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Cannabinoid Modulation of Food-Cocaine Choice in Male Rhesus Monkeys

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ABSTRACT

Marijuana and other cannabinoid (CB) compounds are widely used by cocaine users. Preclinical animal studies suggest that these compounds can increase the reinforcing effects of cocaine under some schedules of cocaine self-administration and reinstatement, but not in all cases. To date, no studies have used a food-cocaine concurrent choice procedure, which allows for assessment of drug effects on response allocation, not just changes in cocaine self-administration. The goal of the present study was to examine the effects of compounds differing in their efficacy at the CB receptor (CBR) on cocaine self-administration using a food-drug choice procedure in monkeys. Four adult male rhesus monkeys were trained to self-administer cocaine in the context of an alternative food (1.0-g banana-flavored pellets) reinforcer, such that complete cocaine dose-response curves (0, 0.003-0.1 mg/kg/injection) were determined each session. Monkeys were tested acutely with the CBR full agonist CP 55,940 (0.001-0.01 mg/kg), the CBR partial agonist Δ^9-THC (0.03-0.3 mg/kg mg/kg), which is also the primary active ingredient in marijuana, and the CBR antagonist rimonabant (0.3-3.0 mg/kg mg/kg). Cocaine choice increased in a dose-dependent manner. Acute treatment with CP 55,940 decreased cocaine choice, while THC and rimonabant enhanced the reinforcing effects of cocaine. Chronic (7-day) treatment with CP 55,940 resulted in tolerance to the decreases in cocaine choice. These findings with Δ^9-THC provide support for a potential mechanism for co-abuse of marijuana and cocaine. Additional research with chronic treatment with full CBR agonists on attenuating the reinforcing strength of cocaine is warranted.

Significance Statement: Co-abuse of THC and cocaine is a significant public health problem. The use of animal models allows for the determination of how cannabinoid receptor stimulation or blockade influences the reinforcing strength of cocaine.

INTRODUCTION

Emerging evidence has implicated a role for the endocannabinoid system in modulating the abuse-related effects of cocaine. The endocannabinoid system is comprised of two major types of cannabinoid receptors (CBR), the cannabinoid type 1 (CB1) and type 2 (CB2) receptor, which are both inhibitory G-protein coupled receptors (Vlachou and Panagis, 2014). Pharmacological studies involving CBR ligands show that they interact with cocaine under a broad range of behavioral measures (Oliere et al., 2013; Wiskerke et al., 2008). Further investigation of these interactions has implications for understanding aspects of polydrug use involving cocaine and cannabinoids as well as developing novel medications for cocaine use disorder.

In general, preclinical studies suggest that pharmacological antagonism of CBR inhibit (e.g., Gobira et al., 2019) or have no effect, while CBR agonists facilitate the behavioral effects of cocaine (Parsons and Hurd, 2015). Nonetheless, varying results have been found depending on the conditions under which the drugs are studied. For example, studies in rodents show that acquisition of cocaine self-administration was unaffected by treatment with the non-selective CBR antagonist SR141716A (Lesscher et al., 2005) or CBR partial agonist Δ^9-THC (Panlilio et al., 2007) but was increased by treatment with the agonist CP55,940 (Higuera-Matas et al., 2008). Consistent with this finding, adolescent Δ^9-THC exposure resulted in increased acquisition of cocaine self-administration and increases in the reinforcing strength of low doses of cocaine in adults (Friedman et al., 2019). On the other hand, cocaine- and cue-induced reinstatement of extinguished cocaine self-administration has been found to be attenuated by CBR antagonists (Adamczyk et al., 2012; De Vries et al., 2001; Filip et al., 2006; Ward et al., 2009; Xi et al., 2006) but enhanced by pretreatment with Δ^9-THC (Justinova et al., 2008) or the non-selective CBR agonist HU210 (De Vries et al., 2001). With regard to maintenance of cocaine self-administration, the effects of CBR antagonists appear to be reinforcement-schedule dependent. That is, several reports show that pretreatment with SR141716A had no effect on

cocaine self-administration under a fixed-ratio (FR) schedule of reinforcement in rodents (Caille and Parsons, 2006; De Vries et al., 2001; Filip et al., 2006) or nonhuman primates (Tanda et al., 2000) but decreased self-administration under a progressive-ratio (PR) schedule (Orio et al., 2009; Panlilio et al., 2007; Soria et al., 2005). Paradoxically, it has been found that pretreatment with Δ^9-THC and the CBR agonist WIN 55,212 also decreased cocaine self-administration under PR (Panlilio et al., 2007) and FR1 (Fattore et al., 1999) schedules of reinforcement. However, it should be noted that the exact nature of the latter finding remains unclear as WIN55,212 was not tested on the full cocaine self-administration dose-response curve.

