Effects of dopamine D1-like receptor ligands on food-cocaine choice
in socially housed male cynomolgus monkeys

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ABSTRACT

Although dopamine plays a prominent role in mediating cocaine’s abuse-related effects, the specific roles of dopamine receptor subtypes are not fully understood. Whereas the effects of drugs acting at dopamine D2-like receptors (D2R) have been characterized, less is known about dopamine D1-like receptors (D1R). The present experiments examined the effect of drugs with varying intrinsic efficacy at D1R on the relative reinforcing strength of cocaine in male cynomolgus monkeys. Use of socially housed monkeys permitted the assessment of whether social status influenced the behavioral effects of D1R-acting drugs. The high-efficacy D1R agonist SKF 81297, low-efficacy D1R agonist SKF 38393 and D1R antagonist SCH 23390 were administered acutely to monkeys self-administering cocaine under a food-cocaine choice procedure in which a cocaine choice dose-effect curve was determined daily. To assess selectivity of behavioral effects on cocaine choice, effects of doses that did not disrupt responding (indicated by a ≥35% decrease in total reinforcers delivered) were analyzed. Neither SKF 81297 nor SCH 23390 affected cocaine choice in dominant or subordinate monkeys. However, the low-efficacy agonist SKF 38393 selectively decreased cocaine choice; this effect was larger and only reached statistical significance in subordinate monkeys. Increasing the pretreatment time did not affect these results. The results indicate that, like D2R-acting drugs, the behavioral effects of D1R-acting drugs on cocaine choice can vary according to intrinsic efficacy and social status. Moreover, they demonstrate that D1R-acting drugs affect behavior under a narrower range of conditions than D2R-acting drugs.

Significance Statement: Cocaine use disorder represents an insidious public health concern with no FDA-approved medications. Although dopamine receptors have been strongly implicated in mediating the abuse-related effects of cocaine, the roles of dopamine receptor subtypes are incompletely understood. The present study in nonhuman primates found that
cocaine choice was decreased only by a low-efficacy D1R agonist, and this effect depended on the social status of the monkey.
INTRODUCTION

Cocaine use disorder continues to be an intractable public health problem for which there are no medications approved by the Food and Drug Administration. Although a great deal of evidence has implicated enhancement of brain dopamine (DA) neurotransmission in the abuse-related effects of cocaine (e.g., Koob and Volkow, 2010), the precise roles of DA receptors have yet to be fully elucidated. Laboratory animal studies have demonstrated that both D1-like receptors (D1R) and D2-like receptors (D2R) can mediate the abuse-related behavioral effects of cocaine. For example, drugs that selectively stimulate either D1R or D2R are self-administered by rats and monkeys (e.g., Woolverton et al., 1984; Self and Stein, 1992; Weed and Woolverton, 1995; Grech et al., 1996; Ranaldi et al., 2001). Moreover, drugs that selectively block these receptors can decrease the reinforcing effects of cocaine (e.g., Bergman et al., 1990; Katz and Witkin, 1992; Caine and Koob, 1994; Nader et al., 1999). Despite the general similarity in the behavioral effects of D1R and D2R agonists and antagonists, subtle differences in drug effects can be detected when behavior is maintained under different schedules of reinforcement. On the whole, evidence indicates a more prominent role for D2R in cocaine’s effects in that D2R agonists function as reinforcers and modulate cocaine’s effects under a wider range of conditions (Caine et al., 1999), but points to the need to examine multiple drugs under a variety of experimental conditions.

