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RTI 113, a 3-phenyltropane analog, produces long-lasting cocaine-like discriminative stimulus effects in rats and squirrel monkeys

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Abstract

The 3-phenyltropane analog, 3β-(4-chlorophenyl)tropane-2β-carboxylic acid phenyl ester hydrochloride (RTI 113), has been shown to decrease cocaine self-administration in rats, squirrel monkeys and rhesus monkeys. Consequently, it has been proposed as a potential agonist pharmacotherapy for cocaine dependence. However, the time course of the discriminative stimulus effects of RTI 113 has not been determined. The present study was designed to compare the time course of the discriminative stimulus effects of RTI 113 with that of cocaine in rats and squirrel monkeys. Tests were conducted using a drug discrimination procedure in which rats and squirrel monkeys were trained to discriminate 10 and 0.3 mg/kg cocaine from saline, respectively. RTI 113 substituted for cocaine in both species. The time course of the discriminative stimulus effects of RTI 113 was approximately five times longer compared to that of cocaine. RTI 113 is a 3-phenyltropane analog that has long acting cocaine-like discriminative stimulus effects in both rats and squirrel monkeys. These results, combined with those indicating that RTI 113 decreases cocaine self-administration, suggest that RTI 113, or analogs of RTI 113, may be useful tools for developing potential agonist therapies for cocaine dependence.

Keywords: Cocaine; RTI 113; Discriminative stimulus effect; Drug discrimination; (Rat); (Squirrel monkey)

1. Introduction

Cocaine abuse is a major health problem in the United States, however, no effective pharmacotherapies for the treatment of cocaine addiction are currently available (Carroll et al., 1999; Howell and Wilcox, 2001). As more knowledge is gained about the mechanisms of action of cocaine, the likelihood of developing effective pharmacotherapies will increase. In vitro studies indicate that cocaine binds to the dopamine, serotonin and norepinephrine transporters and, in turn, blocks neurotransmitter reuptake (Koe, 1976; Reith et al., 1983). Despite this promiscuity at the monoamine transporters, there is considerable evidence suggesting that the psychomotor stimulant (Cook et al., 1998; Fleckenstein et al., 1996; Heikkila and Manzino, 1984; Spealman et al., 1989), discriminative stimulus (Barrett and Appel, 1989; Broadbent et al., 1991; Callahan et al., 1991; Spealman et al., 1991) and reinforcing effects (Caine and Koob, 1994; Mansbach et al., 1994; Negus et al., 1996; Ritz et al., 1987; Winger, 1994) of cocaine are mediated primarily by the dopamine system.

There are several approaches that can be taken to develop potential pharmacotherapies for cocaine dependence. One approach is to develop drugs that, when taken in combination with cocaine, will antagonize the subjective and reinforcing properties of cocaine, whereby the psychoactive effects of cocaine are significantly reduced or eliminated. One drawback to this approach, however, is that the cocaine abuser could increase the amount of cocaine administered to surmount the antagonism induced by the pharmacotherapy. Another potentially more promising approach is to develop agonist pharmacotherapies. For example, methadone has been used successfully as an agonist treatment for heroin dependence (Dole and Nyswander, 1965), in part because of its long duration of action and slow onset (Jasinski and Preston, 1986; Preston et al., 1986). As such, an effective pharmacotherapy for cocaine dependence could posses some pharmacological properties similar to cocaine, but with a

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slower onset and a longer duration of action with less abuse potential than cocaine.