The goal of the present study was to further investigate the effects of CBR modulation on cocaine self-administration in the context of a food-drug choice procedure. It has been suggested that the use of a choice procedure is advantageous because it confers greater predictive validity of drug interactions than simple schedules of reinforcement (Banks and Negus, 2017). That is, substance use disorder has been conceptualized as a "disorder of choice" related to the disproportionate allocation of behavior toward substance procurement and use over nondrug reinforcers (Banks and Negus, 2012; Heyman, 2009). Consequently, a primary goal of treatment is to not only reduce substance use but to also reallocate behavior to more adaptive alternative reinforcers (Comer et al., 2008; Haney and Spealman, 2008; Banks and Negus, 2012). The majority of studies examining the interactions of CBR compounds on cocaine self-administration have been evaluated under FR schedules of reinforcement. Thus, the present study is a critical extension of earlier research.

Here, we examined the acute effects of three different CBR compounds on cocaine self-administration using a food-drug choice procedure. The compounds examined included the non-selective full CBR agonist CP 55,940, the non-selective CBR partial agonist Δ^9-THC, and the CBR inverse agonist/antagonist rimonabant. We hypothesized that the effects of CBR compounds on food-cocaine choice would differ as a function of their efficacy at the cannabinoid receptor. More specifically, because it has been shown that administration of CP55,940

increases DA concentrations (Cheer et al., 2007; Wang et al., 2015), we hypothesized this compound would shift the cocaine dose-response curve to the right, while rimonabant, because CBR antagonists have been shown to decrease DA concentrations (Xi et al., 2008), would shift the cocaine dose-response curve to the left. It was not clear at the outset how Δ^9-THC would affect cocaine choice. We also extended the effects of acute CP 55,940 to include 7-day treatment to examine whether tolerance would develop to the effects on cocaine choice.

METHODS

Subjects: Four adult male rhesus monkeys (*Macaca mulatta*), weighing 8.8-9.2 kg at the start of the study, and with a history of cocaine self-administration (John et al., 2015), served as subjects. Monkeys were fed enough food daily (Purina LabDiet 5045, St. Louis, Missouri, USA) to maintain healthy body weights (~ 98% free-feeding weights); water was available ad libitum in the homecage. Monkeys were individually housed in stainless-steel cages, fitted with an aluminum collar and trained to sit in a primate restraint chair (Primate Products, Redwood City, CA). Environmental enrichment was provided as outlined in the Animal Care and Use Committee of Wake Forest University Non-Human Primate Environment Enrichment Plan. Animal housing, handling and experimental procedures met the 2011 National Research Council Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research. The environmental enrichment plan was approved by the Wake Forest University Animal Care and Use Committee.

Surgery: Under ketamine (initial dose of 15 mg/kg, i.m.), each monkey was implanted with a chronic indwelling intravenous catheter, surgically placed in a major vein (femoral or internal or external jugular), and subcutaneous vascular access port (VAP; Access Technologies, Skokie, IL) under aseptic conditions. One-hour following surgery, animals were administered 30 mg/kg kefzol, i.m. (cefazolin sodium; Marsam Pharamaceuticals, Inc., Cherry Hill, NJ). Metacam

(meloxicam; 0.1 mg/kg, i.m.; Putney Inc., Portland, ME), an analgesic, was administered SID for three days.

Behavioral procedure: Food-cocaine choice sessions were conducted daily in ventilated, sound-attenuating chambers (1.5 x 0.74 x 0.76 m; Med Associates, St. Albans, VT). Two photo-optic switches (Model 117-1007; Stewart Ergonomics, Inc., Furlong, PA), in which responses were recorded, were located on each side of an operant panel. Three stimulus lights, located in a horizontal row, were positioned 14 cm above each switch. Between each photo-optic switch was a food receptacle which was connected to a pellet dispenser (Med Associates) with a Tygon tube. The pellet dispenser was located on the top of the chamber and delivered 1.0-g banana-flavored food pellets (Bio-Serv, Frenchtown, NJ). Also located on top of the chamber was a peristaltic infusion pump (Cole-Parmer Instrument Co., Niles, IL) which delivered drugs at a rate of approximately 1.5 ml/10 s.

Prior to the start of the experimental session, the area of the monkey's back near the vascular access port was cleaned with chlorhexidine and isopropyl alcohol swabs (Prevantics™, Orangeburg, NY). The venous catheter was connected to the infusion pump with the insertion of a 22-guage Huber Point Needle (Access Technologies) into the port. The port was filled with the concentration of drug available that session by operating the pump for approximately 3 s. Pretreatment drug administration was given outside the chamber immediately before the session and the monkey was placed into the operant chamber. To prevent clotting, catheters were flushed with 3 mLs of 100 U/mL heparinized saline at the end of the session.

