although the use of stimulant drugs represents a significant advance in medication development, approximately half of the participants in those studies either dropped out or did not show a consistent treatment response. Clearly, the need for effective medications for the treatment of cocaine use disorders still exists.

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The majority of previous research examining medications for the treatment of substance use disorders has focused on single-drug monotherapies. Several investigators have argued that substance use disorders may benefit from a combination of medications (e.g., [29]), and the National Institute on Drug Abuse (NIDA) called for additional preclinical and clinical research on novel drug combinations for the treatment of substance use disorders [20]. A few studies have examined the effects of drug combinations on measures of drug self-administration, and these studies have reported varying degrees of success (e.g., [14,26,34]). One drug combination that was effective at reducing drug self-administration in both animals and humans was an opioid/stimulant combination consisting of a mu opioid agonist (buprenorphine or methadone) and the monoamine releaser d-amphetamine [7,17,8]. This combination was well tolerated, produced minimal adverse effects, and significantly reduced drug self-administration under a variety of conditions. Such findings are significant because one goal of any combination therapy is to maximize the therapeutic efficacy of treatment while minimizing the potential for side effects that would otherwise limit its use.

The purpose of the present study was to examine the ability of a novel stimulant-opioid combination to reduce cocaine self-administration in an animal model of substance use, and to compare these effects to those of each drug administered alone. To this end, male rats were implanted with intravenous catheters and trained to self-administer cocaine under positive reinforcement contingencies. Once self-administration was acquired, rats were divided into different groups and treated chronically for 20 days with (1) the psychomotor stimulant and monoamine releaser d-amphetamine (amphetamine), (2) the mu/kappa opioid agonist butorphanol, (3) a combination of amphetamine and butorphanol, or (4) vehicle controls. Beginning 10 days after the initiation of chronic treatment, cocaine dose–effect curves were determined under both fixed ratio (FR) and progressive ratio (PR) schedules of reinforcement. Each of these schedules measure different aspects of drug self-administration, with FR schedules more sensitive to satiety factors and PR schedules more sensitive to motivational factors controlling drug intake [1,28,23]. Butorphanol and amphetamine were selected because both medications are commercially available for use in clinical populations, and because both drugs decrease cocaine self-administration when administered alone ([24,15,13,12,21], [22,2,25,4]; but see [32]). Consequently, we predicted that each drug would decrease cocaine self-administration alone, but that greater decreases in cocaine self-administration would be observed when the drugs were administered in combination.

2. Methods

2.1. Subjects

Young, male, adult Long-Evans rats (250–280 g upon arrival) were obtained from Charles River Laboratories (Raleigh, NC, USA). All rats were housed individually in polycarbonate cages in a large colony room maintained on a 12-h light-dark schedule (lights on: 07:00). Excluding the brief period of lever-press training (see below), food and water were freely available in the home cage. All animals were maintained in accordance with the *Guide for the Care and Use of Laboratory Animals* [9], and the Davidson College Animal Care and Use Committee approved all procedures.

2.2. Apparatus

All experimental sessions were conducted in commercially available operant conditioning chambers from Med Associates, Inc. (St. Albans, VT, USA). Each chamber was equipped with two response levers located on the forward wall, one white stimulus light located above each lever, one food receptacle located between the two levers, and one houselight located at the rear of the chamber. Food pellets were delivered via a pellet dispenser located behind the forward wall. Infusion pumps mounted outside the chamber delivered drug infusions via Tygon tubing protected by a stainless steel spring and attached to a counter-balanced swivel suspended above the chamber. All experimental events were programmed and data were collected through software and interfacing supplied by Med Associates, Inc.

2.3. Lever-press training

Approximately one week after arrival, all rats were food restricted to no less than 90% of their free-feeding body weight and trained to lever press using food reinforcement. In these sessions, each lever press produced a 45 mg grain pellet on a fixed ratio (FR1) schedule of reinforcement. Each training session lasted 2 h or until 40 reinforcers were delivered. If any rat failed to acquire the lever press response by the third day of training, the response was shaped by the experimenter using manually delivered food pellets. Training continued in this manner until rats acquired the maximum number of 40 reinforcers in any three training sessions. All rats met this criterion within 7 days and returned to unrestricted feed once they met the acquisition criterion.

2.4. Surgery

Following the completion of lever-press training, rats were anesthetized with a combination of ketamine (100 mg/kg, ip) and xylazine (8.0 mg/kg, ip) and surgically implanted with intravenous catheters (CamCaths, Cambridge, UK). Each catheter was inserted into the right jugular vein, was routed subcutaneously over the shoulder, and exited the body via a port mounted between the scapulae. Ketoprofen (5.0 mg/kg, sc) was given immediately after surgery as an analgesic, and a solution of heparinized saline and ticarcillin (20 mg/kg, iv) was infused through the catheter daily in order to maintain patency and prevent infection. After 7 days, ticarcillin was discontinued and only heparinized saline was used to maintain catheter patency. All rats were given three days to recover before beginning self-administration testing.

2.5. Self-administration training

All self-administration training and testing sessions began with illumination of the house light, illumination of the white stimulus light above the response lever, and a noncontingent priming infusion of the specific dose of cocaine available during that session. During training, each lever press was reinforced on an FR1 schedule of reinforcement. On this schedule, each response activated an infusion pump that delivered 0.5 mg/kg cocaine (Research Triangle Institute, Research Triangle Park, NC, USA) over a 2.5–4.0 s duration (based on body weight). Simultaneous with each infusion, the stimulus light above the lever turned off to signal a 20 s time out in which cocaine was not available. After 20 s, the light turned on and cocaine was available on the FR1 schedule of reinforcement. No limit was placed on the maximum number of infusions that could be earned, other than those set by the session length and postinfusion timeout. All sessions terminated automatically after 120 min. Training continued in this manner for four consecutive days, at which time daily training sessions were discontinued.