One potential agonist candidate that has been suggested is 3β-(4-chlorophenyl)tropane-2β-carboxylic acid phenyl ester hydrochloride (RTI 113), a 3-phenyltropane analog. RTI 113 has several properties potentially conducive for a pharmacotherapeutic agent for treating cocaine dependence disorders. For example, RTI 113, which produces cocaine-like discriminative stimulus effects (Cook et al., 2001), was shown to dose-dependently reduce the number of cocaine infusions self-administered by rats at doses that occupied a significant percentage of the dopamine transporter sites (Dworkin et al., 1998). Similarly, in squirrel monkeys and rhesus monkeys, systemically administered doses of RTI 113 decreased cocaine self-administration (Howell et al., 2000; Wilcox et al., 2002). In Howell et al. (2000), RTI 113 exhibited a duration of action longer than that of cocaine as determined in a fixed-interval stimulus termination procedure. The data from these two studies imply that RTI 113 may have utility as a pharmacotherapy treatment. Although there is an indication that RTI 113 remains active for long periods, no study to date has determined the time course of RTI 113's subjective effects. The subjective effects of a compound can be determinants of its abuse potential, and providing some of the subjective effects of cocaine to an abuser may serve as a therapy to attenuate its abuse. The discriminative stimulus properties of a compound are thought to be similar, if not identical, to its subjective effects in humans (Stolerman, 1992). As such, the present study was designed to determine the duration of the discriminative stimulus effects of RTI 113 compared to those of cocaine in both rats and squirrel monkeys as assessed in a food-reinforced drug discrimination procedure.

2. Materials and methods

2.1. Subjects

Six, individually housed adult male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) were used. Free-feeding body weights were determined at approximately 3 months of age and then the rats were gradually reduced to 85% of this weight and maintained there by supplemental post-session feedings for the remainder of the study. Rats were provided with continuous access to water, except during the experimental sessions. Seven, individually housed adult male squirrel monkeys (*Saimiri sciureus*) were used. Monkeys' weights (650–990 g) were maintained throughout the experiment by supplemental post-session feedings. Multivitamins were provided daily and water was available at all times, except during the experimental sessions. Both rats and monkeys were housed in an accredited (Association for the Assessment and Accreditation of Laboratory Animal Care International) animal facility maintained on a 12-h light–dark cycle and all testing occurred during the light component. Animals used in this study were cared for in accordance with the guidelines of the Institutional Animal Care and Use Committee of the Virginia Commonwealth University, and the "Guide for the Care and Use of Laboratory Animals" (National Research Council, National Academy Press, 1996).

2.2. Apparatus

Rat drug discrimination sessions were conducted in six, two-lever operant chambers (BRS/LVE, Beltsville, MD) equipped with a houselight and a food dispenser that delivered 45-mg food pellets (Noyes, Frenchtown, NJ). For monkey drug discrimination studies, the subjects were seated in Plexiglas primate chairs (BRS/LVE, Laural, MD) located within the experimental chambers. Two response levers were mounted on a panel facing the monkeys. A light was located above each lever and between the levers was located a receptacle into which 97-mg food pellets (Noyes) were delivered via a dispenser (BRS/LVE, Laural, MD). A clear Plexiglas divider with two armholes was installed between the subject and the response levers to ensure that the monkeys could reach only one lever at a time. Illumination of lights, delivery of food pellets, and recording of lever presses were controlled by a computer-based system (MED-PC, MED Associates, Georgia, VT) housed in the room with the test chambers.

2.3. Procedure

The rat drug discrimination procedure has been described previously (Cook et al., 2001). Briefly, initially during daily (Mon–Fri) experimental sessions (15 min in duration), rats were trained to press both levers under an FR 10 schedule of food reinforcement. Once lever-pressing behavior was regular, drug training sessions were initiated during which rats were trained to press one lever in response to an injection of 10 mg/kg cocaine and to press the other lever in response to an injection of saline. A pseudo-random sequence was used to determine which injection was administered with the restriction that the same injection was not given on more than two consecutive sessions and during each 30 training sessions the number of saline and cocaine injections were approximately equal.

Cocaine and RTI 113 dose–effect curves were obtained in rats as described previously (Cook et al., 2001). Briefly, testing began once a rat met the following criteria: (1) the first completed fixed-ratio (FFR) occurred on the lever designated correct on at least 8 of 10 consecutive sessions; and (2) at least 80% of the total responses were made on the correct lever during those 8 sessions. Tests could occur twice a week, on Tuesdays and Fridays, provided that the rats completed the FFR on the correct lever during the most recent training drug and saline sessions; otherwise, a training day was administered. Test sessions were identical to

training sessions except completion of the FR contingencies on either lever resulted in pellet delivery.