The food-cocaine choice procedure was a multiple concurrent fixed-ratio schedule consisting of five 20-min components, which were separated from each other by a 5-min timeout period. During each component, monkeys completed an FR requirement to receive food pellets and/or i.v. injections of cocaine. Food pellets were available in each component; the unit doses of cocaine available during each of the five successive components were 0, 0.003, 0.01, 0.03

and 0.1 mg/kg per injection, respectively. Different discriminative stimuli signaled the availability of each reinforcer such that illumination of a green light above one switch signaled food availability while illumination of combinations of lights signaled different cocaine doses. The drug dose was varied by manipulating the pump duration and consequently the volume delivered. A total of 10 reinforcers were available in each component; components ended after 10 total reinforcers (food + cocaine injections) or 20 min had elapsed, whichever came first. In situations where 10 reinforcers were earned, the component TO was added to the remainder of the component time, to assure 2 h sessions. In the event that a monkey emitted a response on the alternate switch before an FR was completed, the FR requirement on the first switch was reset. Illumination of the red light (CS) in the center of the response panel, above the food receptacle, accompanied each cocaine injection. There was a 30-s timeout (TO) after each reinforcer (food or drug). Food and cocaine FR requirements were adjusted for each monkey to assure dose-dependent increases in cocaine choice (**Table 1**). Sessions were conducted typically 5-7 days/week.

Stable responding was defined as 3 consecutive sessions in which ≤20% of reinforcers earned on the cocaine switch when the alternative to food was no injection (component 1) or 0.003 mg/kg per injection cocaine (component 2) and ≥80% of reinforcers earned on the cocaine switch when the alternative to food was 0.1 mg/kg per injection cocaine (component 5). Once responding was stable, dose-response curves were conducted to determine the acute effects of Δ^9-THC (0.03-0.3 mg/kg), CP 55,940 (0.001-0.01 mg/kg), and rimonabant (0.3-3.0 mg/kg), administered intravenously, immediately before the food-cocaine session. Doses were tested typically twice per week, with at least 2 days between test sessions. Pretreatment with the vehicle of each compound was tested each week as well. The effect of each acute dose was double or triple determined depending on variability between the first two tests.

Because the effects of acute CP 55,940 were positive (i.e., decreases in percent cocaine choice), the “best dose” of CP 55,940 was tested over 7 consecutive sessions. "Best dose" was

defined as the dose of CP 55,940 that either decreased cocaine choice or the highest dose that did not substantially disrupt responding, defined as a reduction in total trials by greater than 50%. The “best dose” was 0.003 mg/kg for R-1661 and R-1688, 0.01 mg/kg for R-1692 and 0.017 mg/kg for R-1689.

Data analysis: The primary dependent variable was percent cocaine choice defined as (number of cocaine injections ÷ total number of reinforcers) x 100. In addition, total reinforcers per session, total food reinforcers, total cocaine injections are shown. Acute pre-treatment dose-effect curves for CP 55,950, Δ^9-THC, and rimonabant included the average of at least two determinations for each monkey. Data for the effects of chronic CP 55,940 treatment on cocaine choice were shown as a single determination on Day 7 of treatment for each monkey. The group mean of these data were analyzed using repeated-measures two-way analyses of variance (ANOVA), with cocaine dose and treatment as the main factors. The total cocaine intake per session was also determined and analyzed using repeated-measures one-way ANOVA across treatment drug conditions. A significant ANOVA was followed by multiple comparisons post-hoc tests to compare test conditions with vehicle conditions. The criterion for significance was set a priori at the 95% level of confidence ($p < 0.05$) in all cases. All analyses were conducted with Prism 6 for Mac OS X software (Graphpad Software, Inc.).

Drugs: Cocaine, Δ^9-THC, CP 55,940, and rimonabant were all obtained from the National Institute on Drug Abuse (NIDA), Bethesda, MD. (−)-Cocaine HCl was dissolved in sterile 0.9% saline. Δ^9-THC, CP 55,940, and rimonabant were dissolved in a vehicle containing one-part Tween 80, one-part ethanol and 18-parts sterile water. Each compound was administered i.v., through the vascular access port followed by a 3-ml saline injection to ensure the entire dose was delivered.

RESULTS

Following vehicle pretreatment (closed circles, **Fig. 1A-C**), monkeys primarily chose food when the alternative was either no injection of cocaine (component 1) or a low unit dose of cocaine (0.003 mg/kg). Behavior was almost exclusively reallocated to cocaine choice during the availability of larger unit cocaine doses (0.01-0.1 mg/kg). The maximum number of 10 reinforcers was typically earned in each component except the last two components when the two highest unit doses of cocaine (0.03-0.1 mg/kg) were available (closed circles, **Fig. 2A-C**). During components 1 and 2, the majority of the reinforcers earned was food (closed circles, **Fig. 2D-F**), with increases in the frequency of cocaine injections associated with higher cocaine doses (closed circles, **Fig. 2G-I**).

Acute pretreatment with CP 55,940 decreased cocaine choice compared to vehicle (**Fig. 1A**). There was a significant interaction between cocaine dose and CP 55,940 dose ($F_{12,36}$=2.80, p<0.01) and *post-hoc* analysis indicated a significant decrease in percent choice of 0.01 mg/kg cocaine following administration of 0.01 mg/kg CP 55,940 compared to vehicle pretreatment (p<0.05). There was a significant interaction between cocaine dose and CP 55,940 dose for total reinforcers earned ($F_{12,36}$=2.18, p<0.05), with CP 55,940 dose-dependently increasing total reinforcers in components 4 and 5 (**Fig. 2A**). Following CP 55,940, there were significant increases in food reinforcers earned ($F_{12,36}$=3.93, p<0.001; **Fig. 2D**). Higher doses of CP 55,950 decreased food pellets earned in the first two components and significantly increased food reinforcers in component 3, consistent with the decrease in cocaine choice in this component. There was a main effect of CP 55,940 dose on cocaine injections ($F_{9,27}$=2.79, p<0.05), with decreases observed in component 2 (**Fig. 2G**).