Prior studies of the effects of D1R-acting drugs on cocaine reinforcement used ratio-based schedules and a single operandum that provide measures of response rate or reinforcement rate as the primary dependent variable. The present studies extended this research by studying the reinforcing effects of cocaine in monkeys responding under a concurrent food-cocaine choice procedure. Preclinical choice procedures have high translational relevance because they measure the subject’s allocation of behavior toward obtaining drugs versus other stimuli in the environment (e.g., Banks and Negus, 2017). In this way choice procedures more closely
resemble the clinical condition in which individuals who choose to use drugs forfeit access to other reinforcers (e.g., food or money; Katz, 1990). This is particularly relevant for medication development because the goal of treatment with a pharmacotherapy for cocaine use disorder is to increase the proportion of times the patient will choose to pursue activities other than drug use (Perkins and Freeman, 2018). Although the effects of D2R agonists and antagonists on food-cocaine choice have been reported (Woolverton and Balster, 1981; Negus, 2003; Bergman, 2008; Thomsen et al., 2008, 2017; Czoty and Nader, 2013), D1R-acting drugs have not been studied in this context. In the present study, we examined the effects of the high-efficacy D1R agonist SKF 81297, the low-efficacy D1R agonist SKF 38393 and the D1R antagonist SCH 23390 on food-cocaine choice in adult male cynomolgus monkeys.

The monkeys in this study were socially housed in groups of four monkeys per pen. We have demonstrated that monkeys that occupy different positions in the social hierarchy (dominant vs. subordinate) differ in D2R availability as measured with PET imaging and in sensitivity to cocaine and other drugs that act at D2R (Morgan et al., 2002; Czoty et al., 2010; Czoty and Nader, 2013). Thus, another aim of the study was to assess whether the effects of D1R drugs on cocaine choice differed as a function of social rank. Previous experiments found no evidence of social rank-related differences in the unconditioned behavioral effects of SKF 81297 or in the effects of the D1R agonist SKF 38393 on cocaine self-administration under a fixed-ratio (FR) schedule of reinforcement (Czoty et al., 2004).
METHODS

Subjects: Subjects were fourteen adult male cynomolgus monkeys (Macaca fascicularis). All had lived for several years in stable social groups of four monkeys per pen. Thus, two of the 14 monkeys in the present study lived in a pen with two other monkeys who did not participate in these experiments. Monkeys lived in stainless-steel cages (0.71 x 1.73 x 1.83 m; Allentown Caging Equipment, Co., Allentown, NJ) with removable wire mesh partitions that could separate monkeys into quadrants (0.71 x 0.84 x 0.84 m). Social status had been determined previously based on outcomes of agonistic encounters using described previously described procedures (Kaplan et al., 1982; Czoty et al., 2009); ranks did not change during the present experiments. #1- and #2-ranked monkeys were considered dominant and #3- and #4-ranked monkeys were considered subordinate. Each monkey was fitted with a nylon collar (Primate Products, Redwood City, CA) and trained to sit calmly in a standard primate chair (Primate Products). Each monkey was also prepared with an indwelling venous catheter and subcutaneous vascular access port using routine surgical procedures (see Czoty and Nader, 2013).

Each day, monkeys were separated for several hours during behavioral sessions and for feeding. To prevent monkeys from becoming obese or developing cardiovascular/metabolic problems, monkeys were not fed ad libitum. They were also not maintained at a target weight set at an arbitrary percentage below their free-feeding weights, because the latter can change with age and other factors, and we did not plan to remove monkeys from the study for periodic redetermination of free-feeding weights. Instead, monkeys were weighed each week and feed enough food each day (Purina Monkey Chow and fresh fruit and vegetables) to maintain a healthy body weight and appearance as determined by daily inspection and periodic veterinary examinations. Body weights did not change significantly during these studies and were not different between dominant and subordinate monkeys. Water was available ad libitum in the home cage. All procedures were compliant with the 2011 National Research Council Guidelines.
for the Care and Use of Mammals in Neuroscience and Behavioral Research and were approved by the Wake Forest University Animal Care and Use Committee. Environmental enrichment was provided as outlined in the Wake Forest University Non-Human Primate Environmental Enrichment Plan.

**Food-cocaine choice: apparatus and procedures.** Each day, monkeys were transferred to a primate chair which was placed into an operant chamber, and their port was connected to an infusion pump located outside the chamber. Two photo-optic switches (Model 117-1007; Stewart Ergonomics, Inc., Furlong, PA) were situated on one side of the chamber with a horizontal row of three stimulus lights positioned 14 cm above each switch. A food receptacle, above which was a single white stimulus light, was located between the switches for delivery of 1-g banana-flavored food pellets (Bio-Serv, Frenchtown, NJ).