Three of the six rats had been subjects in a previous discrimination study in which the dose–response curves for cocaine and RTI 113 had been determined (Cook et al., 2001). These dose–response curves were not re-determined in the present study. Instead, the lowest dose of RTI 113 found not to reduce response rates in this earlier study (3.0 mg/kg) was re-tested at a 10-min pre-session time in all six rats and was found to produce near 100% levels of cocaine-lever responding. The 3.0 mg/kg dose of RTI 113 was then used during time course tests along with the 10 mg/kg training dose of cocaine which was the lowest dose producing a similar level of generalization. Selecting the 3.0 mg/kg RTI 113 dose had the additional advantage that it was the dose reported to reduce rates of cocaine self-administration in rats (Dworkin et al., 1998). During time-course tests, a dose of 10 mg/kg cocaine was administered 10, 15, 30 60 and 120 min before the start of the session and a dose of 3.0 mg/kg RTI 113 was administered 10, 20, 30, 60, 120, 240, 360 and 720 min before the start of the session.

Monkey drug discrimination procedures were initiated following the familiarization of each monkey with the chairing procedure. As with rats, monkey experimental sessions were 15 min in duration and were conducted daily (Mon–Fri). Subjects were initially trained to press both levers under an FR 32 schedule of food reinforcement. The availability of food was signaled by illumination of the stimulus lights above the levers and food receptacle. Drug discrimination training began once the monkeys exhibited stable rates of responding on both levers. Half of the monkeys were trained to press the right lever in response to a 0.3 mg/kg injection of cocaine and the left lever in response to a saline injection. For the remaining monkeys, the cocaine- and saline-associated levers were reversed. Responses on the incorrect lever reset the FR response requirement. Cocaine and saline were administered using a double alternating schedule in which 2 days of cocaine training were followed by 2 days of saline training. This training sequence repeated throughout the study. Tests were conducted on Tuesday and Friday, with training days on the intervening days. Testing was initiated when each monkey responded greater than 80% on the injection-appropriate lever on the previous four test sessions (two of each training condition). During test sessions, responding on both levers was reinforced. Substitution tests were conducted with cocaine (0.01–1.0 mg/kg) and RTI 113 (0.01–0.1 mg/kg) administered 10 min before the start of the session. For the time-course tests, a dose of 1.0 mg/kg cocaine was administered 30, 60, 180 and 360 min before the start of the session and a dose of 0.1 mg/kg RTI 113 was administered 10, 60, 180, 360, 1080 and 1440 min before the start of the session. These doses of cocaine and RTI 113 were selected for time-course tests because they produced comparable effects on response rates (0.14 and 0.20 responses/s for 1.0 mg/kg cocaine and 0.1 mg/kg RTI 113, respectively).

2.4. Data analysis

The percentage of cocaine-lever responding during the 15-min test sessions was calculated for each subject. Individual percentages of cocaine drug lever responding were then averaged (± S.E.M.). Mean response rates for each test session were calculated for each subject and then these rates were averaged (± S.E.M.). If a rat or monkey failed to complete a FFR during a test session, its data were excluded from calculations of mean cocaine-lever responding for that test, but were included for mean rate of responding calculations. Complete substitution was defined as ≥80% cocaine-like responding. ED_{50} values (95% CL) (μmol/kg) were calculated for percentage cocaine-lever responding using a sigmoidal dose–response (variable slope) curve fitting procedure (GraphPad Prism; San Diego, CA, USA). A log transformation on dose was used. For RTI 113, a dose of 0.1 mg/kg was excluded from the ED_{50} calculation as only two of seven monkeys responded. At a dose of 0.2 mg/kg RTI 113, five of seven monkeys were tested as one monkey died of unrelated causes before testing and one monkey was not tested. At a dose of 1.0 mg/kg cocaine, six of seven monkeys were tested.