In contrast to the effects with CP 55,940, pretreatment with Δ^9-THC increased cocaine choice compared to vehicle pretreatment (**Fig. 1B**). There was a significant main effect for Δ^9-THC dose on choice ($F_{3,51}$=3.62, p<0.05) and a significant interaction between cocaine dose and Δ^9-THC dose ($F_{12,51}$=4.08, p<0.001). *Post-hoc* analyses indicated that each does of Δ^9-THC

(0.03-0.3 mg/kg) significantly increased choice for 0.003 mg/kg/injection cocaine compared to vehicle pretreatment (p<0.0001). Δ^9-THC administration decreased the total reinforcers earned per session ($F_{3,9}$=20.06, p<0.001), with significance noted following the highest Δ^9-THC dose (**Fig. 2B**). There was a significant main effect ($F_{3,9}$=15.80, p<0.001) and a significant interaction ($F_{12,36}$=9.30, p<0.0001) of cocaine dose and Δ^9-THC dose on food reinforcers (**Fig. 2E**). Consistent with the increase in cocaine choice, *post-hoc* analyses showed a dose-dependent decrease in food pellets earned in the first two components. There was a significant main effect ($F_{3,9}$=6.26, p<0.05) and a significant interaction between cocaine dose and Δ^9-THC dose for cocaine injections earned ($F_{9,27}$=3.68, p<0.01; **Fig. 2H**). In addition to significant decreases in total reinforcers (**Fig. 2B**), the highest dose of Δ^9-THC (0.3 mg/kg) produced significant decreases in injections of 0.01 mg/kg and 0.03 mg/kg cocaine compared to vehicle pretreatment.

The results from rimonabant pretreatment were qualitatively similar to Δ^9-THC pretreatment. That is, rimonabant produced an increase in choice of the low cocaine dose (0.003 mg/kg/injection) in which there was a significant interaction for choice between cocaine and rimonabant dose ($F_{12,57}$=2.16, p<0.05; **Fig. 1C**). There was also a main effect of rimonabant dose for total reinforcers earned ($F_{3,9}$=9.17, p<0.01; **Fig. 2C**) and a significant interaction between cocaine dose and rimonabant dose for total reinforcers ($F_{12,36}$=2,28, p<0.05; **Fig. 2C**), food reinforcers ($F_{12,36}$=6.09, p<0.0001; **Fig. 2F**), and injections earned ($F_{9,27}$=4.27, p<0.01; **Fig. 2I**). Similar to Δ^9-THC, rimonabant produced a dose-dependent decrease in food pellets earned early in the session, which coincided with a significant increase in the number of 0.003 mg/kg cocaine injections earned in component 2.

To further evaluate the effects of CP 55,940 on cocaine choice, the best dose was administered for seven consecutive sessions, immediately before the session. The acute effects of the CP 55,940 “best dose” on cocaine choice, determined prior to seven-day treatment **(Fig. 3**, triangles), showed a downward shift in cocaine choice, which reached significance when 0.01

mg/kg cocaine was available. Tolerance developed to this effect following seven-day treatment (**Fig. 3**, squares), resulting in a significant increase in % cocaine choice when the lowest dose was available (0.003 mg/kg cocaine).

DISCUSSION

Results from this study indicated that cannabinoid modulation of food-cocaine choice differed as a function of the pharmacological efficacy at the cannabinoid receptor. That is, acute pretreatment with a non-selective cannabinoid receptor partial agonist (Δ^9-THC) and inverse agonist/antagonist (rimonabant) were qualitatively similar such that both potentiated the reinforcing effects of cocaine by increasing cocaine choice at low doses. In contrast, acute administration of a non-selective full cannabinoid receptor agonist (CP 55,940) shifted the cocaine choice dose-response curve downwards, thereby reducing cocaine choice. Chronic (7-day) treatment with an effective dose of CP 55,940 resulted in tolerance to the CP 55,940-induced decreases in cocaine choice.

The reduction in cocaine choice and reallocation of behavior toward food reinforcement following acute CP 55,940 pretreatment suggests that the relative reinforcing efficacy of cocaine was decreased under the present conditions. It should be noted that these effects also corresponded with an initial decrease in food-maintained responding early in the session and a marginal increase in low-dose (0.003 mg/kg) cocaine injections; however, this effect did not result in a significant increase in choice of this low cocaine dose. These data suggest that CP 55,940 pretreatment produced initial and transient reinforcement-independent rate-altering effects (e.g., motor impairment) prior to decreasing cocaine choice that may have manifested in an initial increase in cocaine injections as a response to counteract these effects.