Monkeys self-administered cocaine under a concurrent FR schedule of food and cocaine availability in which complete cocaine dose-response curves were determined during each session (see Czoty and Nader, 2012). Responding on one switch (the “food switch”), above which a yellow light was illuminated, always resulted in delivery of a food pellet. Responding on the other switch (the “drug switch”) resulted in activation of the infusion pump and an injection of cocaine (0.003-0.1 mg/kg/injection). Assignment of food or drug to a switch was counterbalanced across monkeys. Availability of each cocaine dose was associated with illumination of a different set of stimulus lights above the switch; different cocaine doses were studied by varying the duration of pump activation.

Each daily session consisted of 5 components in which monkeys chose between food pellets and ascending doses of cocaine (i.e., no injection, 0.003, 0.01, 0.03 and 0.1 mg/kg/injection cocaine in components 1-5, respectively). Each component ended when 10 total reinforcers had
been earned or 20 minutes had elapsed, whichever came first. Delivery of each reinforcer was accompanied by a 5-sec illumination of the red light above the corresponding switch and a 30-sec timeout (TO); a response emitted on the alternate switch before an FR was completed reset the response requirement on the first switch. In addition, a 120-sec TO followed each component. Ratio requirements were adjusted for each monkey such that allocation of responding to the drug switch increased over the session as the available dose of cocaine increased. A monkey was considered trained when ≤20% of reinforcers were earned on the drug switch when the alternative to food was no injection (component 1) or 0.003 mg/kg/injection cocaine (component 2) and ≥80% of reinforcers were earned on the drug switch when the alternative to food was 0.1 mg/kg/injection cocaine (component 5). An additional criterion was observation of a dose-related increase in drug choice. The ratio requirements required to generate curves of this shape ranged from FR50 to FR125 responses on the food-associated switch and FR50 to FR350 responses on the cocaine-associated switch.

When responding was stable, vehicle or a single dose of SKF 81297 (0.1 – 3.0 mg/kg, 15 min before the session), SKF 38393 (1.0-17.8 mg/kg, 5 min pre-session) or SCH 23390 (0.003 – 0.1 mg/kg, 5 min pre-session) was administered intravenously. Pretreatment times were based on previous nonhuman primate behavioral studies in our laboratory and others. Most doses were tested at least twice, except for the low doses which were ineffective and in cases when the highest doses disrupted behavior markedly in several monkeys. Finally, selected doses of SKF 81297 and SCH 23390 were administered again with a 30-minute longer pretreatment time.

**Data analysis.** The primary dependent variable was percent cocaine choice, defined as the percent of total reinforcers received as injections, calculated for each component. Because monkeys had different FR requirements (which did not differ according to social rank), percent of reinforcers was used for analysis rather than percent responses. Although monkeys were
differentially sensitive to the D1R drugs, the magnitude of effect was positively related to dose in all animals. Thus, rather than average monkeys’ data across D1R drug doses, doses were matched for behavioral effect for data analysis and presentation. In most cases, at least one low dose was tested and found to be without effect, and a high dose was identified that produced nonselective disruption of responding. For this purpose, a dose was deemed to have “disrupted” responding when the total number of reinforcers earned across the session was decreased more than 35% from baseline. Once a disruptive dose was identified, the next lowest dose, which was one-half or one-quarter log units lower than the disruptive dose, was selected for analysis. Table 1 lists these “best doses” for each subject and drug. In addition to percent cocaine choice, the total number of reinforcers, food pellets and injections delivered were also recorded, as was cocaine intake in each session (in mg/kg).