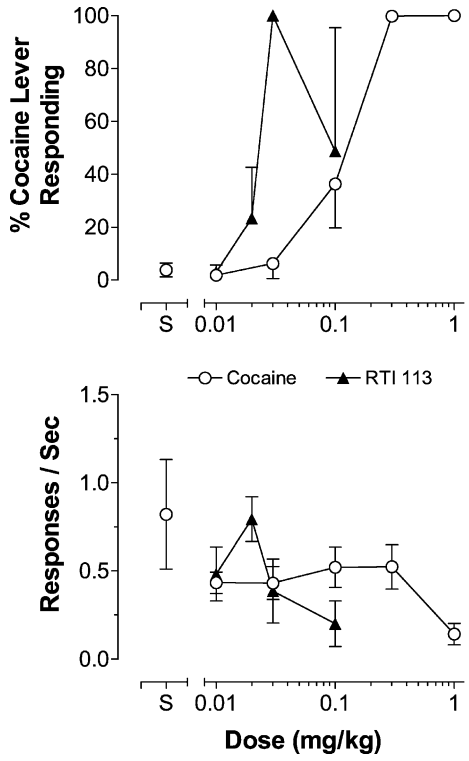

Fig. 1. Effects of cocaine and RTI 113 on the percentage of cocaine-lever responding (top panels) and rate of responding (bottom panels) in squirrel monkeys ($n = 7$) trained to discriminate 0.3 mg/kg cocaine from saline. Data points above "S" indicate the mean percentage of cocaine-lever responding and rate of responding following the administration of saline. At a dose of 0.1 mg/kg RTI 113, only two of seven monkeys responded (see Results). Bars through the data points represent the S.E.M.; when not indicated, the S.E.M. fell within the data point.

2.5. Drugs

Cocaine HCl was obtained from the National Institute on Drug Abuse. RTI 113 was obtained from the Research Triangle Institute (Research Triangle Park, NC). Each drug dissolved in 0.05% saline. The drugs were administered to rats intraperitoneally in a volume equivalent to 1.0 ml/kg and to monkeys intramuscularly in a volume equivalent to 0.5 ml/kg.

3. Results

3.1. Substitution tests with cocaine and RTI 113 in squirrel monkeys

Fig. 1 shows the effects of cocaine and RTI 113 on cocaine-lever responding and rate of responding in monkeys trained to discriminate 0.3 mg/kg cocaine from saline. Cocaine produced increases in cocaine-lever responding with the monkeys exclusively responding on the cocaine-lever at doses of 0.3 (training dose) and 1.0 mg/kg. Relative to saline control levels, rate of responding was suppressed. A dose of 0.03 mg/kg RTI 113 substituted completely ($\geq 80\%$ cocaine-lever responding) for the 0.3 mg/kg cocaine training dose. At a dose of 0.1 mg/kg RTI 113, rate of responding was eliminated in five of the seven monkeys. Of the remaining two monkeys, one responded almost exclusively on the saline lever, whereas the other responded almost exclusively on the cocaine lever. The monkey that responded on the saline lever responded exclusively on the cocaine lever at a dose of 0.03 mg/kg RTI 113. At least one dose of RTI 113 substituted in each of the seven monkeys. The ED_{50} values for cocaine and RTI 113 to produce cocaine-like discriminative stimulus effects were 0.033 (0.025–0.045) μmol/kg and 0.005 (0.0003–0.08) μmol/kg, respectively. Thus, RTI 113 was seven-fold more potent than cocaine at producing cocaine-like discriminative stimulus effects.

3.2. Time-course tests with cocaine and RTI 113 in rats and squirrel monkeys

Time-course tests were initiated with various pretreatment intervals. As seen in the upper left panel of Fig. 2, cocaine (10 mg/kg) produced cocaine-like responding for pretreatment intervals up to 30 min, whereas at pretreatment intervals of 60 and 120 min, cocaine substituted in three of six and one of six rats, respectively. Rate of responding increased as the pretreatment interval was extended to 60 min. RTI 113 (3.0 mg/kg) substituted completely for the cocaine-training stimulus at each test interval up to 120 min. Saline responding was obtained in three of four rats at a pretreatment interval of 720 min. Rate of responding was stable at all test intervals. During these time-course tests, the 3.0 mg/kg dose substituted in four of five rats at a pretreatment interval of 10 min, whereas during dose-effect tests at the same pretreatment interval, this dose substituted in two of six rats. Four rats were tested under both conditions and two of those rats chose the cocaine lever during the time course, but chose the saline lever during the dose-effect test.