One other study has also reported cannabinoid agonist-induced decreases in cocaine self-administration (Fattore et al., 1999). This study showed that acute pretreatment with the synthetic cannabinoid agonist WIN 55,212 dose-dependently decreased cocaine self-

administration under an FR 1 schedule of reinforcement in rats, although only doses on the descending limb of the cocaine dose-response curve were tested. It is possible that these results were due to reinforcement-independent rate-decreasing effects of WIN 55,212 as it was not also tested on responding maintained by a non-drug reinforcer. Therefore, our study extends these findings through the utilization of a concurrent food-cocaine choice procedure to demonstrate that cannabinoid receptor agonist-induced decreases to cocaine self-administration can occur independent of any non-selective rate-decreasing effects of the drug. Other preclinical studies have also shown that the behavioral effects of cocaine were attenuated by pretreatment with full cannabinoid receptor agonists. For instance, WIN 55,212 dose-dependently reduced facilitation of brain stimulation reward in rats as assessed by ICSS (Vlachou et al., 2003) and attenuated cocaine-induced hyperlocomotion in rats (Przegalinski et al., 2005; Vlachou et al., 2008). One possible explanation for cannabinoid agonists to reduce the behavioral effects of cocaine may be associated with CB1 receptor stimulation acting to counteract or attenuate the increased extracellular dopamine (DA) concentrations in the nucleus accumbens produced by cocaine (Centonze et al., 2004). Nevertheless, some studies indicate that cannabinoid receptor antagonists have qualitatively similar effects (i.e., attenuation) on cocaine-induced ICSS (Xi et al., 2008) and hyperlocomotion (Cheer et al., 2007; Corbille et al., 2007; Gerdeman et al., 2008) as the aforementioned studies with cannabinoid receptor agonists. Thus, it has been proposed that these apparently contradictory findings may indicate an inverted U-shaped curve regarding the effects of CB1 receptor stimulation on the behavioral effects of cocaine (Oliere et al., 2013).

Using models of reinforcing strength (i.e., current choice or PR schedules of reinforcement), investigators have shown that chronic administration of *d*-amphetamine can produced sustained decreases in cocaine self-administration (e.g., Negus, 2003; Czoty et al., 2010, 2011). As a result, we tested the dose of CP 55,940 that decreased cocaine choice, individually determined for each monkey, for 7 consecutive sessions. In contrast to the positive

outcomes observed with d-amphetamine, we observed tolerance to the decreases in cocaine choice and subsequent increases in choice at the lower doses. The mechanisms for the acute effects of CP 55,940 and the subsequent tolerance to those effects are not clear. There does not appear to be any preclinical studies that examined the effects of CP 55,940 on extracellular DA concentrations. There is relatively weak evidence that acute Δ^9-THC, under some conditions, can elevate DA (reviewed by Bloomfield et al., 2016 and Thiruchselvam et al., 2017), so it is possible that a full agonist like CP55,940 would produce larger and more robust effects on DA. Whether these effects on DA are diminished with chronic treatment is an important mechanistic question.

Our finding that acute rimonabant increased cocaine choice is in contrast to previous studies that showed rimonabant reduced the reinforcing efficacy of cocaine under a PR schedule in rodents (Orio et al., 2009; Soria et al., 2005). One possible explanation for these discrepant findings may be that cocaine self-administration in the context of a choice paradigm was relatively less confounded by reinforcement-independent rate-decreasing effects of rimonabant. Instead, our findings suggest that increases in self-administration of low doses of cocaine (0.003 mg/kg/injection) may have occurred to counteract the rate-decreasing effects of rimonabant early in the session similar to what was observed with CP 55,940. Other factors to be considered for contrasting findings may also include species differences and route of rimonabant administration (i.p. in rodents vs. i.v. in the present study). One possible explanation, that should be tested in future studies, is that the effects of cannabinoid antagonism using rimonabant on cocaine self-administration are influenced by the schedule of reinforcement controlling cocaine self-administration. In particular, measures of reinforcing efficacy of cocaine may be more sensitive to the effects of cannabinoid antagonism, despite qualitative differences between our study using a choice procedure vs. prior studies using PR reinforcement schedules, considering many studies using FR schedules of reinforcement show no effect (Caille and Parsons, 2006; De Vries et al., 2001; Filip et al., 2006; Tanda et al., 2000).