For each treatment drug, in each group of monkeys (dominant or subordinate), data for percent cocaine choice, total reinforcers, food reinforcers and injections were analyzed separately with a 2-way repeated-measured analysis of variance (ANOVA) with pretreatment condition (vehicle or D1R-acting drug) and available cocaine dose as factors. A significant main effect of cocaine dose on each of these variables was expected. When a significant main effect of pretreatment condition and/or interaction between pretreatment and cocaine dose was observed, post-hoc multiple comparisons testing with Tukey’s test determined cocaine doses at which the effects of the D1R-acting drug differed from the effects of vehicle treatment. Effects of each drug on cocaine intake were analyzed separately by calculating the percent decrease in cocaine intake compared to vehicle administration, then performing an unpaired t-test comparing this effect between dominant and subordinate monkeys. In all instances, differences were considered significant when p<0.05.
Drugs. (−)-Cocaine was supplied by the National Institute on Drug Abuse (Bethesda, MD) and dissolved in sterile 0.9% saline. SKF 81297, SKF 38393 and SCH 23390 were purchased from Sigma-Aldrich (St. Louis, Missouri, USA) and were dissolved in sterile water.
RESULTS

Cocaine choice. In each experiment described below (i.e., each of three D1R-acting drugs tested in both dominant and subordinate monkeys) an expected cocaine dose-related increase in cocaine choice was observed (Fig. 1). In all cases, there was a significant main effect of cocaine dose (all p<0.0001). In addition, as expected for all three drugs in both dominant and subordinate monkeys, there was a significant main effect of cocaine dose on total reinforcers, food pellets and injections delivered, with one exception (no main effect of cocaine dose on total reinforcers delivered in the SCH 23390 experiment in subordinate monkeys).

Effects of SKF 81297 on food-cocaine choice. There was no main effect of treatment (SKF 81297 vs. vehicle) on cocaine choice and no significant interactions between the available cocaine dose and SKF 81297 treatment in either dominant monkeys (Fig. 1A) or subordinates (Fig. 1B). In dominant monkeys, there was a significant main effect of SKF 81297 on total reinforcers delivered (Fig. 2A; F\textsubscript{1,30}=48.50, p<0.0001) and a significant interaction with cocaine dose (F\textsubscript{4,30}=35.91, p<0.001) that was explained by a significant effect of SKF 81297 on food pellets delivered (Fig. 2B; F\textsubscript{1,30}=15.32, p=0.0005), a significant interaction (F\textsubscript{4,30}=14.14; p>0.0001) and a significant decrease in food pellets delivered in the first component (p<0.0001). In subordinates, there was no main effect of SKF 81297 on total reinforcers delivered (Fig. 2D), but the interaction was significant (F\textsubscript{4,15}=3.15, p<0.05) and post-hoc testing revealed a significant decrease in total reinforcers in the first component (p<0.01). There was a main effect of SKF 81297 of food reinforcers delivered (Fig. 2E; F\textsubscript{4,15}=117.7, p<0.0001) and the interaction only approached significance (p=0.095). Post-hoc testing identified a significant difference in food pellets delivered in the first component (p<0.05). There were no effects or interactions of SKF 81297 on injections delivered in either group of monkeys (Fig. 2C, 2F). When the pretreatment time was increased by 30 minutes, decreases in first-component total and food reinforcers were no longer observed, and no effects were seen during availability of any cocaine...
dose (data not shown). In summary, SKF 81297 did not alter cocaine choice; the only significant effects of SKF 81297 that were observed were related to a decrease in food pellets delivered in the first component.