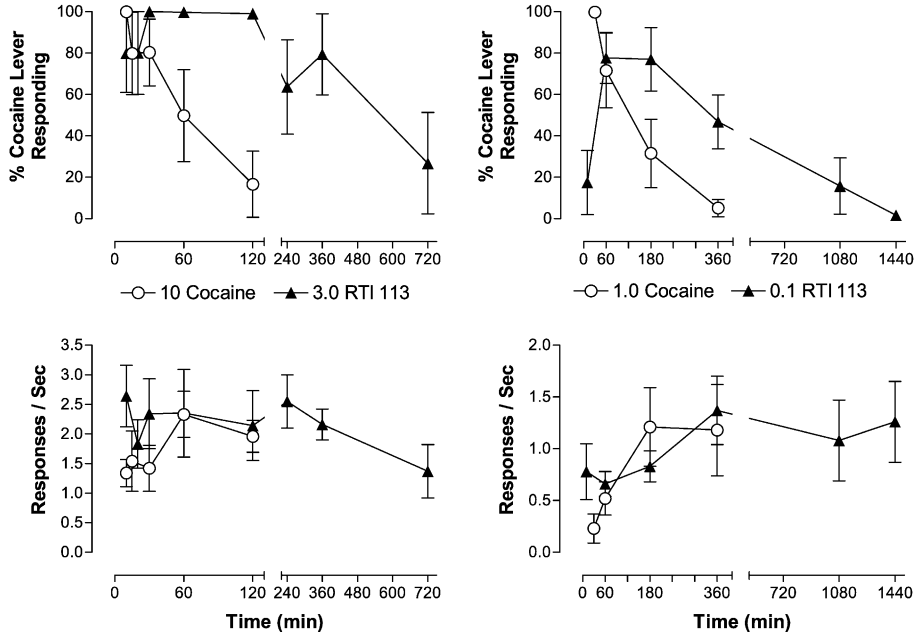

Fig. 2. Time-course effects of cocaine and RTI 113 on the percentage of cocaine-lever responding (top panels) and rate of responding (bottom panels) in rats (left panels, $n = 5–6$) and squirrel monkeys (right panels, $n = 6$) trained to discriminate 10 and 0.3 mg/kg cocaine from saline, respectively. Bars through the data points represent the S.E.M.; when not indicated, the S.E.M. fell within the data point.

In monkeys (right panels), the 1.0 mg/kg dose of cocaine substituted completely at a pretreatment interval of 30 min, whereas intermediate cocaine-like effects were obtained at the 60- and 180-min pretreatment intervals. Predominately saline-like responding was obtained at the 360-min pretreatment interval. At the 30-min interval, responding was eliminated in three of six monkeys. The 0.1 mg/kg dose of RTI 113 produced saline-like responding at the 10-min pretreatment interval, whereas near 80% cocaine-lever responding was obtained at the 60- and 180-min pretreatment intervals. At pretreatment intervals of 1080 and 1440 min, almost all monkeys responded on the saline lever. Rate of responding increased to a plateau when the pretreatment intervals were greater than 180 min. Of the seven monkeys tested in the dose-effect procedure, five of those seven monkeys in addition to one monkey not examined in the dose-effect procedure were tested in the time-course procedure. During the dose-effect test, the 0.1 mg/kg RTI 113 dose eliminated responding in five of seven monkeys at a 10-min pretreatment interval, whereas during the time-course test at the same pretreatment interval, all monkeys responded.