Our finding that acute administration of Δ^9-THC increased cocaine choice is consistent with studies in humans examining the acute effects of smoked cannabis prior to cocaine administration. For example, findings from Foltin and colleagues suggested that smoked marijuana before i.v. cocaine administration (16-32 mg) prolonged subjective effects (i.e., "stimulation", "high") associated with cocaine (Foltin et al., 1993). Another study in humans showed that smoke marijuana 30-min prior to intranasal cocaine (0.9 mg/kg) administration significantly reduced the latency of cocaine-induced effects and increased the duration of cocaine euphoric effects (Lukas et al., 1994). Pharmacokinetic factors may have been associated with these findings such that THC-induced vasodilatation led to increased cocaine absorption (Lukas et al., 1994). In contrast, a previous study in rodents showed that Δ^9-THC decreased the reinforcing efficacy of cocaine under a PR reinforcement schedule (Panlilio et al., 2007). However, the generalizability of these findings to the present study are limited such that cocaine self-administration did not occur in the presence of acute Δ^9-THC administration but rather following a period of daily Δ^9-THC exposure. Furthermore, our study suggests that increased cocaine-self administration may have also occurred to counteract the rate-decreasing effects of high Δ^9-THC doses (0.1-0.3 mg/kg). Nevertheless, pretreatment with the lowest Δ^9-THC dose (0.03 mg/kg) increased cocaine choice without producing significant decreases in food-maintained responding early in the session. These results suggest that the reinforcing efficacy of cocaine was increased independent of a counteracting mechanism associated with "aversive" Δ^9-THC effects, at least as it relates to a low THC dose.

In summary, acute administration of a full CBR agonist (CP 55,940) decreased cocaine choice, while acute administration of a CBR partial agonist (Δ^9-THC) and antagonist (rimonabant) increased cocaine choice. Tolerance to the effects of CP 55,940 were observed after seven days of daily treatment. The present study adds to our current understanding of the interaction between cannabinoids and cocaine by demonstrating an additional context (i.e., concurrent food-cocaine choice) for cannabinoid receptor compounds to modulate the

reinforcing efficacy of cocaine. Additional studies are warranted to better understand the influence of specific cannabinoid receptor subtypes, considering evidence to suggest that cannabinoid CB1 and CB2 receptors may have distinct effects in regulating the abuse-related effects of cocaine (Delis et al., 2017). Future studies employing choice procedures may also consider the use of alternative non-drug reinforcers other than food given the anorectic/orexigenic effects of cannabinoids. Research shows that cannabis is widely used by cocaine users (Jutras-Aswad et al., 2010) and one study showed that over one-fourth of patients with cocaine use disorder had a concurrent cannabis use disorder (John et al., 2018). A study among individuals with cocaine dependence who received treatment in an inpatient program found that cannabis use after discharge from the program was associated with increased relapse to cocaine use (Aharonovich et al., 2005). These negative implications of cannabis use on cocaine treatment outcomes are supported by the present findings indicating a Δ^9-THC-induced increase in cocaine choice; however, chronic Δ^9-THC studies are clearly necessary.

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AUTHOR CONTRIBUTIONS.

Participated in research design: WSJ, TJM, and MAN

Conducted experiments: WSJ.

Performed data analysis: WSJ

Wrote or contributed to writing of the manuscript: WSJ, TJM, and MAN

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FIGURE CAPTIONS

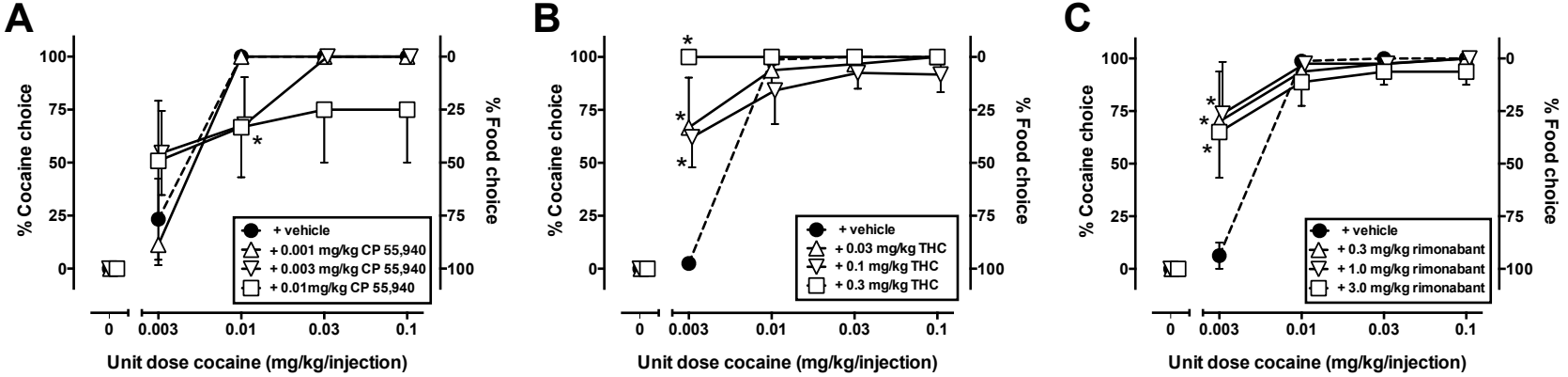
Figure 1. Effects of acute pretreatment of CP 55,940 (0.001-0.01 mg/kg, i.v.), Δ^9-THC (0.03-0.3 mg/kg, i.v.), or rimonabant (0.3-3.0 mg/kg, i.v.) on choice between cocaine and food in rhesus monkeys (n=4). Ordinate: percent of reinforcers earned on the cocaine-associated switch. Abscissae: unit dose of cocaine in mg/kg per injection available as an alternative to a food pellet. All data represent mean ± SEM of 4 monkeys for at least 2 determinations of acute pretreatment of vehicle (filled symbols) or each test drug (open symbols). *p<0.05 compared to respective vehicle pretreatment.