**Effects of SKF 38393 on food-cocaine choice.** Unlike the high-efficacy agonist SKF 81297, the low-efficacy D1R agonist SKF 38393 produced effects on cocaine choice that differed between dominant and subordinate monkeys (Figs. 1C and 1D, respectively). No significant main effect or interaction was observed in dominant monkeys (Fig. 1C); however, in subordinate monkeys there was a significant main effect of treatment with SKF 38393 (Fig. 1D; $F_{1,20}=7.81; p<0.01$) and the interaction approached significance ($p=0.053$). Post-hoc testing revealed that choice of 0.03 mg/kg per injection cocaine was significantly different after vehicle vs. SKF 38393 treatment ($p<0.05$). There were no significant main effects or interactions of SKF 38393 on total reinforcers delivered in either group of monkeys (Figs. 3A, 3D). However, in subordinates but not dominants, there was a main effect of SKF 38393 on food pellets (Fig. 3E; $F_{1,25}=4.34; p<0.05$) and injections (Fig. 3F; $F_{1,25}=9.55; p<0.005$) and significant interactions with each ($F_{4,25}=4.88; p<0.005$ and $F_{1,25}=4.46; p<0.01$, respectively). Post-hoc testing indicated that, in subordinates, SKF 38393 significantly increased food pellets delivered when 0.03 and 0.1 mg/kg were available (Fig. 3E) and decreased injections when 0.03 was available (Fig. 3F, both $p<0.05$). The effect of SKF 38393 on injections of 0.1 mg/kg cocaine approached significance (Fig. 3F, $p=0.091$). In summary, SKF 38393 did not alter choice behavior in dominant monkeys, but in subordinates it decreased choice of higher cocaine doses by decreasing cocaine injections and increasing food pellets delivered.

**Effects of SCH 23390 on food-cocaine choice.** The D1R antagonist SCH 23390 had no significant effects on cocaine choice and there were no interactions in either dominant monkeys (Fig. 1E) or subordinates (Fig. 1F). As with SKF 81297, there was a main effect of SCH 23390
administration on total reinforcers delivered in both dominant monkeys (Fig. 4A; F_{1,25}=12.40; p<0.005) and subordinates (Fig. 4D; F_{1,20}=11.69; p<0.005). There were significant interactions between SCH 23390 and cocaine dose on total reinforcers delivered in both groups (F_{4,25}=11.90; p<0.0001 and F_{4,20}=2.92; p<0.05, respectively). In both groups, total reinforcers differed only in the first component (p<0.005). In dominant monkeys the main effect of SCH 23390 on food pellets delivered (Fig. 4B) approached significance (F_{1,25}=4.175; p=0.052) and the interaction with cocaine dose reached significance (F_{4,25}=8.97; p=0.0001). In subordinates there was a main effect of SCH 23390 treatment on food pellet deliveries (Fig. 4E, F_{1,20}=9.35; p<0.01) but no significant interaction. Consistent with the effects on total reinforcers but not injections, food pellet deliveries were decreased in the first component in both groups (p<0.05). There were no significant effects or interactions on injections delivered (Figs. 4C, 4F). When the pretreatment time was increased by 30 minutes, decreases in first-component total and food reinforcers were no longer observed, and no effects were seen during availability of any cocaine dose (data not shown). In summary, SKF 23390 did not alter cocaine choice; the only significant effects of SKF 81297 that were observed were related to a decrease in food pellets delivered in the first component.

**Effects of D1R-acting drugs on cocaine intake.** The best doses of neither SKF 81297 nor SCH 23390 altered the average amount of cocaine earned in the session in dominant and subordinate monkeys (Fig 5A). In contrast, after administration of SKF 38393 the average cocaine intake per session was reduced slightly in dominant monkeys and by 50% in subordinates. Although the difference in the effects of SKF 38393 on cocaine intake in dominant or subordinate monkeys was not statistically significant, inspection of individual subject data revealed that SKF 38393 reduced cocaine intake by more than 40% in 4 of 6 subordinates and only 1 of 5 dominant monkeys (Fig. 5B).
DISCUSSION