4. Discussion

The present investigation compared the time course of the cocaine-like discriminative stimulus effects of cocaine and the 3-phenyltropane analog, RTI 113, in both rats and squirrel monkeys. In vitro data indicate that RTI 113 is approximately 1500- and 1200-fold more potent at binding to the dopamine transporter relative to the norepinephrine and serotonin transporters, respectively, whereas cocaine is only 37- and 12-fold more potent, respectively (Carroll et al., 1995). RTI 113 produced cocaine-like discriminative stimulus effects in squirrel monkeys as well as rats (Cook et al., 2001). This is in agreement with prior studies demonstrating that drugs that inhibit the reuptake of dopamine produce discriminative stimulus effects similar to those of cocaine (e.g. Baker et al., 1993; Melia and Spealman, 1991; Spealman et al., 1991). Furthermore, the duration of the cocaine-like discriminative stimulus effects of RTI 113 was approximately five times longer than that of cocaine.

In squirrel monkeys, RTI 113 was approximately sevenfold more potent than cocaine at producing cocaine-like discriminative stimulus effects. Although Howell et al. (2000) found in squirrel monkeys that cocaine and RTI 113 were equally potent, in the present study, the in vivo potency relationship obtained in squirrel monkeys was similar to the in vitro potency relationship for the affinity of cocaine and RTI 113 at the dopamine transporter (Carroll et al., 1995). That is, RTI 113 was more potent than cocaine at producing cocaine-like discriminative stimulus effects and more potent at binding to the dopamine transporter. It does not appear that the rate of onset of the discriminative stimulus effects of RTI 113 was a factor in mediating these potency differences between the two studies. In the present experiment, RTI 113 was administered 10 min before testing and in the Howell et al. (2000) experiment, RTI 113 was administered 30 min before testing, and if, for example, the peak effects of RTI 113 are obtained 10–30 min following administration than in the current study it might be predicted that with a 10-min pretreatment RTI 113 would have been not as potent, or even less potent than cocaine. That this was not the case implies that factors other than absorption and distribution are responsible for the potency differences found between these two studies. Indeed, a recent examination of several RTI compounds that exhibit various affinities at and relative selectivities for the dopamine, serotonin and norepinephrine transporters indicated that the potency of the RTI compounds, including RTI 113, to produce cocaine-like discriminative stimulus effects, was correlated with their rank order of potency at the dopamine as well as the norepinephrine transporter (Cook et al., 2001).

RTI 113 exhibited a long duration of action and has high affinity at the dopamine transporter (Carroll et al., 1995), both of which are characteristics deemed favorable of a compound under consideration as an agonist therapy for cocaine dependence (Carroll et al., 1999; Rothman, 1995). RTI 113 has been shown to decrease cocaine self-administration in squirrel monkeys (Howell et al., 2000), rats (Dworkin et al., 1998) and rhesus monkeys (Wilcox et al., 2002). Pretreatment with 3.0 mg/kg RTI 113, a dose exhibiting 60% dopamine transporter occupancy, resulted in a 92% reduction in cocaine self-administration (Dworkin et al., 1998). In the present study, this dose, when administered 10 min before the start of the session, substituted in four of five rats during the time-course tests, and when examined previously in dose-effect tests, substituted in two of six rats (Cook et al., 2001), suggesting that 10 min may be the threshold for the onset of its cocaine-like effects. Therefore, in rats, the cocaine-like discriminative stimulus effects of RTI 113 appeared rapidly (approximately 10 min post-administration), and sooner than in monkeys which were not evident at 10 min post-administration but fully evident at 60 min post-administration. It remains possible that the cocaine-like discriminative stimulus effects of RTI 113 may have appeared sooner than 60 min post-administration, but shorter pretreatment intervals were not tested.

RTI 113 exhibits persistent cocaine-like discriminative stimulus effects and decreases cocaine self-administration, which together are thought to be favorable of a potential cocaine pharmacotherapy. Because RTI 113 is self-administered (Howell et al., 2000; Wilcox et al., 2002), it likely has the potential for abuse. However, in rhesus monkeys, RTI 113 was self-administered at levels generally lower than those obtained with cocaine (Wilcox et al., 2002). Taken together, the present results indicating that RTI 113 has a long duration of action, and given reports that it decreases cocaine self-administration (Dworkin et al., 1998; Howell et

al., 2000; Wilcox et al., 2002), suggest that RTI 113, or analogs of RTI 113, may be useful tools in furthering the development of an agonist pharmacotherapy for cocaine dependence disorders.

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