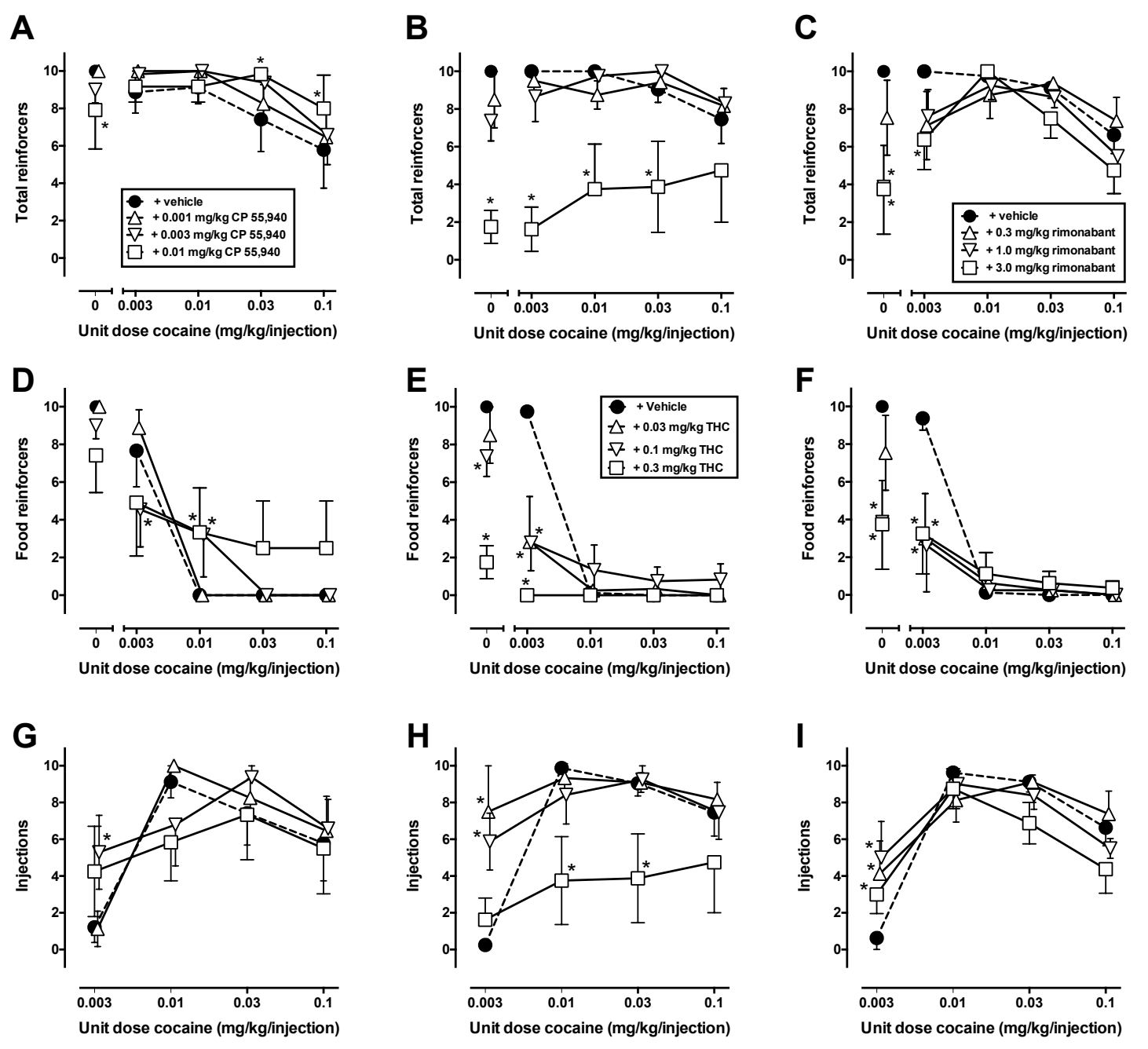
Figure 2. Effects of acute pretreatment of CP 55,940 (0.001-0.01 mg/kg, i.v.), Δ^9-THC (0.03-0.3 mg/kg, i.v.), or rimonabant (0.3-3.0 mg/kg, i.v.) on total reinforcers earned (top row), food pellets earned (middle row), or total injections earned (bottom row). Ordinate: number of respective reinforcer type earned out of a maximum of 10 available per component. Abscissae: unit dose of cocaine in mg/kg per injection available as an alternative to a food pellet. All data represent mean ± SEM of 4 monkeys for at least 2 determinations of acute pretreatment of vehicle (filled symbols) or each test drug (open symbols). *p<0.05 compared to respective vehicle pretreatment.