These studies characterized the effects of drugs acting at D1Rs on food-cocaine choice. Because the ability of D1R-acting drugs to produce behavioral effects can vary according to their intrinsic efficacy (see Bergman et al., 1996), we selected three drugs to study that vary widely in this characteristic. We compared the effects of the high-efficacy D1R agonist SKF 81207, the low-efficacy D1R agonist SKF 38393 and the D1R antagonist (i.e., zero efficacy) SCH 23390. Additional rationale for examining drugs of varying intrinsic efficacy arose from our previous study in which effects of D2R ligands on food-cocaine choice differed depending on their intrinsic efficacy at D2R (Czoty and Nader, 2013). Another independent variable assessed in this study was the monkey’s social status. We have documented a robust influence of social rank on brain D2Rs and on the behavioral effects of cocaine (e.g., Morgan et al., 2002). Moreover, social rank influenced the ability of D2R ligands to alter cocaine choice under conditions identical to those used in the present study (Czoty and Nader, 2013). Prior to this study, the only pharmacological evaluation of D1Rs in socially housed monkeys examined an unconditioned behavior (SKF 81297-induced eye blinking) and cocaine self-administration under an FR schedule of reinforcement and reported no effects of social rank on these variables (Czoty et al., 2004).

In most published studies in which D1R-acting drugs decreased cocaine self-administration, behavioral selectivity was not determined. That is, in most studies, the effects of D1R-drugs on behavior maintained by other reinforcers (e.g., food pellets) were not assessed. The possibility cannot be ruled out that decreases in cocaine self-administration in those studies were due to effects other than an attenuation of the reinforcing effects of cocaine (e.g., sedation). Of the studies that did examine drug effects on other behaviors, some reported a lack of behavioral selectivity of high- and low-efficacy D1R agonists and antagonists including SKF 81297 and SCH 23390 (Woolverton and Virus, 1989; Caine et al., 2000; Platt et al., 2001) and others.
reported that selectivity was low (2- to 4-fold; Barrett et al., 2004) or occurred only in a subset of animals (Kleven and Woolverton, 1990). In only two studies, SKF 38393 and SCH 23390 were found to have selective effects on cocaine vs. food self-administration (Katz and Witkin, 1992; Caine and Koob, 1994, respectively). Although few drugs have been tested in multiple studies, whether effects of D1R-acting drugs are behaviorally selective does not appear to depend on species (rat versus monkeys) or the schedule of reinforcement used.

To focus the present studies on drug doses whose effects on cocaine choice could be behaviorally selective, we used a “best dose” approach to identify the dose of each drug that produced maximal effects on cocaine choice without disrupting behavior. A dose defined as behaviorally disruptive was that which resulted in a ≥35% reduction of total reinforcers across a session. A reduction of this magnitude in total reinforcers is indicative of drug effects unrelated to cocaine reinforcement, which may include sedation or motor impairment. Such effects may be considered a model of potential side effects in a clinical setting. Once a disruptive dose was identified, the next lowest dose was selected for analysis. In this manner we were able to compare the effects of doses of each drug that were behaviorally equivalent: specifically, the highest dose that could be tested that did not produce nonspecific decreases in behavior.

The “best dose” of the high-efficacy agonist SKF 81297 did not alter cocaine choice. This result is consistent with previous studies in which high-efficacy D1R agonists decreased cocaine reinforcement only at doses that also decreased food-maintained responding (Caine et al., 2000; Platt et al., 2001; Barrett et al., 2004). Similarly, the D1R antagonist SCH 23390 only decreased cocaine choice at doses that decreased total reinforcers more than 35% compared to vehicle administration. Previous studies with SCH 23390 and other D1R antagonists have produced mixed but generally negative results regarding whether these drugs can decrease cocaine reinforcement selectively (Woolverton and Virus, 1989; Kleven and Woolverton, 1990;
Caine and Koob, 1994; Platt et al., 2001; Barrett et al., 2004). Even the “best doses” of SKF 81297 and SCH 23390 drugs produced some decreases in responding. These decreases were observed only in the first component and were not prominent enough to render the dose “disruptive” by our definition. Response rate-decreasing effects of D1R agonists and antagonists have previously been observed in animals whose responding was maintained under fixed-interval or FR schedules of reinforcement (e.g., Katz and Witkin, 1993; Bergman et al., 1995, 1996; Katz et al., 1995). To address the possibility that rate-decreasing effects of these D1R-acting drugs may have masked effects on cocaine reinforcement in the present study, the time between drug administration and the cocaine self-administration session was increased by 30 minutes to permit these effects to dissipate. There remained no effect on cocaine choice. Thus, although these drugs showed some nonspecific decreases in responding in the first component, it is unlikely that these effects confounded the assessment of their effects on cocaine choice.

The profile of effects of the low-efficacy D1R agonist SKF 38393 differed from those of the high-efficacy D1R agonist and the antagonist. First, the “best dose” of SKF 38393 lacked the first-component response-decreasing effects observed with “best doses” of SKF 81297 and SCH 23390. Moreover, SKF 38393 decreased choice of higher doses of cocaine. The pattern of effects on the number of food pellets and injections delivered confirmed that this represented a shift in allocation of responding away from cocaine and toward food. The ability of SKF 38393 to selectively decrease cocaine reinforcement is consistent with the only other study that assessed its selectivity (Katz and Witkin, 1992). Taken together, the present data and published studies indicate that, whereas drugs with high-, low- and no efficacy (antagonists) at D1R can produce decreases in cocaine reinforcement, only low-efficacy drugs are likely to do so at doses that lack disruptive effects. Although the behavioral and pharmacological mechanisms by which low-efficacy D1R agonist reduce cocaine reinforcement are unclear, they may involve the ability of
low efficacy agonists to attenuate cocaine-induced increases in extracellular dopamine, while providing a low enough level of D1R stimulation to prevent disruption of responding.

In addition to studying food-cocaine choice, another novel aspect of the present studies was the use of socially housed monkeys. The effects of SKF 81297 and SCH 23390 did not differ between dominant- and subordinate-ranked monkeys. In a previous study using an identical choice procedure and many of the same monkeys, the effects of acute administration of the high-efficacy D2R agonist (-)-NPA and the D2R antagonist eticlopride also did not differ according to social rank (Czoty and Nader, 2013). These drugs did, however, selectively alter cocaine choice. Administration of (-)-NPA decreased choice of the highest cocaine dose whereas eticlopride increased choice of lower cocaine doses. In contrast to the effects of these four drugs and the low-efficacy D2R agonist aripiprazole which did not differ according to social rank, the effects of the low-efficacy D1R agonist SKF 38393 were more prominent, and only statistically significant, in subordinate monkeys. This result may suggest that chronic social stress in subordinates and/or environmental enrichment in dominant monkeys results in divergent effects on dopamine D1R function. However, a previous study in our laboratory found no rank-related differences in the ability of SKF 81297 to elicit eye blinks or in the ability of SKF 38393 to decrease cocaine self-administration under a FR 50 schedule of reinforcement (Czoty et al., 2004). However, one caveat to that conclusion is that behavioral selectivity was not assessed in the Czoty et al., (2004) study; a comparison of the effective SKF 38393 doses in that study with the “best doses” in the present study suggest that effects in the previous study may have been selective. If so, the difference between the two studies is likely be due to the use of the choice procedure vs. FR 50 schedule.

There are some limitations to this study. Although there are limited studies on sex differences involving D1R-acting compounds (e.g., Campi et al., 2014 studies of rodent social behavior), the
present study only utilized male monkeys. A second limitation is that only acute drug administrations were evaluated. The only previous study to assess the effects of chronic treatment with a D1R-acting drug on cocaine self-administration found that chronic administration of the low-efficacy D1R agonist, SKF 77434, shifted the cocaine dose-effect curve to the right without affecting food-maintained responding (Mutschler and Bergman, 2002). Moreover, in our previous study of D2R-acting drugs (Czoty and Nader, 2013), differential effects of (-)-NPA and aripiprazole according to social rank emerged during chronic treatment. Thus, different conclusions might be reached if D1R-acting drugs, specifically low-efficacy agonists, were studied in female subjects and/or were administered chronically. Overall, the present results do not provide strong support for further evaluation of D1R compounds as candidate medications for cocaine use disorder. However, the significant effect of the low-efficacy agonist SKF 38393 in subordinate monkeys may indicate therapeutic potential of this approach in a subset of patients.