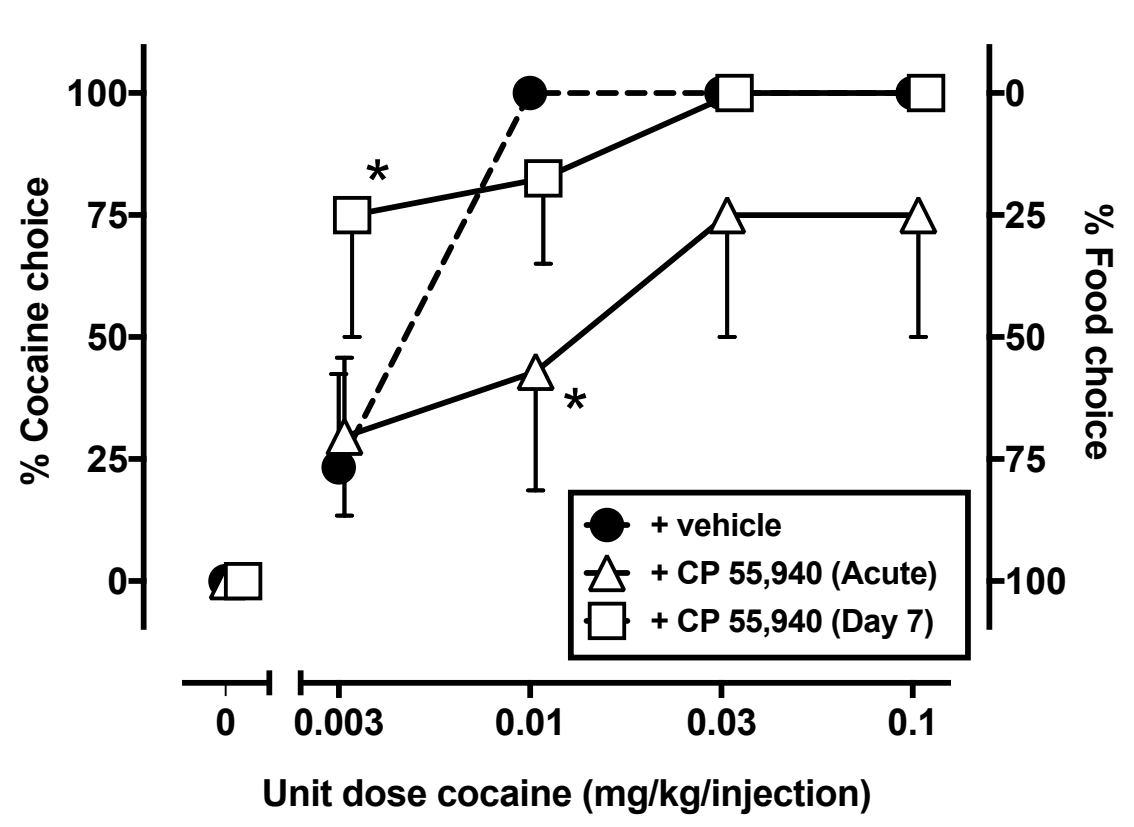
Figure 3. Effects of acute (open triangles) and day 7 of chronic treatment (open squares) of CP 55,940 on percent cocaine choice. The dose of CP 55,940 was individually determined (see text). All data represent mean ± SEM of 4 monkeys. Other details are as described in Figure 1. *p<0.05 compared to respective vehicle pretreatment.

Table 1. Parameters for individual monkeys

Subject	Food FR	Cocaine FR
R-1661	50	10
R-1688	50	60
R-1689	10	100
R-1692	50	120


A
% Cocaine choice
% Food choice
100
75
50
25
0
0
25
50
75
100
+ vehicle
+ 0.001 mg/kg CP 55,940
+ 0.003 mg/kg CP 55,940
+ 0.01mg/kg CP 55,940
0
0.003
0.01
0.03
0.1
Unit dose cocaine (mg/kg/injection)
B
% Cocaine choice
% Food choice
+ vehicle
+ 0.03 mg/kg THC
+ 0.1 mg/kg THC
+ 0.3 mg/kg THC
Unit dose cocaine (mg/kg/injection)
C
% Cocaine choice
% Food choice
+ vehicle
+ 0.3 mg/kg rimonabant
+ 1.0 mg/kg rimonabant
+ 3.0 mg/kg rimonabant
Unit dose cocaine (mg/kg/injection)


A
B
C
D
E
F
G
H
I
Total reinforcers
Food reinforcers
Injections
+ vehicle
+ 0.001 mg/kg CP 55,940
+ 0.003 mg/kg CP 55,940
+ 0.01 mg/kg CP 55,940
+ 0.3 mg/kg rimonabant
+ 1.0 mg/kg rimonabant
+ 3.0 mg/kg rimonabant
+ Vehicle
+ 0.03 mg/kg THC
+ 0.1 mg/kg THC
+ 0.3 mg/kg THC
0
0.003
0.01
0.03
0.1
Unit dose cocaine (mg/kg/injection)


% Cocaine choice
% Food choice
100
75
50
25
0
0
25
50
75
100
*
*
+ vehicle
+ CP 55,940 (Acute)
+ CP 55,940 (Day 7)
0
0.003
0.01
0.03
0.1
Unit dose cocaine (mg/kg/injection)