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AUTHORSHIP CONTRIBUTION

Participated in research design: Czoty, Nader.

Conducted experiments: Czoty, Nader.

Contributed new reagents or analytic tools: not applicable.

Performed data analysis: Czoty.

Wrote or contributed to the writing of the manuscript: Czoty, Nader.
FINANCIAL DISCLOSURE

Neither author has an perceived or actual conflict of interest with the any aspect of this article.
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FOOTNOTE

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FIGURE LEGENDS

Figure 1. Effects of acute administration of SKF81297 (top row), SKF38393 (middle row) and SCH23390 (bottom row) on cocaine choice in dominant monkeys (left column) and subordinates (right column). Ordinates, percent of reinforcers earned on cocaine-associated switch (mean ± SEM). Abscissae, dose of cocaine (mg/kg per injection) available as an alternative to a food pellet. *, p<0.05 between treatments at the same cocaine dose.

Figure 2. Effects of acute administration of SKF81297 on number of total reinforcers (S^R, left column), food pellets (center column) and injections (right column) delivered across the session in dominant monkeys (top row) and subordinates (bottom). Ordinates, numbers of reinforcers (mean ± SEM) per component. Abscissae, dose of cocaine (mg/kg per injection) available as an alternative to a food pellet. *, p<0.05 between treatments at the same cocaine dose.

Figure 3. Effects of acute administration of SKF 38393 on number of total reinforcers (S^R, left column), food pellets (center column) and injections (right column) delivered across the session in dominant monkeys (top row) and subordinates (bottom). Ordinates, numbers of reinforcers per component (mean ± SEM). Abscissae, dose of cocaine (mg/kg per injection) available as an alternative to a food pellet. *, p<0.05 between treatments at the same cocaine dose.

Figure 4. Effects of acute administration of SCH 23390 on number of total reinforcers (S^R, left column), food pellets (center column) and injections (right column) delivered across the session in dominant monkeys (top row) and subordinates (bottom). Ordinates, numbers of reinforcers per component (mean ± SEM). Abscissae, dose of cocaine (mg/kg per injection) available as an alternative to a food pellet. *, p<0.05 between treatments at the same cocaine dose.
Figure 5. Effects of best doses of SKF 81297, SKF 38393 and SCH 23390 on cocaine intake expressed a percent of cocaine intake observed after vehicle administration in dominant monkeys (DOM, D) and subordinates (SUB, S). A, mean ± SEM; B, individual subject data.
Table 1. “Best doses” of D1R drugs (mg/kg, i.v.) for each subject

<table>
<thead>
<tr>
<th>Monkey</th>
<th>“Best dose” N 81297</th>
<th>“Best dose” SKF38393</th>
<th>“Best dose” SCH23390</th>
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</thead>
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<td>0.056</td>
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<td>C-7998</td>
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**Dominant-ranked monkeys**

**Subordinate-ranked monkeys**

<table>
<thead>
<tr>
<th>Monkey</th>
<th>“Best dose” N 81297</th>
<th>“Best dose” SKF38393</th>
<th>“Best dose” SCH23390</th>
</tr>
</thead>
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Figure 2

Graph A: Total reinforcers for Dominant compared to Cocaine (mg/kg per injection) with vehicle, best dose, and SKF81297.

Graph B: Food pellets for Dominant compared to Cocaine (mg/kg per injection).

Graph C: Injections for Dominant compared to Cocaine (mg/kg per injection).

Graph D: Total reinforcers for Subordinate compared to Cocaine (mg/kg per injection) with vehicle, best dose, and SKF81297.

Graph E: Food pellets for Subordinate compared to Cocaine (mg/kg per injection).

Graph F: Injections for Subordinate compared to Cocaine (mg/kg per injection).
Figure 3

A. Total reinforcers for Dominant

B. Food pellet deliveries for Dominant

C. Injections for Dominant

D. Total reinforcers for Subordinate

E. Food pellet deliveries for Subordinate

F. Injections for Subordinate
Figure 5